Fundamentals of allergy and immunology

Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases

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There have been extensive developments on cellular and molecular mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumor development, organ transplantation, and chronic infections during the last few years. Better understanding the functions, reciprocal regulation, and counterbalance of subsets of immune and inflammatory cells that interact through interleukins, interferons, TNF-α, and TGF-β offer opportunities for immune interventions and novel treatment modalities in the era of development of biological immune response modifiers particularly targeting these molecules or their receptors. More than 60 cytokines have been designated as interleukins since the initial discoveries of monocyte and lymphocyte interleukins (called IL-1 and IL-2, respectively). Studies of transgenic or gene-deficient mice with altered expression of these cytokines or their receptors and analyses of mutations and polymorphisms in human genes that encode these products have provided essential information about their functions. Here we review recent developments on IL-1 to IL-38, TNF-α, TGF-β, and interferons. We highlight recent advances during the last few years in this area and extensively discuss their cellular sources, targets, receptors, signaling pathways, and roles in immune regulation in patients with allergy and asthma and other inflammatory diseases. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

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Since the discovery of IL-1 in 1977, approximately 360,000 published scientific articles have referred to interleukins. Secreted proteins that bind to their specific receptors and play a role in intercellular communication among leukocytes are named interleukins. The nomenclature has been continuously evolving, and assignments of new members to the IL-1 family have been taking place (see Table E1 in this article's Online Repository at www.jacionline.org).[1] Interleukins are assigned to each family based on sequence homology and receptor chain similarities or functional properties (Fig 1). We have learned in the last decades since the discovery of T_H subsets[2,3] that almost all immune cells display different functional subsets characterized by distinct surface receptors and cytokine profiles, such as CD4 and CD8 T cells, B cells, innate lymphoid cells (ILCs), natural killer (NK) cells, and dendritic cells (DCs).[4-6]

Investigations of the mechanisms of immune and inflammatory cell functions have identified a growing list of interleukins. Their interactions among different cell types that contribute to their effector and suppressive functions are shown in Table I. Phenotypes of cytokine- or receptor-deficient, as well as cytokine-overexpressing, transgenic mice and mutations and relevant polymorphisms in human subjects are listed in Table E2 in this article's Online Repository at www.jacionline.org. Association of cytokines

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Abbreviations used
AIT: Allergen-specific immunotherapy
APC: Antigen-presenting cell
Breg: Regulatory B
γc: Common γ chain
CRS: Chronic rhinosinusitis
DC: Dendritic cell
FOXP3: Forkhead box P3
ILC: Innate lymphoid cell
KO: Knockout
NK: Natural killer
Ra: Receptor antagonist
TLR: Toll-like receptor
Treg: Regulatory T
TSLP: Thymic stromal lymphopoietin
TSLPR: TSLP receptor

with diseases together with anticytokines/anticytokine receptor treatment options are shown in Table II. Fig 1 shows receptor families and common use of receptors between interleukins. Cytokine-driven differentiation of T-cell subsets is shown in Fig 2. The intensive interaction of cytokines and other mediators with cell subsets during type 2 inflammation, which takes places in patients with asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis (CRS), and helminth infections, is shown in Fig 3.

In the main text below we present a functional approach in subgrouping these cytokines, linking various categorization systems. First, we describe different cell subsets named or defined by the main cytokines produced. Next, we describe the cytokine families based on their sequence homology and evolutionary relationship, common receptor chains, or major function of the whole group. Groups of cytokines are listed in Table E1 in this article's Online Repository. Additionally, all of the interleukins have been listed in numeric order, with an extensive emphasis on their structure, receptors, cellular sources, targets, signaling pathways, and roles in immune regulation in patients with allergy, asthma, and other inflammatory diseases in the text portion in this article's Online Repository at www.jacionline.org.

EFFECTOR CD4 T-CELL SUBSETS

$CD4^+$ T cells are divided into distinct subsets according to their cytokine profile.[2] They differentiate from naive T cells, and their cytokine expression profile depends on the types of antigen-presenting cells (APCs), the type of the initial innate immune response, the adjuvanticity of the molecules presented with the antigen, and the existence and dose of many small molecules and other cytokines in the microenvironment.[7] $CD4^+$ naive T cells can differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, and follicular effector T cells, as well as different subsets of regulatory T (Treg) cells.[4,8,9] Based on their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T-cell subsets can promote the development of different types of inflammatory responses (Fig 2). Both innate and effector mechanisms play essential roles during the development of allergic disease.[10]

Effector T_H2 cells produce IL-4, IL-5, IL-9, and IL-13.[11] In addition, thymic stromal lymphopoietin (TSLP), IL-25, IL-31, and IL-33 contribute to the development and intensity of T_H2 responses and inflammation.[12-14] These cytokines have roles in the production of allergen-specific IgE, eosinophilia, mucus, tissue migration of T_H2 cells and eosinophils, regulation of tight junctions, and epithelial barrier integrity.[15-18] They are essential players in immune response to helminths.[19] T_H1 cells produce IFN-γ, which protects against intracellular pathogens and plays a role in activation and chemokine production of resident tissue cells and activation-induced cell death of skin keratinocytes, mucosal epithelial cells, and T cells.[20-22]

The discovery of T_H17 cells has enabled a novel approach to inflammatory processes, autoimmunity, and immune response to extracellular infections. T_H17 cells are characterized by their expression of IL-17A, IL-17F, IL-6, IL-8, TNF-α, IL-22, and IL-26.[23,24] There is still an ongoing debate and no clear distinction between T_H17 and T_H22 cells in human subjects because the main cytokine of T_H22 cells, IL-22, can be produced by T_H17 cells.[25] The combination of TGF-β and IL-4 reprograms the differentiation of T_H9 cells, which produce IL-9 and IL-10.[26] These cells show a distinction to T_H2 cells and might represent a clinically relevant T-cell subset linked to food allergy.[27] Follicular helper T cells represent a large subset of effector T cells in lymphoid tissues and provide help to B cells.[28,29] They support the differentiation of antigen-specific B cells into memory and plasma cells.

Treg CELLS AND OTHER REGULATORY CELLS

Treg cell subsets have distinct phenotypes and include constitutive and inducible subsets of $CD4^+CD25^+$ forkhead box P3 $(FOXP3)^+$ Treg cells and type 1 Treg cells.[30,31] Allergen tolerance and allergen-specific immunotherapy (AIT) are one of the most representative areas in which Treg cells display their major role.[32-34] The production of IL-10 and TGF-β from other cells is decisive for their immune regulatory functions. Subsets of $CD8^+$ T cells, γδ T cells, IL-10–producing B cells, IL-10–producing NK cells, DCs, and macrophages might contribute to immune suppression or regulation.[3,35]

ILC SUBSETS

Immune responses in populations of lymphoid cells that lack rearranged antigen receptors and markers for myeloid and lymphoid lineages, such as T, B, and NK cells, show similarities to T_H1, T_H2, and T_H17/T_H22 types of immune responses. These cells are defined as ILC1s, ILC2s, and ILC3s. ILC1s mainly produce IFN-γ, ILC2s produce IL-5 and IL-13,[36] and ILC3s produce IL-17 and IL-22.[5] ILCs control the mucosal environment through close interaction with epithelial cells and other tissue cells, cytokine production, and induction of chemokines that recruit suitable cell populations to initiate and promote distinct types of immune response development and tissue inflammation.[14] These cells can be detected in several body fluids and tissues, such as sputum, peripheral blood, nasal polyps, and the esophagus, for their characterization in patients with allergy and asthma.[36,37]

MAST CELLS AND BASOPHILS

Mast cells and basophils play a crucial role in type I allergy, as well as in innate and adaptive immune responses.[38] Recent studies in human and mouse models have shown that basophils perform nonredundant effector functions and significantly contribute to

the development and progression of T_H2 cytokine–mediated inflammation.[38,39] Mast cells are localized at the interface with the external environment, such as the skin, respiratory tract, conjunctiva, and gastrointestinal tract. Mast cells contribute to the maintenance of tissue homeostasis, with important roles in wound repair, revascularization, and protective responses to bacterial infection and venoms. They synthesize many interleukins and release them on activation through IgE cross-linking or innate immune response receptors.[38,40]

EPITHELIAL CELLS

Airway epithelial cells, gut epithelium, keratinocytes, and other epithelia are at the interface of the human body and the environment. Thus they form a complex physicochemical barrier and the first line of defense against environmental cues, such as viruses, bacteria, fungi, parasites, allergens, and inorganic particles. Epithelial cells regulate both innate and adaptive immunity, among others, through the production of various costimulatory molecules, chemokines, cytokines, and lipid mediators in response to environmental stimuli sensed by the rich panel of intracellular sensors, such as Toll-like receptors (TLRs), NOD-like receptors, melanoma differentiation-associated protein 5, and retinoic acid–inducible gene 1.[41] After sensing of allergens, epithelial cells can produce IL-1α, IL-25, IL-33, TSLP, and GM-CSF.[41] These cytokines start to orchestrate T_H2 immunity. However, when allergens have additional protease activity and/or are accompanied by microbial components, such as endotoxins or inorganic particles, epithelial secretory responses can lead to mixed T_H2 and T_H17 immunity or even T_H1 responses.[42,43] In response to viruses, epithelial cells produce a wide range of mediators, such as type I interferons, GM-CSF, RANTES/CCL5, and IFN-γ–induced protein 1/CXCL10.[44] These mediators orchestrate further downstream innate and adaptive antiviral immune responses.

PHENOTYPES AND ENDOTYPES OF CHRONIC DISEASES AND INTERLEUKINS AS THERAPEUTIC TARGETS

It is generally expected that drug development in the next decades will show a significant shift from chemicals to biological agents.[45] The new era of drug development is now leading to development of biomarkers and endophenotyping of diseases for better patient care, which is called stratified medicine, precision medicine, or personalized medicine.[46] Distinguishing phenotypes of a complex disease will help to cover the observable clinically relevant properties of the disease but do not show a direct relationship to disease etiology and pathophysiology. In a complex disease, such as asthma, different pathogenetic mechanisms can cause similar disease symptoms; however, they might require different treatment methods.[47]

These putative pathophysiologic mechanisms identifying disease subgroups are addressed by the term endotype. Classification of complex diseases based on the concept of endotypes provides advantages for epidemiologic, genetic, and drug-related studies.[48] Accurate endotyping with biomarkers reflects the natural history of the disease and aims to predict treatment response. Accordingly, recent studies have focused on better understanding of endotypes of allergic diseases, allergen-specific immunotherapy (AIT), asthma, CRS,[49] and chronic obstructive pulmonary disease and development of biomarkers to stratify patients that also include novel interleukins and microRNAs that regulate their expression.[50] Many cytokines and their receptors have been therapeutic targets in clinical studies, and several anticytokine antibodies and/or cytokine receptor antagonists (Ras) have been approved and registered (Table II). Because several clinical trials with anticytokine approaches did not fulfill the primary outcomes in patients with highly heterogeneous diseases, such as asthma, there is a hope that implementing the endotype concept of these diseases will help to tailor the right treatment to the right patient.

THE IL-1 FAMILY

IL-1 was first described as a protein that induced fever and was called human leukocytic pyrogen, which comprises 2 major proteins: IL-1α and IL-1β.[51] Although IL-1α and IL-1β have minimal sequence homology, they were thought to have similar biological properties; however, these properties are becoming more distinct because of different clinical responses to biological targeting of these 2 interleukins. There are fundamental differences in their localization, maturation, and secretion.[51] IL-1α is translated into pro–IL-1α, an already biologically active form, whereas IL-1β is translated into pro–IL-1β, which has no biological activity, until it is processed by the activation of inflammasome and caspase-1. IL-1α and IL-1β exert similar effects by binding to the IL-1 type I receptor. They can also bind to the IL-1 type II receptor, which acts as a decoy receptor and is not involved in signal transduction. The IL-1 family of cytokines comprises 11 members, including 7 proinflammatory agonists (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, and IL-36γ) and 4 defined or putative antagonists (IL-1Ra, IL-36Ra, IL-37, and IL-38) exerting anti-inflammatory activities.

IL-1Ra and IL-1 are synthesized and released in response to the same stimuli.[52] IL-1Ra lacks the IL-1 receptor accessory protein interacting domain, so that its binding to IL-1 type I receptor inhibits IL-1 signaling.[53] Therapies under development for some inflammatory disorders involve neutralization of IL-1 activity through administration of IL-1Ra and anti–IL-1 neutralizing mAbs.[54] IL-1Ra–deficient mice spontaneously have chronic inflammatory polyarthropathy (see Table E2). In a phase 1 clinical study IL-1Ra has reduced inhaled LPS-induced airway neutrophilia as a candidate for the treatment of neutrophilic asthma.[55] The balance between expression levels of IL-1 family cytokines and activation and inhibition of inflammasomes, their Ras, and functional and decoy receptors, is decisive in the generation of proinflammatory and/or homeostatic functions.[56,57]

IL-18

IL-18 is a member of the IL-1 family expressed by a range of inflammatory cell types.[58] Assembly of the inflammasome in cells activates caspase-1 and, subsequently, proteolysis and release of the cytokines IL-1β and IL-18, as well as pyroptotic cell death.[54] Although it was originally discovered as an inducer of IFN-γ production, IL-18 alone induces only small amounts, whereas its combination with IL-12 induces high levels of IFN-γ production by T cells. The biological activity of IL-18 can be neutralized by the IL-18–binding protein, which binds mature IL-18 with a high affinity. IL-18 expression correlates with disease activities of rheumatoid arthritis and Crohn disease.

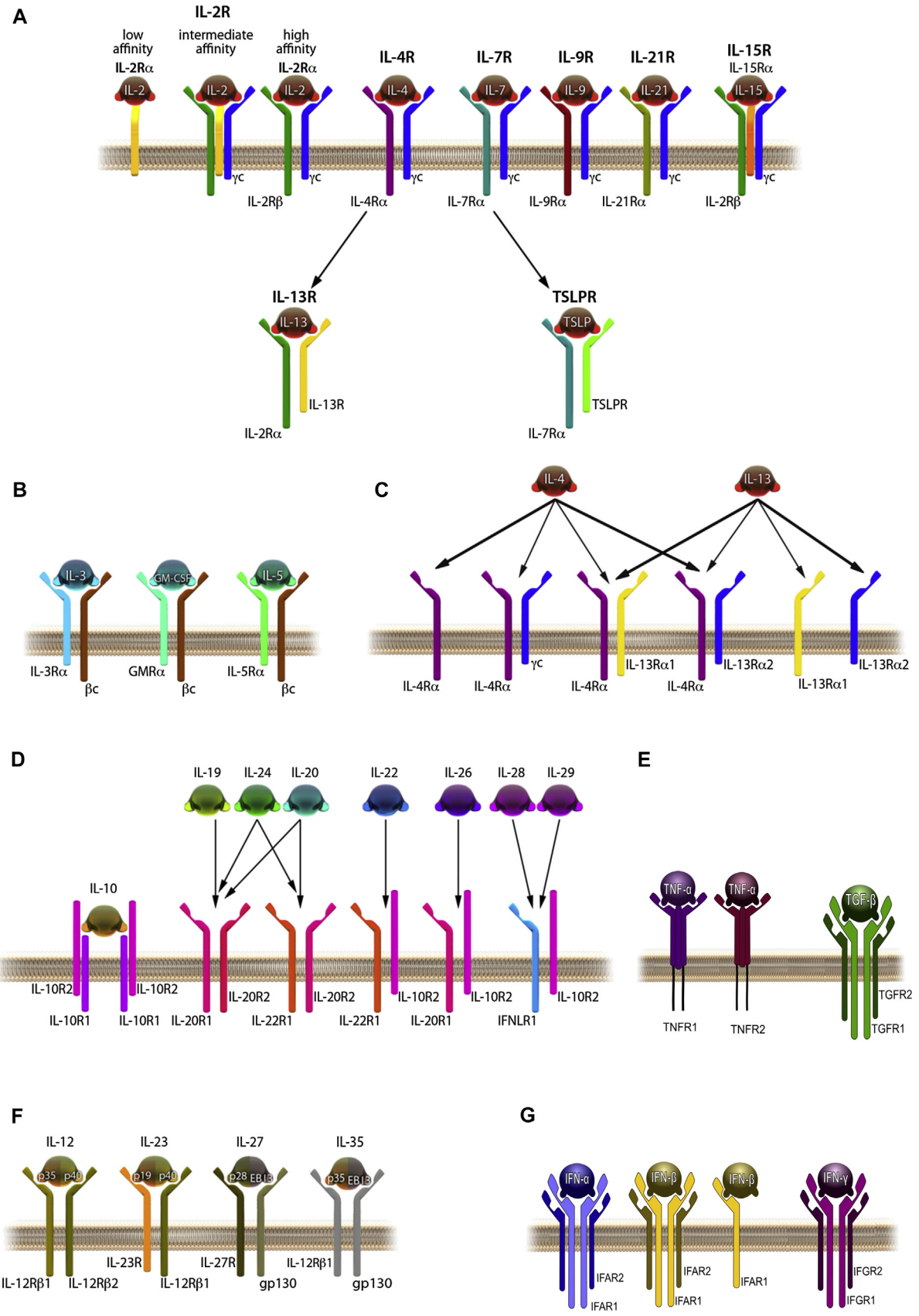


FIG 1. Cytokine receptors. **A,** Receptors of the IL-2 family, which is composed of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Receptors contain the common cytokine receptor γ chain (CD132, γc). IL-13R shares IL-4Rα with

IL-18–deficient mice are more susceptible to bacterial infections than normal mice and have uncontrolled disease progression that is accompanied by reduced T_H1 cell responses (see Table E2). IL-37, a recently described cytokine, requires the receptors IL-18Rα and IL-1R8 to carry out its signal transduction.[59]

IL-33

As a member of the IL-1 family, IL-33 is a potent inducer of type 2 responses in T cells and ILCs through its receptor, ST2.[60,61] The soluble form of ST2 is released by fibroblasts, macrophages, and monocytes in the presence of LPS, TNF-α, IL-1, or T_H2 cell clones. Soluble ST2 inhibits binding of IL-33 to its receptor and is a negative regulator of its activity. Levels of soluble ST2 are increased in patients with inflammatory conditions, such as systemic lupus erythematosus, rheumatoid arthritis, idiopathic pulmonary fibrosis, asthma, progressive systemic sclerosis, Behçet disease, Wegener granulomatosis, severe trauma, and sepsis. ST2-deficient mice have normal maturation of T_H2 cells but altered antigen-specific T_H2-type responses, increased rates of ventricular fibrosis, and cardiomyocyte hypertrophy in response to ventricular pressure overload. *IL33-IL1RL1* pathway polymorphisms are associated with asthma and specific wheezing phenotypes; most of the single nucleotide polymorphisms are associated with intermediate-onset wheeze, a phenotype closely associated with allergic sensitization.[62] In addition, infection of the respiratory epithelium with rhinovirus can antagonize tolerance to inhaled antigen through combined induction of TSLP, IL-33, and OX40 ligand.[63] As an interesting recent finding, IL-33 can impair barrier function of the skin by downregulating filaggrin expression.[17]

IL-36

IL-36 is another proinflammatory family member of IL-1 and a common mediator of innate and adaptive immune responses. It is inhibited by IL-36Ra[64] and uses mitogen-activated protein kinase and nuclear factor κB pathways, exerting proinflammatory effect *in vivo* and *in vitro*. IL-38 binds to IL-36 receptor, as does IL-36Ra, and has similar biological effects on immune cells. Both IL-38 and IL-36Ra have anti-inflammatory biological effects. Recently, high expression of IL-36 has been reported in transcriptomic analyses of AD lesions.[65]

IL-37

IL-37 was originally defined as IL-1 family member 7, which is found in monocytes, tonsil plasma cells, and breast carcinoma cells.[66] Recently, IL-1R8 was found to act as the coreceptor for IL-37–IL-18Rα, and this interaction was required for the anti-inflammatory function of IL-37.[59] TGF-β and several TLR ligands induce production of high levels of IL-37 by PBMCs, and proinflammatory cytokines, such as IL-18, IFN-γ, IL-1β, and TNF, moderately increase IL-37 levels.[67] IL-37b transgenic mice are protected from LPS-induced shock through reductions in proinflammatory cytokine levels and inhibition of DC activation (see Table E2).[67]

IL-38

IL-38 is also a member of the IL-1 cytokine family and shares some characteristics of IL-1Ra, binding the same IL-1 receptor type I. The *IL1F10* gene is located in the IL-1 family cluster on chromosome 2 in human subjects and mice between the genes encoding IL-36Ra and IL-1Ra. IL-38 is highly homologous to IL-36Ra and IL-1Ra, suggesting that it might act as an IL-1 family antagonist. IL-38 expression was reported in skin, tonsil, thymus, spleen, fetal liver, and salivary glands.[68] IL-38 plays a role in the pathogenesis of inflammatory diseases, exerting a protective effect in some autoimmune diseases. The effects of IL-38 might resemble those of IL-36Ra because it binds to the IL-36 receptor and inhibits its effects, particularly the T_H17 response.[53]

THE COMMON γ CHAIN CYTOKINE FAMILY

The common γ chain (γc) family consists of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 and was named for binding of these factors to the γc receptor (CD132; Fig 1). They act mainly as growth and proliferation factors for progenitors and mature cells and also have roles in lineage-specific cell differentiation.[69]

IL-2

IL-2, which was discovered more than 30 years ago in supernatants of activated T cells, is mainly produced by $CD4^+$ and $CD8^+$ T cell–activated DCs and NK and NKT cells.[70] IL-2R consists of 3 subunits: the ligand-specific α chain IL-2Rα (CD25), the β chain IL-2Rβ (CD122, which is also part of the IL-15R complex), and γc (Fig 1). All 3 subunits are required for assembly of the high-affinity IL-2R. On T-cell activation, IL-2Rα is rapidly upregulated and participates in the formation of a high-affinity quaternary complex, which activates multiple signal transduction pathways. IL-2 is essential for the development of Treg cells, and IL-2Rα is a marker for the flow cytometric identification of Treg and regulatory B (Breg) cells in resting conditions.[71,72] IL-2 is a regulator of ILCs and acts as a B-cell growth factor, stimulates antibody synthesis, and promotes proliferation and differentiation of NK cells to increase their cytolytic functions.[73]

IL-4, and TSLPR shares IL-7R with IL-7. **B,** Receptors for IL-3, IL-5, and GM-CSF are heterodimers of a unique α chain and the common β chain (βc, CD131) subunit. **C,** Receptors for IL-4 and IL-13 consist of 2 receptor chains: IL-4Rα (CD124) and γc. IL-4 and IL-13 bind to IL-4R, which consists of IL-4Rα and the IL-13Rα1 chain. IL-13R consists of 2 subunits, IL-13Rα1 and IL-13Rα2, and signaling occurs through the IL-4R complex type II, which consists of IL-4Rα and IL-13Rα. **D,** Based on similarities in their intron-exon structure, conserved secondary protein structures, and similar types of receptors, the following cytokines have been classified as IL-10 family members: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29. They share common receptor subunits, as shown. **E,** TNF-α binds to TNFRI and TNFR2, and TGF-β binds to heterodimer receptor consisting of TGF-βR1 and TGF-βR2. **F,** IL-12R consists of 2 subunits: IL-12Rβ1 and IL-12Rβ3. A heterodimer of IL-12Rβ1 and IL-23R binds IL-23. IL-12Rβ2 shows homology to the gp130 subunit of IL-27R. **G,** IFN-α and IFN-β bind to the heterodimer receptor consisting of IFNAR1 and IFNAR2; in addition, IFN-β binds to IFNAR1, and IFN-γ binds to the IFN-γR1 and IFN-γR2 heterodimer.

TABLE I. Cytokines and their major functions

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-1α and IL-1β	Heterodimer	17 kDa	IL-1 type 1 receptor, IL-1 type 2 receptor	Macrophages, monocytes, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts, synovial lining cells	T cells, fibroblasts, epithelial and endothelial cells	Induction of proinflammatory proteins; hematopoiesis; differentiation T_H17 cells; development of IL-10–producing Breg cells in mouse spleens and mesenteric lymph nodes
IL-1Ra (antagonist)	Heterodimer	16.1-20 kDa	IL-1 type 1 receptor, IL-1 type 2 receptor	Monocytes, macrophages, fibroblasts, neutrophils, endothelial and epithelial cells, and keratinocytes	T cells, fibroblasts, epithelial and endothelial cells	Antagonism of IL-1
IL-2	Monomer	15.5 kDa	IL-2R	$CD4^+$ and $CD8^+$ activated T cells, DCs, NK and NKT cells, mast cells, and ILCs	$CD4^+$ and $CD8^+$ T cells, NK and B cells, and ILCs	Proliferation of effector T and B cells; development of Treg cells; differentiation and proliferation of NK cells; growth factor for B cells and stimulus for antibody synthesis; proliferation and cytokine production in ILCs
IL-3	Monomer	15 kDa	IL-3 receptor α + β c (CD131)	T cells, macrophages, NK cells, mast cells, eosinophils, stromal cells	Erythroid progenitors, granulocytes, macrophages progenitors, $CD34^+$ progenitor cells, basophils, eosinophils, megakaryocytes, monocytes, Treg and endothelial cells	Hematopoietic growth factor; activation of basophils and eosinophils; differentiation of DCs and Langerhans cells; enhancement of IL-2–induced proliferation and differentiation of B cells; improvement of antigen uptake; phagocytosis in macrophages
IL-4	Monomer	15 kDa	IL-4R type I, IL-4R type II	T_H2 cells, basophils, eosinophils, mast cells, NKT cells and γ/δ T cells	T and B cells	Induction of T_H2 differentiation; IgE class-switching; upregulation of class II MHC expression on B cells; upregulation of CD23 and IL-4R; survival factor for B and T cells; role in tissue adhesion and inflammation
IL-5	Homodimer	15 kDa	IL-5R	T_H2 cells, activated eosinophils and masts cells, T_C2 cells, γδ T cells, NK and NK T cells and $CD4^-$c-$Kit^-CD3\varepsilon^-IL2R\alpha^-$ (Peyer patches), ILC2s	Eosinophils, basophils and mast cells, Treg cells, neutrophils and monocytes	Differentiation and function of myeloid cells; increment of eosinophils chemotactic activity and adhesion capacity; involvement in remodeling and wound healing

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-6	Homodimer	19-26 kDa	IL-6R (sIL-6R) gp130	Endothelial cells, fibroblasts, monocytes/ macrophages, T cells, B cells, granulocytes, smooth muscle cells, eosinophils, chondrocytes, osteoblasts, mast cells, glial cells, and keratinocytes	Hepatocytes, leukocytes, T cells, B cells, hematopoietic cells	Induction of acute-phase proteins in hepatocytes; leukocyte trafficking and activation; T-cell differentiation, activation, and survival; B-cell differentiation and production of IgG, IgM, and IgA; hematopoiesis; involvement in osteoclastogenesis and bone resorption and recruitment of mesenchymal vascular cells; neoangiogenesis *in vivo*; synovial fibroblast proliferation and cartilage degradation; survival of cholinergic neurons and induction of adrenocorticotropic hormone synthesis
IL-7	Monomer	25 kDa	IL-7R and sIL-7R	Epithelial cells, keratinocytes, DCs, B cells, and monocytes/ macrophages	Developing B and T lymphocytes, mature T cells, NK cells, and ILCs	Proliferation of pre-B and pro-B cells (mice); megakaryocyte maturation; V(D)J recombination; naive T-cell survival; proliferation of thymocytes; development and maintenance of ILCs; synthesis induction of inflammatory mediators in monocytes
IL-8	Homodimer	16 kDa	CXCR1 and CXCR2	Monocytes, macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells, fibroblasts, keratinocytes, chondrocytes, synovial cells, hepatocytes, smooth muscle and skeletal muscle cells	Neutrophils, NK cells, T cells, basophils, eosinophils, mast cells, monocytes, and endothelial cells	Chemoattractant for neutrophils, NK cells, T cells, basophils, and eosinophils; mobilization of hematopoietic stem cells; angiogenesis
IL-9	Monomer	14 kDa	IL-9R	T_H2, T_H9, T_H17, and Treg cells, mast cells, eosinophils, ILCs	B, T, and mast cells; hematopoietic cells; airway epithelial cells; airway smooth muscle cells; and intestinal epithelial cells	T and mast cell growth factor; inhibition of T_H1- cytokines; proliferation of $CD8^+$ T cells and mast cells; IgE, chemokine, and mucus production in bronchial epithelial cells

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-10	Homodimer	20.5 kDa (predicted size of precursor protein) 18.6 kDa (predicted size mature protein, monomer)	IL-10R1/IL-10R2 complex	T cells, B cells, monocytes, macrophages, and DCs	Macrophages, monocytes, T cells, B cells, NK cells, mast cells, DCs, and granulocytes	Immunosuppressive effect through APCs or direct effects on T-cell subsets; suppression of IgE and induction of IgG by B cells in human subjects
IL-11	Monomer	19 kDa	IL-11Rα + gp130	Bone marrow cells, fibroblasts, epithelial cells, endothelial cells, vascular smooth muscle cells, synoviocytes, osteoblasts	Myeloid, erythroid, and megakaryocyte progenitors, osteoclasts, epithelial cells, hepatocytes, macrophages, neurons	Growth factor for myeloid, erythroid, megakaryocyte progenitors and plasmacytoma cells; protection of epithelial cells and connective tissue; induction of acute-phase proteins; inhibition of monocytes and macrophage activity; promotion of neuronal development; bone remodeling, by stimulation of osteoclasts and inhibition of osteoblasts
IL-12 (p35/p40)	Heterodimer	35 kDa (IL-12a p35) + 40 kDa (IL12b p40)	IL-12Rβ1 and IL-12Rβ2	Monocytes, macrophages, neutrophils, microglia, DCs, B cells	T cells (T^H1 cells), NK cells	Development and maintenance of T_H1 cells; activation of NK cells; support of DC maturation; induction of cytotoxicity
IL-13	Monomer	10 kDa	IL-13R1α1 and IL-13R1α2	T, NKT, and mast cells; basophils and eosinophils; and ILCs	B cells, mast cells, epithelial cells, eosinophils, smooth muscle cells, and macrophages	Switching to IgG_4 and IgE, upregulation of CD23, MHC class II on B cells, and induction of CD11b, CD11c, CD18, and CD29; CD23 and MHC class II on monocytes; activation of eosinophils and mast cells; recruitment and survival of eosinophils; defense against parasite infections
IL-14	Monomer	53 kDa	IL-14R	T cells, T-cell clones, B-lineage and T-lineage lymphoma cell lines	B cells, certain leukemia cells	Proliferation of activated B cells
IL-15	Monomer	14-15 kDa	IL-15R	Monocytes, macrophages, DCs and activated $CD4^+$ T cells, keratinocytes, skeletal muscle cells, fibroblasts, various epithelial cells, bone marrow stromal cells, nerve cells	NK cells, NKT cells, monocytes, macrophages, DCs, neutrophils, eosinophils, mast cells, T cells and B cells	T-cell activation; proliferation and activation of NK cells; differentiation of γ/δ T cells; homeostasis of $CD8^+$ memory, NK, and NKT cells; enhancement of T_H2 differentiation; prevention of neutrophils and eosinophils from apoptosis

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-16	Homotetramer	56 kDa	CD4	T cells, eosinophils, mast cells, eosinophils, monocytes, DCs, fibroblasts, epithelial cells, synoviocytes	T cells, monocytes, macrophages, DCs, eosinophils, mast cells	Modulation of T-cell response; chemoattractant for $CD4^+$ T cells, $CD8^+$ T cells, monocytes, mast cells, and eosinophils
IL-17A	Cysteine knot, homodimer or heterodimer	35 kDa	IL-17RA (= IL-17R)	T_H17 cells, $CD8^+$ T cells, NK cells, NKT cells, γδ T cells, neutrophils, ILCs	Epithelial/endothelial cells, fibroblasts, osteoblasts, monocytes, macrophages, B and T lymphocytes, myelomonocytic cells and marrow stromal cells	Induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment and activation of neutrophils
IL-17B,C,D	Cysteine knot, homodimer	41, 40, and 52 kDa	For IL-17 B: IL-17RB (= IL-17H1, IL-25R) For IL-17C: IL-17RA to IL-17RE For IL-17D: SEF	IL-17B: neuronal cells, chondrocytes; IL-17C: mucosal epithelial cells; IL-17D: resting B and T cells, skeletal muscle, brain, adipose tissue, heart, lung, and pancreas	Monocytes, endothelial cells, myofibroblasts, epithelial cells	Induction of antimicrobial peptides, proinflammatory cytokines, chemokines. and metalloproteases; IL-17B: chondrogenesis and osteogenesis; IL-17C: influence on intestinal barrier function; IL-17D: suppression of myeloid progenitor cell proliferation
IL-17F	Cysteine knot, homodimer or heterodimer	44 kDa	IL-17RA (= IL-17R) and IL-17RC (= IL-17RL)	T_H17 cells, $CD8^+$ T cells, NK cells, NKT cells, γδ T cells neutrophils, basophils, mast cells, monocytes	Epithelial/endothelial cells, fibroblasts, osteoblasts, monocytes, macrophages, B and T lymphocytes, myelomonocytic cells and marrow stromal cells	Induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment and activation of neutrophils
IL-18	Heterodimer	22.3 kDa	IL-18 receptor	Macrophages, DCs, epithelial cells, chondrocytes, osteoblasts, Kupffer cells, keratinocytes, astrocytes, renal tubular epithelial cells	T cells, NK cells, macrophages, epithelial cells, chondrocytes	Induction of IFN-γ in the presence of IL-12; enhancement of NK cell cytotoxicity, promoting T_H1 or T_H2 cell responses depending on cytokine milieu
IL-19	Monomer	20.5 kDa: predicted size of precursor; 17 kDa: predicted size of mature protein; 35-40 kDa: found in transfected cells, glycosylated	IL-20R1/IL-20R2	Monocytes, keratinocytes, endothelial and epithelial cells, B cells	Keratinocytes	Induction of T_H2 cytokines; enhanced production of IL-6, TNF-α, and IL-10 in monocytes
IL-20	Monomer	20 kDa (predicted size of precursor), 17.5 kDa (predicted size of mature protein)	IL-20R1/IL-20R2 and IL-22R1/ IL-20R2	Monocytes, keratinocytes, epithelial and endothelial cells	Keratinocytes, monocytes, epithelial cells, and stromal cells in skin, lung, pancreas, and breast tissues	Role in skin biology
IL-21	Four-helix bundle, monomer	15 kDa	IL-21R	T cells (predominantly T_H17 and T_H9), NK T cells	$CD4^+$ T cells, $CD8^+$ T cells, B cells, DCs, macrophages, keratinocytes	B-cell proliferation, differentiation, and survival; T-cell growth factor; NKT cell proliferation when combined with either IL-2 or IL-15

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-22	Six anti-parallel α-helices, monomer	23 kDa	IL-22R	Activated T cells (predominantly T_H17 and T_H22 cells), NKT cells, activated NK cells, lymphoid tissue-inducer cells, ILCs	Keratinocytes and epithelial cells of kidney, small intestine, liver, colon, lung, and particularly pancreas and skin	Pathogen defense; wound healing; tissue reorganization
IL-23 (p19+p40)	Heterodimer	IL-12b p40 = 40 kDa, IL-23 p19 = 19 kDa	IL-23R	Phagocytic cells, macrophages, and activated DCs from peripheral tissues, including the skin, intestinal mucosa, and lungs	T cells (T_H17 cells), NK and NKT cells, eosinophils, monocytes, macrophages, DCs, and epithelial cells	Stimulation of production of proinflammatory IL-17; enhancement of T-cell proliferation and promotion of memory T cells; activation of NK cells; regulation of antibody production
IL-24	Homodimer and monomer	23.8 kDa (predicted size of unprocessed precursor), 18 kDa (unglycosylated mature protein), 35 kDa (observed size of secreted IL-24, glycosylated)	IL-20R1/IL-20R2 and IL-22R1/IL-20R2	Melanocytes, T cells, monocytes, normal human epidermal keratinocytes, B cells	Cancer cells	Tumor suppression
IL-25 (IL-17E)	Homodimer	19 kDa	IL-17RA and IL-17RB	T_H2 cells, mast and epithelial cells, eosinophils, and basophils from atopic subjects	T_H2 memory cells, fibroblasts, basophils, NKT cells, macrophages, and ILC2s	Induction of T_H2 responses and inhibition of both T_H1 and T_H17 cell responses; induction of IgE, IgG_1, IL-4, IL-5, IL-13, and IL-9 production
IL-26	Six α-helices, homodimer	38 kDa	IL-10R2 chain and IL-20R1 chain	Memory T cells, NK cells, activated T_H17 cells	Epithelial cells, binds heparin	Activation and regulation of epithelial cells
IL-27 (p28+EBI3)	Heterodimer	IL-27a p28 = 28 kDa; IL-27b EBI-3 = 25.4 kDa	WSX-1 and gp130	Activated DCs, macrophages, epithelial cells	T cells, NK cells	Induction of T-bet, promoting T_H1 cell differentiation; inhibition of T_H17 cells response through STAT1
IL-28A/B/IL29 (IFN-λ family)	Monomer	IL-28A = 22.3 kDa; IL-28B = 22.2 kDa; IL-29 = 21.9 kDa	IL-28R1/IL-10R2	Nucleated cell types, particularly DCs, in response to viral infection	Tissue-resident cells, primary monocytes, myeloid and plasmacytoid DCs, and $CD4^+$ cells	Downregulation of T_H2 response and upregulation of T_H1 response; induction of tolerogenic DCs and consequent promotion and expansion of Treg cells
IL-30 (p28 subunit of IL-27)	Heterodimer	28 kDa				Prevention and treatment of cytokine-induced liver injury
IL-31	Four-helix bundle	24 kDa	IL-31RA/OSMRβ	Activated $CD4^+$ T cells (mainly T_H2) and $CD8^+$ T cells, monocytes, macrophages, DCs, mast cells, keratinocytes, and fibroblasts	Keratinocytes, epithelial cells, dorsal root ganglia, eosinophils, mast cells, basophils, and monocytes	Induction of IL-6, IL-8, CXCL1, CXCL8, CCL2, and CCL8 production in eosinophils; upregulation of chemokine mRNA expression in keratinocytes and induction of growth factor and chemokine expression in epithelial cells; inhibition of proliferation and apoptosis in epithelial cells

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-32	Unknown	14.9-26.6 kDa	Unknown	Monocytes, macrophages, NK cells, T cells, epithelial cells	Macrophages, DCs, T cells, PBMCs, monocytes	Induction of TNF-α, IL-8, and IL-6 and apoptosis of epithelial cells
IL-33	β-Trefoil fold	30 kDa (active form = 18 kDa)	ST2	Necrotic cells, nuocytes, and fibroblasts on mechanical stress; stromal cells on cell damage; epithelial cells	Basophils, mast cells, eosinophils, DCs, macrophages, NK cells, NKT cells, T lymphocytes, B lymphocytes, endothelial cells, epithelial cells, fibroblasts, ILCs	Transcriptional repressor activity; induction of T_H2-type inflammation on mucosal tissues; maturation factor for bone marrow–derived DCs accompanied by the release of proinflammatory cytokines; enhanced integrin expression in basophils and eosinophils; inducer of ILCs
IL-34	Homodimer	39-kDa monomers	Colony-stimulating factor 1 receptor	Heart, brain, liver, kidney, spleen, thymus, testes, ovary, small intestine, prostate, and colon; most abundant in spleen	Monocytes, macrophages	Regulator of myeloid lineage differentiation, proliferation, and survival; microglial proliferation
IL-35 (p35+EBI3)	Heterodimer	60 kDa	IL-12Rβ2/gp130; IL-12Rβ2/IL-12Rβ2; gp130/gp130	Treg cells, monocytes, vascular endothelial cells, smooth muscle cells, and epithelial cells	NK cells and activated T cells	Reduction of effector T-cell proliferation; increase of IL-10 production and Treg cell proliferation
IL-36			IL-36Ra	Internal endothelial tissues and skin, bone marrow–derived macrophages	Keratinocytes and other epithelial barriers; at lower levels on DCs, naive $CD4^+$ T cells, differentiated T_H1 and T_H2 cells; very low levels on T_H17 cells	Promotion of the early inflammatory response to tissue injury or infection
IL-37	Unknown	17-24 kDa	IL-18Rα and IL-18BP	Monocytes, tonsil plasma cells, breast carcinoma cells, some colon carcinoma cells, melanomas, and lung carcinomas	DCs	Inhibition of IL-18 activity and innate immunity
IL-38		17 kDa	IL-1R1 with low affinity, IL-36R	Basal epithelia of skin, spleen, fetal liver, placenta, and thymus and proliferating B cells of the tonsils		Inhibition of the production of T_H17 response cytokines; antagonism of IL-36
IFN-α, IFN-β	Homodimer	15–21 kDa (IFN-α) and 22 kDa (IFN-β)	IFNAR	Mainly plasmacytoid DCs, but all nucleated cells can produce IFN-αβ in response to viral infection	All cells express IFNAR in low numbers	Defense against viral infection by orchestrating adaptive immune responses; stimulation of DC capability to present antigens; stimulation of macrophage antibody-dependent cytotoxicity; activation of naive T cells; promotion of development and proliferation of the B1 subset; trigger of apoptosis of tumor cells, as well as virus-infected cells

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IFN-γ	Homodimer	40-60 kDa	IFNGR1/IFNGR2	NK and NKT cells, macrophages, myelomonocytic cells, T_H1 cells, cytotoxic T lymphocytes, and B cells	Epithelial cells, macrophages, DCs, NK cells, T and B cells	Antiviral properties; promotion of cytotoxic activity and T_H1 differentiation; upregulation of MHC class I and II; inhibition of cell growth; proapoptotic effects and control of activation-induced cell death; induction of epithelial apoptosis in skin and mucosa
TGF-β	Homodimer	25 kDa	TβR-I and TβR-II	A large variety of cells, including epithelial cells, fibroblasts, and immune cells, such as eosinophils, macrophages, and Treg cells	Epithelial and endothelial and mesenchymal and immune cells, including CD8 T cells, CD4 T cells, NK cells, monocytes, macrophages, neutrophils, and eosinophils	Coordination of the proper development of the cardiac system and bone formation; induction of epithelial and endothelial to mesenchymal transition; balance of proinflammatory and anti-inflammatory effects by decreasing the cellular growth of almost all immune cell precursors; regulation of the differentiation of several T_H cell subsets and induction of Treg cells; immune tolerance
TNF-α	Homotrimer	26 kDa membrane-bound form + 17 kDa soluble form	TNFR1 (p55/60, CD120a) and TNFR2 (p75/80, CD120b)	Activated macrophages, monocytes, $CD4^+$ T cells, B cells, neutrophils, NK cells and mast cells, fibroblasts, astrocytes, microglial cells, endothelial cells, smooth muscle cells, adipocytes, intrinsic renal cells, and others	Nucleated cells	Host defense; double role as a proinflammatory mediator by initiating a strong inflammatory response and an immunosuppressive mediator by limiting the extent and duration of inflammatory processes and by inhibiting the development of autoimmune diseases and tumorigenesis; epithelial apoptosis

SEF, Similar expression to FGFs; *STAT*, signal transducer and activator of transcription.

IL-4

IL-4 is produced by T_H2 cells, type 2 ILCs, basophils, mast cells, and eosinophils. There are 2 types of IL-4Rs (Fig 1).[5] IL-4 regulates allergic conditions and the protective immune response against helminths and other extracellular parasites.[74] IL-4 is the major stimulus of T_H2 cell development and induces IgE class-switching in B cells (Figs 2 and 3). It also suppresses type 1 immunity development, including T_H1 cells and M1 macrophages. IL-4 increases expression of class II MHC molecules in B cells, upregulates B-cell receptors, increases expression of CD23, prolongs the lifespan of T and B cells in culture, and mediates tissue adhesion and inflammation. IL-4 and IL-4Rα knockout (KO) mice have defects in T_H2 cell differentiation and reduced serum IgG_1 and IgE levels. There have been extensive clinical trials targeting IL-4 and IL-13 pathways, with more promising results on anti–IL-13 approaches for the treatment of asthma and atopic dermatitis.[75]

IL-7

IL-7 is also known as pre–B-cell growth factor or lymphopoietin 1. IL-7R is present on most T cells and on progenitors of B cells and bone marrow macrophages. It consists of IL-7Rα (CD127) and γc (CD132) chains (Fig 1).[76] IL-7 responses are determined by expression of IL-7Rα, which is shared with the TSLP receptor, because γc is ubiquitously expressed on lymphocytes. IL-7 critically acts cooperatively with signaling through the pre–T-cell receptor to coordinate proliferation, differentiation, and T-cell receptor α recombination of thymocytes.[77] IL-7 signaling contributes to survival, proliferation, and development

TABLE II. Disease association and therapeutic application of cytokines

Cytokine	Disease association	Therapeutic application
IL-1α and IL-1β	Rheumatoid arthritis, multiple sclerosis, systemic lupus erythematous, psoriasis, inflammatory bowel disease, Graves disease, diabetes, cryopyrin-associated periodic syndromes, cancer, bacterial and viral infections, atopic dermatitis, asthma, osteoarthritis, chronic obstructive pulmonary disease, Alzheimer disease, atherosclerosis, myocardial infarction	*Treatment*: Cryopyrin-associated periodic syndromes, gout *Drugs*: Human mAbs targeting only IL-1β (ILARIS/canakinumab), dimeric fusion protein consisting of human IL-1R (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) linked with Fc region of human IgG_1 that neutralizes IL-1 (IL-1 Trap/rilonacept) *Clinical trials*: Adult-onset Still disease, systemic juvenile idiopathic arthritis, Schnitzler syndrome, osteoarthritis, hereditary periodic fevers, atrial fibrillation, HIV, cardiovascular disease (see also IL-1Ra)
IL-1Ra (antagonist)	Rheumatoid arthritis, multiple sclerosis, systemic lupus erythematous, psoriasis, juvenile idiopathic arthritis, Still disease, type 1 diabetes, inflammatory bowel disease, atopic dermatitis, asthma	*Treatment*: Rheumatoid arthritis *Drugs*: Recombinant nonglycosylated human IL-1Ra (anakinra) *Clinical trials*: Type I diabetes, metabolic syndrome, hypersecretion, type 2 diabetes mellitus, HIV, neurologic disorders, heart failure, acute myocardial infarction, Kawasaki disease, cancer
IL-2	T cell–mediated autoimmune and inflammatory diseases, X-Linked severe combined immunodeficiency 1	*Treatment*: Cancer, leukemia, and infectious diseases; use in bone marrow transplantation and to prevent kidney transplantation rejection *Drugs*: Recombinant human IL-2 (Proleukin, Interking), recombinant protein combining IL-2 and diphtheria toxin (Denileukin Diftitox), humanized IL-2Rα chain blocking mAbs (daclizumab, basiliximab) *Clinical trials*: Cancer, chronic graft-versus-host disease, multiple sclerosis, type I diabetes, thrombocytopenia, ulcerative colitis, Sjögren syndrome, different autoimmune and inflammatory diseases
IL-3	Allergic asthma, cancer, lymphocytic and acute myeloid leukemias, inflammatory arthritis	*Drugs*: Fusion toxin composed of catalytic and translocation domains of diphtheria toxin (DT388) linked to IL-3 (DT388Il3), recombinant human IL-3 (IL-3) *Clinical trials*: Breast neoplasms, leukemia, myelodysplastic syndromes, blastic plasmacytoid DC neoplasm, HIV infections; cytopenias
IL-4	Allergic asthma, allergic rhinitis, diabetes mellitus, parasite infection, chronic lymphocytic leukemia	*Therapy*: Asthma *Drugs*: Soluble recombinant human IL-4 receptor (pitrakinra), humanized blocking mAbs specific for IL-4 (pascolizumab) *Clinical trials*: tuberculosis
IL-5	Asthma, atopic dermatitis, chronic obstructive pulmonary disease, eosinophilic gastrointestinal diseases, hypereosinophilic syndrome, Churg-Strauss syndrome and eosinophilic nasal polyposis	*Therapy*: Asthma *Drugs*: Humanized blocking mAbs specific for IL-5 (mepolizumab), mAbs targeting IL-5 receptor (MEDI-563/benralizumab), humanized mAbs (reslizumab) *Clinical trials*: Hypereosinophilic syndrome, COPD, atopic dermatitis, asthma
IL-6	Systemic lupus erythematosus, psoriasis, rheumatoid arthritis, juvenile idiopathic arthritis, B-cell malignancy, Castleman disease, pulmonary fibrosis, chronic inflammatory diseases, plasmacytoma/multiple myeloma, cardiac myxoma, asthma	*Treatment*: Rheumatoid arthritis, systemic juvenile idiopathic arthritis, Castleman disease *Drugs*: Humanized mAbs targeting IL-6R (Actemra/tocilizumab) *Clinical trials*: Acute graft-versus-host disease, type 1 diabetes mellitus, dermatomyositis, schizophrenia, sclerosis, hemophagocytic lymphohistiocytosis, myocardial infarction, diabetic macular edema, arthritis, cardiovascular disease, primary Sjögren syndrome, leukemia
IL-7	Multiple sclerosis, type 1 diabetes, rheumatoid arthritis, primary biliary cirrhosis, inflammatory bowel disease, atopic dermatitis, inhalation allergy, sarcoidosis, graft-versus-host disease	*Drugs*: Human recombinant IL-7 (CYT107) *Clinical trials*: Cancer treatment, improving recovery after allogeneic stem cell transplantation, HIV therapy, sepsis, lymphopenia, cancer

(Continued)

TABLE II. *(Continued)*

Cytokine	Disease association	Therapeutic application
IL-8	Rheumatoid arthritis, psoriasis, bacterial and viral infections, chronic obstructive pulmonary disease, cystic fibrosis; cancer, acute myeloid leukemia, myelodysplastic syndromes, HIV infection	*Drugs*: Full human mAbs targeting IL-8 (HuMax-IL-8, ABX-IL-8) *Clinical trials*: Pustulosis palmoplantaris, cancer, chronic bronchitis and COPD
IL-9	Helminth infections, Hodgkin lymphoma, asthma and food allergy	*Drug*: Humanized mAbs specific for IL-9 (MEDI-528) *Tested in clinical trials*: Asthma treatment
IL-10	Systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, inflammatory bowel disease, allergic asthma, allergic rhinitis, atopic dermatitis, bee venom allergy, contact dermatitis, cancer	*Drugs*: Human recombinant IL-10 (Tenovil), fusion protein consisting of targeting antibody and IL-10 (Dekavil/F8-IL-10) *Clinical trials*: Rheumatoid arthritis
IL-11	Allergic asthma and cancer	*Drugs*: Recombinant human IL-11 (oprelvekin) *Clinical trials*: Chemotherapy-induced thrombocytopenia, leukemia, hemostatic disorders
IL-12 (p35/p40)	Bacterial infections, inflammatory bowel disease, psoriasis, cancer	*Treatment*: Psoriatic arthritis and severe plaque psoriasis *Approved drugs*: Anti–IL-12/23 human IgG_1 mAbs (ustekinumab), recombinant human IL-12 (NM-IL-12) *Clinical trials*: Lymphoma, wound infection, cancer, leukemia, HIV, infectious disease, multiple sclerosis, Behçet disease, acute radiation syndrome, CVID
IL-13	Asthma, allergic rhinitis, and fibrosis	*Drugs*: Humanized mAbs specific for IL-13 (lebrikizumab), soluble IL-13Rα2–Fc fusion protein (QAX576, IMA638), human anti–IL-13 mAbs (tralokinumab) *Clinical trials*: Asthma, atopic dermatitis, idiopathic pulmonary fibrosis, COPD
IL-14	Systemic lupus erythematosus, Sjögren syndrome, lymphoma	
IL-15	Rheumatoid arthritis, psoriasis, diabetes mellitus, autoimmune vasculitis, systemic lupus erythematosus, pemphigus vulgaris, multiple sclerosis, celiac disease, Behçet disease, asthma, sarcoidosis, inflammatory bowel diseases, inflammatory synovitis	*Drugs*: Recombinant human IL-15 (rhIL-15), fusion protein IL-15N72D:IL-15RαSu/Fc (ALT-803), human mAbs against IL-15 (AMG-714) *Clinical trials*: AML, cancer, HIV infection (as adjuvant), cancer, rheumatoid arthritis, celiac disease
IL-16	Atopic dermatitis, allergic asthma, Crohn disease, rheumatoid arthritis, HCV, tuberculosis, HIV, multiple sclerosis, cancer, multiple myeloma	
IL-17A	Rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, psoriasis, allergic asthma, atopic dermatitis, contact hypersensitivity, graft-versus-host-disease	*Treatment*: Severe plaque psoriasis *Drugs*: Human mAb binding to IL-17A (secukinumab/AIN457) *Clinical trials*: Psoriatic arthritis, rheumatoid arthritis, nail psoriasis, ankylosing spondylitis, chronic plaque-type psoriasis
IL-17B, C, D	Rheumatoid arthritis, allergic asthma, inflammatory cardiomyopathy, Wegener granuloma, multiple sclerosis, psoriasis	
IL-17F	Inflammatory bowel disease, psoriasis, allergic asthma, rheumatoid arthritis, Crohn disease	
IL-18	Bacterial and viral infections, rheumatoid arthritis, psoriasis, multiple sclerosis, type I diabetes, Crohn disease, Alzheimer disease, allergic rhinitis, atopic dermatitis, asthma	*Drugs*: Recombinant human IL-18 (SB-485232, Tadekinig alfa) *Clinical trials*: Cancer and lymphoma (in combination with other therapies), psoriasis, Still disease
IL-19	Psoriasis, asthma, atopic dermatitis, arthritis, cancer	
IL-20	Psoriasis, rheumatoid arthritis, obesity, atherosclerosis, ulcerative colitis, asthma, cancer, osteoporosis	
IL-21	Cancer, systemic lupus erythematous, rheumatoid arthritis, EAE, Behçet disease	*Drugs*: Recombinant human IL-21 (Denenicokin/BMS-982470), IL-21–specific mAbs (NNC0114-0006) *Clinical trials*: Cancer, lymphoma, leukemia, rheumatoid arthritis, diabetes mellitus (type 1), Crohn disease
IL-22	Psoriasis, inflammatory bowel disease, cancer	*Drugs*: Recombinant protein containing a human IL-22 dimer (F652), human mAbs specific for IL-22 (fezakinumab/ILV-094) *Clinical trials*: Acute graft-versus-host disease, atopic dermatitis, rheumatoid arthritis, psoriasis

(Continued)

TABLE II. *(Continued)*

Cytokine	Disease association	Therapeutic application
IL-23 (p19+p40)	Exacerbate organ-specific autoimmune inflammation, Crohn disease, and psoriasis	*Drugs*: Human mAbs directed against IL-12 and IL-23 (Ustekinumab), mAbs against IL-23 (LY 3074828, guselkumab, tildrakizumab) *Clinical trials*: Systemic lupus erythematosus, graft-versus-host disease, axial spondyloarthritis psoriasis, colitis, Crohn disease, type 1 diabetes mellitus, dermatitis, Behçet disease, CVID, multiple sclerosis
IL-24	Melanoma, psoriasis	
IL-25 (IL-17E)	Gastrointestinal disorders, chronic rhinosinusitis, atopic dermatitis, allergic asthma	
IL-26	Inflammatory bowel disease	
IL-27 (p28+EBI3)	Immune pathology caused by uncontrolled inflammatory response, Crohn disease or ulcerative colitis, asthma, and HIV	
IL-28A/B/IL29 (IFN-λ family)	Allergy (IgE-mediated food allergy, atopic dermatitis) and atopic asthma, autoimmune diseases, HBV, HCV, and cancer	*Drugs*: Pegylated interferon Lambda-1a (pegIFNλ), pegylated recombinant IL-29 (PEG-rIL-29) *Clinical trials*: Hepatitis C infection
IL-30 (p28 subunit of IL-27)		
IL-31	Atopic dermatitis, allergic contact dermatitis, prurigo nodularis, chronic spontaneous urticaria, nonatopic eczema, asthma, and other inflammatory disorders	*Drugs*: Anti–IL-31 mAbs (BMS-981164) *Tested in clinical trials*: Atopic dermatitis
IL-32	Autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, Crohn disease, chronic rhinosinusitis, atopic dermatitis, asthma, cancer	
IL-33	Autoimmune and cardiovascular diseases, asthma, rheumatoid arthritis, gastrointestinal tract and lung disorders, parasite infections	
IL-34	Synovitis, rheumatoid arthritis, Sjögren syndrome	
IL-35 (p35+EBI3)	Tumor pathogenesis, asthma, atopic dermatitis, allergic rhinitis and celiac disease	
IL-36	Psoriasis, asthma	
IL-37	Rheumatoid arthritis, systemic lupus erythematosus, atopic dermatitis	
IL-38	Systemic lupus erythematosus	
IFN-α, IFN-β	Viral infections, systemic lupus erythematosus, polymyositis, rheumatoid arthritis, multiple sclerosis, asthma	IFN-α *Treatment*: Hairy cell leukemia, malignant melanoma, AIDS-related Kaposi sarcoma, hepatitis C infections, multiple sclerosis, genital warts, hepatitis C with HIV coinfection, hepatitis B, general viral infections, myelogenous leukemia, cutaneous T-cell lymphoma, follicular non-Hodgkin lymphoma, renal cell carcinoma, *Drugs*: IFN-α-con-1 (Infergen), IFN-α-n3 leukocyte derived (Alferon-N), Pegylated IFN-α-2a (Pegasys), Recombinant IFN-α-2a (Roferon-A), Recombinant IFN-α-2b (Intron A), PEG recombinant IFN-α-2b (PEG Intron) *Clinical trials*: HIV infections, polycythemia vera, thrombocythemia, leukemia, myeloproliferative disorders, hepatocellular carcinoma, cancer, chronic myeloid leukemia, COPD, diabetes mellitus type 1 IFN-β *Treatment*: Clinically isolated syndrome, relapsing multiple sclerosis, early/relapsing multiple sclerosis *Drugs*: IFN-β-1a (Avonex, Rebiferon), IFN-β-1b (Betasteron) *Clinical trials*: Ulcerative colitis, asthma, respiratory disease syndrome, cancer, HTLV-I Infection
IFN-γ	Susceptibility to intracellular pathogen infection and tumor development, type 1 diabetes, rheumatoid arthritis, atopic dermatitis, EAE	*Treatment*: Chronic granulomatous disease, osteoporosis, autoimmune diseases (Crohn disease) *Drugs*: Humanized anti–IFN-γ mAbs (fontolizumab), Bioengineered IFN-γ1b (Actimmune) *Clinical trials*: HIV infection, Friedreich ataxia, glioblastoma, gliosarcoma, autosomal dominant osteopetrosis type 2, pulmonary fibrosis, sepsis, uveitis, inherited ophthalmic diseases, cancer

(Continued)

TABLE II. *(Continued)*

Cytokine	Disease association	Therapeutic application
TGF-β	Alzheimer disease, cardiovascular pathologies, cancer, allergic rhinitis, fibrosis	*Drugs*: Synthetic antisense oligodeoxynucleotide (trabedersen/AP12009), human mAbs against TGF-β1, TGF-β2, and TGF-β3 (fresolimumab/GC1008); acetic salt of a 14mer peptide from human TGF-β1 type III receptor (P144); TβR-I inhibitor (Galunisertib/LY2157299) *Clinical trials*: Anaplastic astrocytoma, glioblastoma, pancreatic neoplasms, melanoma, colorectal neoplasms, anaplastic astrocytoma, metastatic breast cancer, diffuse systemic sclerosis, primary focal segmental glomerulosclerosis, non–small cell lung cancer, primary brain tumors, skin fibrosis, hepatocellular carcinoma and non–small cell lung cancer (recurrent)
TNF-α	Psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile arthritis, ankylosing spondylitis, inflammatory bowel disease, Crohn disease, ulcerative colitis, systemic sclerosis, systemic lupus erythematosus, pulmonary diseases, allergic diseases (asthma, allergic rhinitis, and atopic dermatitis), insulin resistance, depression, cancer, vascular diseases, neurological diseases	*Treatment*: Crohn disease, ulcerative colitis, psoriasis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, Behçet disease, ulcerative colitis, moderate-to-severe chronic psoriasis, juvenile idiopathic arthritis, ankylosing spondylitis, moderate-to-severe plaque psoriasis, ulcerative colitis *Drugs*: Chimeric blocking mAbs specific for TNF-α (infliximab/INN), human anti–TNF-α mAbs (adalimumab/D2E7), humanized anti–TNF-α mAbs (certolizumab pegol), human anti–TNF-α mAbs (golimumab), soluble p75 TNF receptor–Fc fusion (etanercept) *Clinical trials*: Peripheral spondyloarthritis, osteoarthritis, hidradenitis suppurativa, uveitis, sarcoidosis, mucocutaneous lymph node syndrome, Kawasaki disease, leukemia and lymphoma, graft-versus-host disease

AML, Acute myeloid leukemia; *COPD*, chronic obstructive pulmonary disease; *CVID*, common variable immunodeficiency; *EAE*, experimental autoimmune encephalomyelitis; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *HTLV-I*, human T-lymphotropic virus type I.

of naive and memory B and T cells, mature T cells, and NK cells. Studies of IL-7 and IL-7Rα KO mice have shown that IL-7 is important for homeostatic T- and B-cell development (see Table E2). IL-7R expression is a marker of ILCs.[5]

IL-9

IL-9 was first discovered in mice, where it was found to be a potent antigen-independent growth factor for T cells[78] and mast cells. T_H2 cells and ILC2s are the main sources of IL-9 production; mast cells (mainly within the airways of asthmatic subjects) and eosinophils secrete IL-9 to a lesser extent. IL-9 inhibits cytokine production by T_H1 cells, promotes IgE production by B cells, induces chemokine and mucus secretion by bronchial epithelial cells, and promotes proliferation of mast cells. IL-9 has important roles in the pathogenesis of asthma models and in helminth infections. A new population of T cells, T_H9 cells, which produce IL-9 and IL-10, have been proposed to contribute to inflammation, mast cell accumulation, and activation (Figs 2 and 3).[26,79] Allergen-specific T_H1 and T_H2 responses are both enhanced by IL-9.[27,80]

IL-15

IL-15 is structurally homologous to IL-2 and was discovered to have the ability to induce T-cell, NK cell, and ILC proliferation, like IL-2.[81] IL-15R consists of the IL-15Rα chain, the IL-2Rβ chain, and γc (Fig 1).[76,82] IL-15 is produced by nonimmune (keratinocytes and skeletal muscle cells) and immune (monocytes and activated $CD4^+$ T cells) cells in response to signals that induce innate immunity.[82] Although IL-15 shares some functions with IL-2, such as activation of T cells, stimulation of NK cell proliferation, and cytolytic activity, differences in their biological functions have been identified based on differences observed between phenotypes of IL-2 and IL-15 KO mice.

IL-21

IL-21 is produced by T cells, NKT cells, and the follicular helper subset of CD4 T cells. The receptor for IL-21 is expressed on various cells, indicating a broad spectrum of action. IL-21 affects B-cell functions by strongly inducing their proliferation, regulating antibody production, and preventing their apoptosis and differentiation into plasma cells.[29] Cytotoxic activity and proliferation of $CD8^+$ T cells, NK cells, and NKT cells increase on stimulation with IL-21.

THE IL-10 FAMILY

The IL-10 subfamily of cytokines comprises IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29.[83,84] Their binding to IL-10R2, IL-20R1, IL-20R2, IL-22R1, and IL-28R1 and distinct expression of these receptors in immune system and tissue cells characterize their functions (Fig 1).

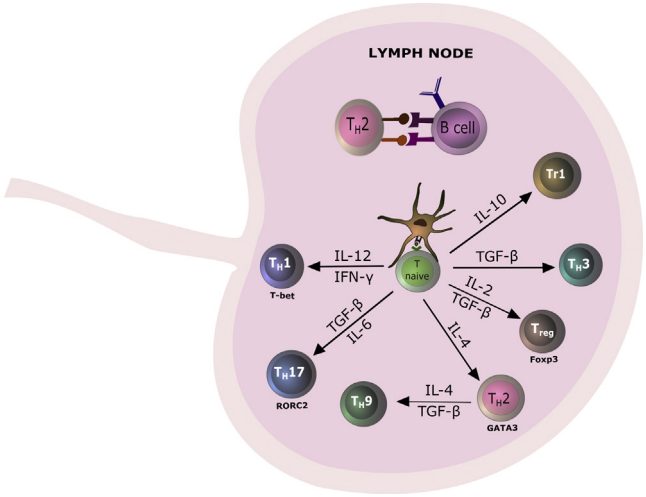


FIG 2. Differentiation of naive T cells to functional T-cell subsets. Differentiation of naive CD4 T cells into distinct phenotypes occurs on TCR activation driven by dendritic cells, which migrate into the lymph nodes after allergen uptake. IL-4 is important for differentiation of naive T cells into T_H2 cells, which can further differentiate into the T_H9 lineage. Development of T_H1 cells requires the presence of IFN-γ and IL-12. The transcription factors T-bet and GATA-3 play an important role in differentiation of T_H1 and T_H2 cell lineages, respectively. The combination of TGF-β and IL-6 facilitates T_H17 differentiation, which is regulated by the transcription factor RORC2, whereas Treg cell programming requires TGF-β and IL-2 and is controlled by FoxP3.

IL-10

IL-10 is an anti-inflammatory interleukin produced mainly by monocytes, T cells (mainly type 1 Treg cells), B cells (mainly Breg cells), a small fraction of NK cells, macrophages, and DCs. Recently demonstrated human Breg cells play a significant role in immune suppression and increase in AIT,[35,71] and their IL-10 production is regulated by B-cell linker protein.[85] Mast cells can also produce IL-10, which limits the rate of leukocyte infiltration, inflammation, and skin disorders, such as contact dermatitis; this also occurs after chronic UVB irradiation. The receptor complex for IL-10 is comprised of 2 chains: IL-10R1 and IL-10R2 (Fig 1). IL-10 directly affects APC functions by downregulating the expression of MHC class II and costimulatory molecules on the surfaces of macrophages and monocytes. IL-10 inhibits the expression of many proinflammatory cytokines, chemokines, and chemokine receptors. Clinically, it might mediate allergen tolerance in AIT and exposure to high doses of allergens, such as beekeepers and cat owners.[30,86,87] IL-10 directly affects T-cell activation by suppressing CD28, CD2, and signaling of the inducible T-cell costimulator through the tyrosine phosphatase Src homology domain 2–containing protein tyrosine phosphatase 1 (SHP-1). In contrast to its inhibitory effects on T cells, IL-10 promotes the survival, proliferation, and differentiation of human B cells and increases IgG_4 production.[35,71,88]

Several mouse models demonstrate the importance of IL-10 in regulation of the inflammatory response (see Table E2). IL-10 KO mice have normal lymphocyte and antibody responses but show reduced growth and anemia and spontaneous chronic colitis. In patients with colitis with IL-10/IL-10R deficiency in hematopoietic lineage cells, hematopoietic stem cell transplantation should be considered as a potentially curative therapeutic option.[89] In addition, coassociations between *IL10* polymorphisms, IL-10 production, helminth infection, and asthma/wheeze have been found, suggesting that polymorphisms related to protection against helminths during evolution might be associated with increased risk of allergic diseases.[90]

IL-19

IL-19 binds to a heterodimeric receptor comprising IL-20R1 and IL-20R2: this receptor complex also binds IL-20 and IL-24. IL-19 is expressed by LPS-stimulated monocytes, and low levels have been observed in B cells.[91] Mouse IL-19 stimulates production of IL-6 and TNF-α and induces apoptosis and production of reactive oxygen species in monocytes, indicating a role in proinflammatory responses. IL-19 might promote T_H2 cell responses because it induces IL-4, IL-5, IL-10, and IL-13 expression by activated T cells.[84] Increased levels of IL-19 have been observed in asthmatic patients, whereas lower circulating levels and increased epidermal expression of IL-19 were observed in patients with psoriasis. An immunosuppressive role has been suggested for IL-19, IL-20, and IL-24 during *Staphylococcus aureus* infection because of their signaling through the IL-20 receptor.[92]

IL-20

The IL-20 subfamily of cytokines (ie, IL-19, IL-20, IL-22, IL-24, and IL-26) have been grouped together to form the IL-20 subfamily based on their use of common receptor subunits and similarities in their biological functions.[83] IL-20 can signal through a complex of IL-20R1 and IL-20R2 (also binds IL-19 and IL-24) or a complex of IL-22R1 and IL-20R2 (also binds IL-24; Fig 1). IL-20 is mainly produced by LPS-stimulated monocytes and DCs but also by epithelial and endothelial cells and keratinocytes. IL-20 has important functions in the skin. Transgenic overexpression in mice caused skin abnormalities that include hyperkeratosis, a thickened epidermis, and a compact stratum corneum.[93] Together with IL-19, IL-20 appears to have a role in the pathogenesis of psoriasis: mRNA of these cytokines and their receptors was detected in psoriatic lesions but not in uninvolved skin from the same subjects.

IL-22

IL-22 is expressed by activated T_H22 cells, ILC3s, mast cells, and NK-22 cells.[94] The IL-10R2 chain, which is shared with other cytokine receptors, is ubiquitously expressed. In contrast, the IL-22R1 chain is not detected on immune cells but rather in the kidneys, small intestine, liver, colon, lung, and particularly the pancreas and skin. IL-22 induces genes that are involved in the antimicrobial defenses of keratinocytes. IL-22 is upregulated during bacterial infection, psoriasis, and atopic dermatitis.[95] Although IL-22 has been associated with inflammatory disorders, it might also have anti-inflammatory effects.[96,97] For example, IL-22 inhibits IFN-γ–induced secretion of the proinflammatory chemokines CCL5/RANTES and CXCL10/interferon-inducible protein 10 and antagonizes IFN-γ in lung inflammation.[98] $IL\text{-}13^+$ T cells display increased IL-22 levels in patients with atopic dermatitis, whereas IL-17 and IFN-γ coexpression with IL-22 becomes predominant in patients with psoriasis.[99] IL-22 and IFN-λ act synergistically for the induction of interferon-stimulated genes and control of rotavirus infection.[100]

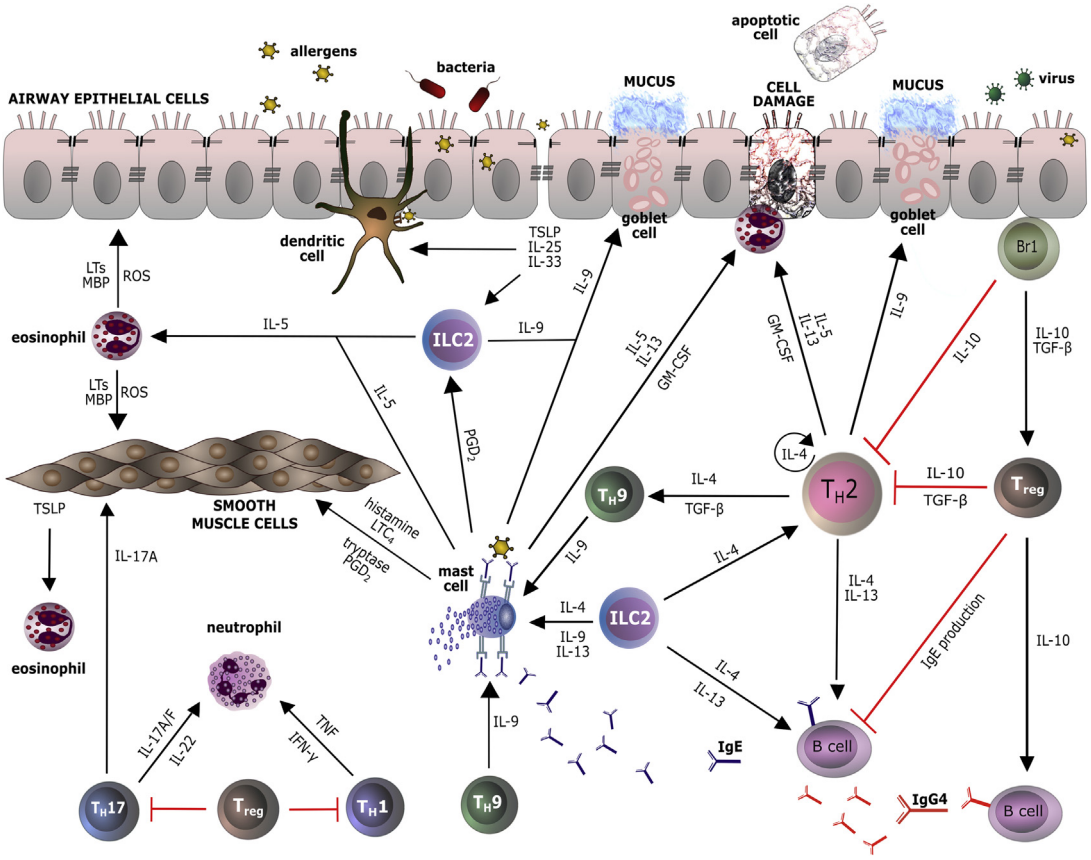


FIG 3. Cytokine and other mediator networks in allergic inflammation. Epithelial barrier impairment during inflammation can allow penetration of allergens through the tissues. Allergens with protease activity can cleave epithelial cell tight junction proteins and gain access to submucosal DCs. Once activated and loaded with antigens, DCs mature and migrate to local lymph nodes and present processed allergen peptides to naive T cells through MHC class II molecules. Naive T cells in the presence of IL-4 differentiate into T_H2 cells. The T_H2-type cytokines IL-4 and IL-13, which are produced not only by T_H2 cells but also by ILC2s, are involved in immunoglobulin class-switch recombination in B cells, which leads to IgE production. IgE binds to FcεRI on the surfaces of tissue-resident mast cells, sensitizing them. Subsequent release of mast cell–associated mediators, such as histamine, tryptase, prostaglandins, leukotrienes, and cytokines, induced goblet cell hyperplasia, smooth muscle contraction, vasodilation, increased vascular permeability, and intensified mucus production. During allergic inflammation, activated epithelial cells release TSLP, IL-25, and IL-33, which also contribute to the T_H2 response. Highly activated epithelial cells undergo apoptosis. T_H17 and T_H1 cells mediate neutrophil recruitment, whereas eosinophilia is induced by IL-5, IL-25, and IL-33. Immunoregulatory cytokines, such as IL-10 and TGF-β, released by Treg cells can suppress T_H2-type immune responses and control airway inflammation and remodeling. IL-10–producing B_R1 cells inhibit effector T cells. *LTs*, Leukotrienes; *LTC4*, leukotriene C_4; *MBP*, major basic protein; *PGD2*, prostaglandin D_2; *ROS*, reactive oxygen species.

IL-24

IL-24 is expressed by normal melanocytes, T cells, and monocytes[101] and binds to complexes comprising IL-22R1 and IL-20R2 or IL-20R1 and IL-20R2 (Fig 1).[102] IL-24 specifically inhibits tumor growth, and its antitumor activities require phosphorylation.[103] In a phase I clinical trial intratumoral injections of a nonreplicating adenovirus vector that carried *IL24* were well tolerated and induced apoptosis in large volumes of tumor tissue.[104] T cell–derived microvesicles induce mast cells to produce IL-24, which might have implications for allergic inflammations of the skin and lung.[105]

IL-26

IL-26 was discovered during the analysis of human T cells after transformation by *Herpesvirus saimiri*.[106] Interestingly, mice and rats do not have the *IL26* gene, whereas zebrafish, chickens, and frogs do, and its evolutionary conservation is limited. IL-26 expression seems to be restricted to memory T cells, NK cells, and T_H17 cells.[107] The receptor for IL-26 consists of the IL-10R2 chain, which is part of other receptors in this cytokine family, and the IL-20R1 chain (Fig 1).[108] In contrast to IL-10R2, IL-20R1 has not been detected in immune cells, but IL-20R1 is expressed on several types of epithelial cells and skin, testis, heart, placenta, salivary gland, and prostate cells.[93] There have been few studies on its physiologic function or role in disease processes because mice do not carry *IL26*. IL-26 is expressed by T_H17 cells and might have proinflammatory effects in disorders such as Crohn disease. A recent functional study suggested that T_H17 cells promote microbial killing and innate immune sensing of DNA through IL-26.[109]

IL-28A, IL-28B, and IL-29 (IFN-λ)

IL-28A, IL-28B, and IL-29 (alternatively termed IFN-λ2, IFN-λ3 and IFN-λ1, respectively) have homology with type I interferons, although the intron-exon structure of their genes more closely resembles that of the IL-10 family.[110] A new gene upstream of IL-28B was discovered in 2013, and it was designated *IFNL4*. This gene encodes IFN-λ4 and is similar to IFN-λ3.[111] IL-28A, IL-28B, and IL-29 all signal through the same receptor complex, which is composed of a single IL-28R1 (alternatively named IFN-λR1, CRF2-12, or LICR) chain and an IL-10R2 chain (Fig 1). Expression of IL-28 and IL-29 is induced by exposure of cells to polyinosinic-polycytidylic acid or viral infection, indicating their antiviral activities. IL-28 and IL-29 inhibit replication of hepatitis B and C viruses, and therefore they might be used to treat patients infected with these viruses.[112] Interestingly, IL-28 and IL-29 might also promote the development of tolerogenic DCs.[113]

THE IL-12 FAMILY

IL-12, IL-23, IL-27, and IL-35 share receptor and ligand chains (Fig 1). Their functions differ because of their expression on different cell types and combinations of different receptor chains. IL-30 is the alternative designation for the p28 subunit of IL-27.

IL-12

The bioactive form of IL-12 (IL-12p70), first described as NK-stimulating factor, is a heterodimer that consists of 2 subunits: a 35-kDa light chain (p35) and a 40-kDa heavy chain (p40).[114] It is produced by activated monocytes, macrophages, neutrophils, microglia, and DCs. In contrast, the p40 subunit, referred to as IL-12p40 and secreted in the absence of p35 as either monomer or homodimer by APCs, was shown to inhibit IL-12–dependent immune functions acting as an antagonist of IL-12 receptors.[115] Bioactive IL-12 mediates the development and maintenance of T_H1 cells by inducing IFN-γ production by T_H1 and NK cells. In addition, it plays an important role for the induction of ILC1s.[116] IL-12 indirectly activates the antimicrobial, antiparasitic, and antitumor activity of macrophages and promotes cytolytic activity of NK cells and lymphokine-activated killer cells.[117] Reduced IL-12 production impairs T_H1 responses and increases susceptibility to infection with intracellular pathogens. In neonatal DCs dectin-1 activation unlocks *IL12A* expression and reveals their T1-inducing potency.[118] IL-12 controls the homeostasis of Treg cells by eliminating them, as observed during the elimination of pathogen-specific Treg cells during *Mycobacterium tuberculosis* infection.[119]

IL-23

IL-23 includes the IL-12p40 subunit and a distinct IL-23p19 subunit (Fig 1). IL-23 is mainly produced by phagocytic cells, macrophages, and activated DCs from peripheral tissues, including the skin, intestinal mucosa, and lungs. Activated and memory T cells express high levels of IL-23R, along with NK and NKT cells, eosinophils, monocytes, macrophages, DCs, and epithelial cells.[120] IL-23 contributes to the development of T_H17 cells,[5] and a population of ILCs respond to IL-23 and might have a role in the pathogenesis of inflammatory bowel disease.[121] A recent study has shown a link of IL-23 to alopecia areata lesional cytokine profiles.[122]

IL-27

IL-27 is a heterodimeric cytokine consisting of p28 and EBI3 subunits. The p28 chain is related to IL-12p35, whereas the EBI3 chain is related to IL-12p40 and structurally resembles soluble IL-6R (Fig 1).[123] IL-27 is expressed predominantly by DCs and macrophages and endothelial cells. IL-27 promotes early commitment of naive T cells to the T_H1 cell lineage.[124] It directly antagonizes the development of T_H17 cell responses and limits the induction of inflammation by cells that produce IL-17 in the central nervous system.[125] IL-27 also limits the development of uveitis and scleritis by cells that produce IL-17 and induces FOXP3 expression by Treg cells.[126] Recent studies also suggested mechanisms that might play a role in immune privilege and immune tolerance.[127] $CD4^+$ T cells of asthmatic patients are resistant to IL-27–mediated inhibition. This can be linked to resistance of T_H2 cells by their IL-4– to IL-27–induced reprogramming toward T_H1 cells. IL-27 expression in bronchoalveolar lavage cells associates with type 2 immunity and asthma severity.[128] In addition, IL-27 stimulates the effector functions of human NK cells and increases their IL-18 responsiveness.[129] IL-27 induces CD39, which acts on DCs to suppress the T-cell response and autoimmunity.[130] IL-27 plays a role in antitumor immunity, as shown in patients with prostate cancer.[131]

IL-35

IL-35 is a heterodimeric cytokine consisting of EBI3 and the p35 subunit of IL-12 (Fig 1).[132] EBI3 is specifically expressed in mouse $FOXP3^+$ Treg cells, and the EBI3/p35 heterodimer is constitutively secreted by these cells.[133] The increased expression of EBI3 and IL12 p35 in mouse $FOXP3^+$ Treg cells compared with effector T cells and transcription analyses indicated that EBI3 expression is regulated by FOXP3.[133] IL-35 stimulation of mouse $CD4^+CD25^+$ Treg cells induced IL-10 production but did not influence FOXP3 expression. $CD4^+CD25^+$ T cells expanded in the presence of IL-35 were able to suppress the proliferation of $CD4^+CD25^-$ effector T cells. IL-35, but not EBI3 alone, inhibited differentiation of mouse $CD4^+$ T cells into T_H17 cells that produce IL-17. Furthermore, IL-35 reduced the incidence of arthritis, numbers of arthritic paws, and pathologic features in mice with collagen-induced arthritis in parallel to increased serum levels of IL-10 and IFN-γ and reduced induction of IL-17.

CYTOKINES OF TYPE 2 IMMUNE RESPONSE

Cytokines produced during the induction and function of T_H2 and ILC2 responses with the contribution of epithelial cells, DCs, ILCs, T cells, eosinophils, mast cells, and basophils include IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33, and TSLP. A default role for these cytokines can be suggested in immunity against helminth infections, with IgE production and eosinophilia, as well as decreased tissue injury, during severe type 1 inflammation (Fig 3). IL-4 and IL-9 have been highlighted at the "common γ chain cytokines" and IL-33 in the "IL-1 family" sections above.

IL-5

IL-5 was initially described as an eosinophil and B-cell growth factor; it is mainly produced by $CD4^+$ T_H2 cells, activated eosinophils, mast cells, $CD8^+$ Tc2 cells, γδ T cells, NK cells, NKT cells, and $CD4^-$c-$Kit^-CD3\varepsilon^-IL\text{-}2R\alpha^+$ cells in Peyer patches. Its receptor shares the β chain (CD131) with IL-3 and GM-CSF

(Fig 1). IL-5 promotes proliferation, activation, differentiation, survival, and adhesion of eosinophils. T_H2 cells that secrete IL-5 recruit eosinophils and contribute to the induction of airway hyperreactivity in asthmatic patients.[134] Levels of IL-5, T_H2 cells, and eosinophils are increased in cases of bronchoalveolar lavage and correlate with asthma severity. IL-5–deficient mice develop normally but are resistant to induction of experimental asthma, reduce expulsion of *Nippostrongylus brasiliensis*, and have fewer IgA^+ cells in the lamina propria compared with control mice. Anti–IL-5 therapy seems to be efficient in patients with eosinophilic asthma, eosinophilic esophagitis, and CRS.[75,135,136]

IL-13

IL-13 is expressed by activated T_H2 cells, mast cells, basophils, eosinophils, and NKT cells. Its receptors are IL-13Rα1 and IL-13Rα2, and signaling occurs through the IL-4R complex type II, which consists of IL-4Rα and IL-13Rα1 (Fig 1).[137] IL-13R chains are regulated during viral infection and inflammation.[138] IL-13 activates the same signal transduction pathways as IL-4 and induces IgE production. It also activates and recruits mast cells and eosinophils and promotes their survival. A combination of polymorphisms in genes, which takes place in the IL-4 and IL-13 pathways, increases the risk of asthma by 16.8-fold; polymorphisms in only the *IL13* gene increase the incidence of asthma exacerbations in children and increase total IgE levels and eosinophil numbers in blood samples.[139] IL-13 KO mice produce less IL-4, IL-5, IL-10, and IgE and do not have goblet cell hyperplasia (see Table E2). They are unable to expel *N brasiliensis*, indicating the role of IL-13 in parasite defense. IL-13Rα1–deficient mice lack features of asthma and airway remodeling. IL-5 and IL-13 from the ILC2s play an important role in the setting of eosinophilic asthma. There were significantly greater numbers of sputum $IL\text{-}5^+IL\text{-}13^+$ ILC2s in patients with severe asthma whose airway eosinophilia was greater than 3%, despite normal blood eosinophil numbers.[140]

IL-25 (IL-17E)

Because of homology with IL-17 family members, IL-25 has also been named IL-17E. It is produced by polarized T_H2 cells,[141] mast cells, eosinophils, and basophils from atopic subjects. IL-25 induces production of T_H2-associated cytokines. IL-25 KO mice do not expel *N brasiliensis* efficiently because of subtle changes in the induction of T_H2-type cytokine responses and are very susceptible to experimental autoimmune encephalomyelitis. Transgenic expression of IL-25 leads to blood eosinophilia and increased levels of IgE, IgG_1, IL-5, and IL-13. IL-25 might be involved in asthma pathogenesis. It is expressed at high levels in the lungs of sensitized mice after allergen challenge, and transgenic mice that express IL-25 only in lungs have increased numbers of eosinophils and $CD4^+$ T cells on allergen-specific stimulation. Anti–IL-25 treatment reduced the number of polyps, mucosal edema and thickness, collagen deposition, and infiltration of inflammatory cells, such as eosinophils and neutrophils, in a mouse chronic rhinitis model, suggesting a role in the pathogenesis of CRS with nasal polyps.[142]

IL-31

IL-31 is expressed by activated $CD4^+$ T cells (mostly by T_H2 cells) and at lower levels by $CD8^+$ T cells. IL-31 signals through a heterodimeric receptor complex that consists of the IL-31RA and oncostatin M receptor β; this receptor is expressed mainly by keratinocytes but also by epithelial cells, dorsal root ganglia, eosinophils, basophils, and monocytes. IL-31 is induced by IL-4 and promotes T_H2-driven inflammation.[143] IL-31 expression is increased in patients with atopic dermatitis, contact dermatitis, and prurigo nodularis. IL-31RA is a functional receptor expressed by a small subpopulation of $IL\text{-}31Ra^+/TRPV1^+/TRPA1^+$ neurons and is a critical neuroimmune link between T_H2 cells and sensory nerves for the generation of T cell–mediated itch.[144] Transgenic overexpression of IL-31 in mice results in a phenotype that resembles nonatopic dermatitis.[13] *IL31* mRNA is upregulated in the lungs after antigen challenge in a mouse model of airway inflammation.[13] In addition, serum IL-31 levels are increased in a subset of patients with mastocytosis and correlate with disease severity.[145]

TSLP

Cellular sources of TSLP include keratinocytes, airway epithelial cells, intestinal epithelial cells, thymic stromal cells, tonsillar crypt epithelial cells, mast cells, and basophils.[146] Structurally, TSLP resembles IL-7. TSLP is released in response to viral, bacterial, and parasitic pathogens; TLR engagement; and other cytokines, such as IL-1β, TNF-α, IL-4, and IL-13.[146] TSLP acts through a heterodimeric receptor, TSLP receptor (TSLPR), which consists of the IL-7Rα chain and a unique TSLPR chain resembling the common cytokine receptor γ chain.[147] Activation of TSLPR leads to signal transducer and activator of transcription 5 phosphorylation. TSLP acts on DCs, monocytes, $CD4^+$ T cells, mast cells, and B cells, promoting development of the T_H2 inflammatory response, often in cooperation with IL-25 and IL-33 and other cytokines.[146,148] TSLP has been reported to play a pivotal role in allergic asthma, with anti-TSLP (AMG157) antibody showing promising efficacy in reducing allergen-induced inflammation in primates and human subjects.[149,150] TSLP is also associated with atopic dermatitis.[151] Aside from its role in allergic inflammation, TSLP has been implicated to play a role in CRS with nasal polyps, idiopathic pulmonary fibrosis, primary spontaneous pneumothorax, breast cancer, pancreatic cancer, cervical cancer, and lung cancer. TSLP has been extensively reviewed elsewhere.[146,152,153]

INTERLEUKINS WITH CHEMOKINE ACTIVITY

IL-8

IL-8 was identified as a neutrophil-specific chemotactic factor and later classified as a member of the CXC chemokine family. IL-8 is produced by a variety of cells, such as monocytes and macrophages, neutrophils, lymphocytes, and endothelial and epithelial cells, after stimulation with IL-1α, IL-1β, IL-17, TNF-α, or TLRs.[154] The receptors for IL-8 are CXCR1 (IL-8RA) and CXCR2 (IL-8RB).[155] The major effector functions of IL-8 are activation and recruitment of neutrophils to the site of infection or injury. In addition to neutrophils, IL-8 also attracts NK cells, T cells, basophils, and GM-CSF– or IL-3–primed eosinophils.[156] Increased IL-8 concentrations were found in inflammatory sites in patients with diseases such as psoriasis, rheumatoid arthritis, respiratory syncytial virus infection, asthma, and chronic obstructive pulmonary diseases.[157]

IL-16

IL-16 was discovered as a T cell–specific chemoattractant.[158] Pro–IL-16, its 80-kDa precursor protein, is cleaved by caspase-3, resulting in a 60-kDa N-terminal fragment and a 14- to 17-kDa C-terminal fragment.[159] The N-terminal fragment regulates the cell cycle, whereas the C-terminal fragment forms homotetramers (56 kDa) that mediate cytokine functions. *IL16* mRNA and pro–IL-16 are constitutively expressed in T cells, eosinophils, and monocytes, whereas nonimmune cells, such as epithelial cells and fibroblasts, must be activated to transcribe *IL16* mRNA. IL-16 mediates its biological activity through CD4. IL-16 inhibits T-cell proliferation, promotes T_H1-mediated responses, and reduces T_H2-mediated inflammation by activating the release of TNF-α, IL-1β, and IL-15 and concomitantly inhibiting IL-4 and IL-5 production.[160]

THE IL-17 FAMILY

IL-17A, also called IL-17 in some studies, is the founding member of this structurally distinct cytokine family. It binds as a homodimer or a heterodimer with IL-17F to its receptor, IL-17RA.[161] IL-17A is expressed by activated $CD4^+$ T_H17 cells (Fig 3),[23] but its expression has also been detected in $CD8^+$ T cells, γδ T cells, NK cells, and neutrophils.[161] During T_H17 differentiation, human naive T cells must be exposed to IL-1β, IL-6, IL-23, and TGF-β before they express maximum levels of IL-17.[162] RORC2 in human subjects acts as the main transcription factor.[24] Consistent with the broad expression pattern of its receptor, IL-17A acts on a variety of cells, which respond by upregulating expression of proinflammatory cytokines, chemokines, and metalloproteases. By inducing cells to produce chemokines, IL-17A attracts neutrophils to mediate defenses against different pathogens. IL-17A and T_H17 cells are involved in several inflammatory disorders, including rheumatoid arthritis[163] and multiple sclerosis.[161] Similarly, they are upregulated in mouse models of collagen-induced arthritis and experimental autoimmune encephalitis.[161] Increased IL-17A levels have also been found in patients with psoriasis, inflammatory bowel disease, and allergic asthma and atopic dermatitis.[164] Diesel exhaust is one of the factors that induce IL-17 in asthmatic patients.[165] IL-17A is not inhibited by steroids in asthmatic patients, whereas 1α,25-dihydroxyvitamin D_3 shows an inhibitory role.[166] Steroid-resistant asthma was suggested to have IL-17A (high) and IFN-γ (high) endotypes.[167]

In contrast to its homologue IL-17A, IL-17B and its receptor IL-17RB are not expressed in immune cells but instead in spinal cord, testis, small intestine, pancreas, stomach, prostate, ovary, colon mucosa, and cartilage. IL-17C induces production of proinflammatory cytokines and metalloproteases by certain cells[168] and has been associated with pathologic conditions, such as arthritic paws of mice with collagen-induced arthritis. IL-17D is highly expressed in skeletal muscle, brain, adipose tissue, heart, lung, and pancreas tissue.[169] Lower levels are also found in bone marrow, fetal liver, kidney, lymph node, placenta, spleen, thymus, tonsils, resting $CD4^+$ T cells, and resting B cells.

Among the IL-17 family members, IL-17A and IL-17F have the highest degree of homology; they are 50% identical at the protein level.[170] IL-17F binds to the same receptor as IL-17A (IL-17RA), although with lower affinity.[171] IL-17A and IL-17F form heterodimers, as expected from their structural similarities. There are 2 isoforms of IL-17F expressed by activated T_H17 cells.[23] Like IL-17A, IL-17F acts on many cell types and induces similar proinflammatory cytokines and chemokines. Double-positive $IL\text{-}17^+IL\text{-}22^+$ cells with memory characteristics are observed in lung draining lymph nodes of patients with cystic fibrosis,[172] and IL-17A and neutrophils have a central role in fibrosis in the lungs of patients with hypersensitivity pneumonitis.[173] IL-17A seems to be more expressed in patients with psoriasis and intrinsic-type atopic dermatitis skin compared with those with extrinsic-type atopic dermatitis skin. Severe atopic dermatitis is characterized by selective expansion of circulating T_H2/T_C2 and T_H22/T_C22 cells, but not T_H17/T_C17 cells, within the skin-homing T-cell population.[174]

OTHER INTERLEUKINS

IL-3

IL-3, IL-5, and GM-CSF share a common receptor subunit β chain (CD131), and their functions partially overlap (Fig 1). IL-3 is expressed by T cells, macrophages, stromal cells, NK cells, mast cells, and eosinophils. On binding to IL-3, the β chain forms a heterodimer with the cytokine-specific α chain. IL-3 is a multilineage hematopoietic growth factor that functions in synergy with other cytokines during early stages of hematopoiesis. In combination with erythropoietin or GM-CSF and granulocyte colony-stimulating factor, IL-3 induces erythroid or granulocyte-macrophage lineages, respectively. IL-3 and TNF-α promote proliferation of $CD34^+$ progenitor cells; IL-3 also increases the activation and release of mediators from eosinophils and basophils in response to IgE FcεR crosslinking.[175] Mice that do not produce β chains lack IL-3, IL-5, or GM-CSF signaling; these hematopoietic cytokines mediate T_H2-mediated allergic airway inflammation by inducing eosinophil accumulation, airway hyperresponsiveness, mucus hypersecretion, and IgE production. IL-3 is essential in basophil activation in patients with allergic asthma.[176]

IL-6

IL-6 is a member of the IL-6–type family of cytokines, which includes leukemia inhibitor factor, ciliary neurotrophic factor, and oncostatin M. Its receptor consists of an IL-6–binding chain (IL-6Rα) and the signal-inducing component (gp130). IL-6R exists in membrane-bound and soluble forms.[177] IL-6 is a multifunctional pleiotropic cytokine involved in regulation of immune responses, acute-phase responses, hematopoiesis, and inflammation. It is produced by endothelial cells, fibroblasts, monocytes, and macrophages in response to different stimuli (IL-1, IL-17, and TNF-α) during systemic inflammation. In innate immunity IL-6 directs leukocyte trafficking and activation and induces production of acute-phase proteins by hepatocytes. IL-6 promotes T-cell proliferation, B-cell differentiation and survival, and plasma cell production of IgG, IgA, and IgM.[178] In addition, allergen-induced IL-6 promotes type 2 and type 17 airway inflammation.[179]

IL-11

IL-11 is expressed by stromal cells, including fibroblasts, epithelial cells, endothelial cells, osteoblasts, and several tumor cell lines. It binds a heterodimeric receptor consisting of IL-11Rα and gp130.[180] IL-11Rα binds IL-11 with high levels of specificity, whereas gp130 is shared by receptors for IL-11, IL-6, ciliary neurotrophic factor, leukemia inhibitory factor, oncostatin M, and cardiotrophin-1. IL-11 stimulates hematopoiesis by supporting

the proliferation of myeloid, erythroid, and megakaryocyte progenitor cells.[181] Recombinant IL-11 has been approved for the treatment of thrombocytopenia, a major dose-limiting hematologic complication of chemotherapy for cancer,[182] and recombinant human IL-11 is a protective factor in patients with severe sepsis with thrombocytopenia.[183]

IL-14

IL-14 was first described as a high-molecular-weight B-cell growth factor. Two transcripts are produced from opposite strands of the *IL14* gene, termed IL-14α and IL-14β.[184] IL-14 is produced by T cells and B- and T-lineage lymphoma cell lines.[185] IL-14 binds and signals through a 90-kDa receptor expressed on activated B cells to promote B-cell proliferation. This receptor is expressed especially on germinal center B cells and surface IgD^{low} human tonsil B cells, including B1 cells and activated B2 cells, and is expressed in patients with autoimmune thyroiditis.[186] Phenotypes of transgenic mice that overexpress IL-14α resemble features of systemic lupus erythematosus or Sjögren syndrome; older transgenic mice have B-cell malignancies ($CD5^+$ B-cell lymphoma) similar to these observed in patients with these disorders, and the mice have hypergammaglobulinemia with IgG, IgA, and IgM autoantibodies.[184]

IL-32

IL-32 was originally described as an mRNA that was called NK cell transcript 4, which encoded a protein with many characteristics of a cytokine. The main sources of IL-32 are activated T cells and NK cells; epithelial cells express IL-32 on stimulation with TNF-α, IFN-γ, IL-1β, and IL-18.[187] Proteinase 3 cleaves IL-32α, resulting in formation of 2 peptides that upregulate production of proinflammatory cytokines by mouse and human monocytes.[187] IL-32 is highly expressed in synovial tissue samples from patients with rheumatoid arthritis, and expression levels are associated with disease severity.[187] IL-32 also regulates keratinocyte apoptosis and contributes to eczema formation in patients with atopic dermatitis.[188]

IL-32 is induced by IFN-γ, TNF-α, T_H1 cells, and rhinovirus in bronchial epithelial cells. It inhibits angiogenesis, and its serum levels are associated with a good treatment response in asthmatic patients.[189] Although IL-32 is not expressed by rodents, transgenic overexpression of IL-32 by endothelial and hematopoietic cells in mice intensified vascular inflammation and exacerbated sepsis.

IL-34

IL-34 is expressed in various tissues, including the heart, brain, liver, kidney, spleen, thymus, testes, ovary, small intestine, prostate, and colon, and is most abundant in the spleen.[190] The receptor for IL-34 is colony-stimulating factor 1 receptor, and it is required for the development of Langerhans cells and microglia.[191] IL-34 stimulates monocyte and macrophage proliferation and development. It is highly expressed in atopic dermatitis lesions.[192]

IFN-γ

Cells from the innate (eg, NK cells, NKT cells, macrophages, and myelomonocytic cells) and adaptive (eg, T_H1 cells, cytotoxic T lymphocytes, and B cells) immune systems produce IFN-γ. High IFN-γ levels are expressed by T_H1 cells, activating macrophages to kill microbes, promoting cytotoxic activities of other cells, and inducing apoptosis of epithelial cells in the skin and mucosa (Fig 3).[193] In addition to its role in the development of a T_H1-type response and the B-cell isotype switch to IgG_{2a} (in mice), IFN-γ regulates MHC class I and II protein expression and antigen presentation. IFN-γ also inhibits cell growth and apoptosis and controls extension of the immune response by inducing activation-induced cell death of $CD4^+$ T cells.[20,22] IFN-γ plays a role in keratinocyte apoptosis in eczema formation,[22] and loss-of-function variants in *IFNGR1* are linked to atopic dermatitis complicated by eczema herpeticum.[194] In addition, steroid-resistant severe asthma is characterized by IL-17A (high) and IFN-γ (high) endotypes.[167]

IFN-α and IFN-β

All nucleated cells can produce and respond to IFN-αβ in the context of a viral infection, but plasmacytoid DCs are the most abundant source, producing up to 1000-fold more IFN-αβ (and IFN-λ) than other cell types.[195] After viral entry, pathogen-associated molecular patterns and danger and stress signals can lead to type I interferon production.[196] Cytosolic (eg, melanoma differentiation-associated protein 5 and retinoic acid–inducible gene 1) and endosomal (TLR3, TLR7, and TLR9) receptors can sense nucleic acids of viral origin and induce their production.[197] IFN-αβ bind both to a specific cell-surface receptor complex (IFNAR) on both the virus-infected cell and nearby uninfected cells. The receptor complex consists of 2 known subunits: IFNAR-1 and IFNAR-2. Their biological effects are mainly mediated by the transcriptional control of interferon-inducible genes (approximately 1000), but direct mechanisms acting on translation have also been described.[198]

Antiviral activity mediated by IFNAR requires induction of the enzyme 2′-5′-oligoadenylate synthetase, a double-stranded RNA–dependent protein kinase, as well as a myxovirus resistance protein. Early production of IFN-β is very important because it induces other cells (infected or noninfected) to make IFN-α, thus amplifying and maintaining the type I interferon response. IFN-α and IFN-β can directly influence immune cells through IFNAR and indirectly by inducing chemokines for recruitment of immune cells to the site of infection. Type I interferons induce secretion of a second wave of cytokines, such as IL-15, to regulate NK cell and memory CD8 T-cell numbers and activities.[199]

IFN-α and IFN-β are critical for DC stimulation and activation of naive T cells, B-cell development, and antibody production. Normally, self-nucleic acids do not activate adaptive immune responses, but their coupling to host antimicrobial components can activate TLR9 and induce type I interferon secretion by DCs, providing the initial scenario for boosting autoreactive clones in susceptible subjects.[200] Increased type I interferon levels are found in patients with several autoimmune diseases and have been associated with disease mechanisms.[201] In regard to allergic diseases, type I interferons inhibit type 2 responses through different mechanisms, such as IL-21 and IL-13Rα2 (a decoy receptor) upregulation.[138] Allergic patients produce less type I interferons in response to viruses.[202] Different mechanisms have been suggested to be related to dampened type I interferon responses in atopic subjects,[203] such as suppression by suppressor of cytokine signaling genes, which might play a role in decreased viral clearance in the epithelium of asthmatic patients.[203]

TGF-β

The 3 highly homologous isoforms of TGF-β belong to the large TGF-β superfamily. They are made up of a secretory peptide, the prodomain, also called latency-associated peptide, and the active C-terminal peptide. Before secretion, TGF-β dimerizes and forms, together with latency-associated peptide and the latent TGF-β–binding protein, a large complex that binds to the extracellular matrix.[204] TGF-β needs to be released and activated with proteolysis, pH drop, reactive oxygen species, or αV integrins to bind to its receptor.[204] The canonical signaling pathway for TGF-β uses the SMAD2/3 pathway, but after binding to TGF-βRI and TGF-βRII, a variety of other pathways are activated. TGF-β is produced by a variety of cells, such as epithelial cells, fibroblasts, and immune cells (eg, macrophages, eosinophils, and lymphocytes). TGF-β is one of the major cytokines for the suppressive function of Treg cells[205] and differentiation of proinflammatory T_H17 and T_H9 cells.[206] Most body cells express TGF-β receptors and can respond to TGF-β signaling. TGF-β plays a role in embryonic development, especially of the skeleton and cardiovascular system. It influences structural changes of tissues through induction of mesenchymal transition from epithelial and endothelial cells[207] by controlling extracellular matrix deposition,[208] apoptosis induction, and inhibition of proliferation. Inhibition of proliferation is also a major feature in the balancing influence of TGF-β on the immune system. TGF-β is part of the pathologic mechanisms behind autoimmune diseases,[209] Marfan syndrome and Duchenne muscle atrophy,[210] Alzheimer disease,[211] fibrotic disorders,[208] cancer,[212] allergic diseases, and osteoarthritis. Several studies suggest that TGF-β1 might play a role in remodeling in patients with several diseases, including eosinophilic esophagitis.[213,214] Because of its variety of functions, TGF-β often has a double-faced effect in patients with these diseases but still represents a promising therapeutic target.[215,216]

TNF-α

TNF-α was first described as TNF, a protein in sera of mice infected with BCG and treated with LPS, which caused hemorrhagic necrosis of different transplanted tumors *in vivo* and cytolysis of a mouse fibrosarcoma cell line *in vitro*.[217] TNF-α is an important pleiotropic cytokine involved in host defense, inflammation, and apoptosis. It plays a double role in regulation of immune responses, acting both as a proinflammatory mediator, initiating a strong inflammatory response, and an immunosuppressive mediator, inhibiting the development of autoimmune diseases and tumorigenesis, and exhibiting a vital role in maintenance of immune homeostasis by limiting the extent and duration of inflammatory processes. TNF-α plays an important role in host defense against viral, bacterial, fungal, and parasitic pathogens, in particular against intracellular bacterial infections, such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*. High systemic TNF-α levels can lead to septic shock. Local increases in TNF-α concentrations cause the 5 cardinal signs of inflammation: heat, swelling, redness, pain, and loss of function. TNF-α is involved in the development of allergic diseases, particularly asthma[218] and atopic dermatitis.[193]

FUTURE DIRECTIONS

Several new cytokines are likely to be categorized as interleukins within the several hundred secreted proteins that regulate communication among immune system cells and between the immune system and resident tissue cells. The growing list of interleukins requires a better classification strategy and improved understanding of their functions. Classification according to sequence homogeneity, structure, and common receptor chains is useful; however, most interleukins do not fit into any particular structural category. Bioinformatics data and information about their roles in the evolution of the immune system, as well as their nonimmune functions, in mammals should also be taken into consideration. Categories according to sequence homology and evolutionary relationship (IL-1, IL-10, and IL-17 families) and common receptor chains (γ chain cytokines), as well as subgrouping according to major functions (type 2 interleukins and chemokines), have been taken into consideration in this extensive review article.

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Table E1. List of cytokine families and cytokines

Cytokine family	Cytokine name
IL-1 Family	IL-1α
	IL-1β
	IL-1Ra
	IL-18
	IL-33
	IL-36Ra
	Il-36α
	IL-36β
	IL-36γ
	IL-37
	IL-38
common γ chain cytokine family	IL-2
	IL-4
	IL-7
	IL-9
	IL-15
	IL-21
IL-10 family	IL-10
	IL-19
	IL-20
	IL-22
	IL-24
	IL-26
	IL-28A (IFN-λ2)
	IL-28B (IFN-λ3)
	IL-29 (IFN-λ1)
IL-12 Family	IL-12p40/p70
	IL-23
	IL-27
	IL-35

Cytokine family		Cytokine name
Cytokines of type 2 immune response		IL-5
		IL-13
		IL-25 (IL-17E)
		IL-31
Interleukins with chemokine activity		IL-8
		IL-16
IL-17 family		IL-17A
		IL-17F
		IL-17A/F heterodimer
		IL-17C
		IL-17E (IL-25)
		IL-17B
		IL-17D
IFN family	Type I	IFN-α
		IFN-β
	Type II	IFN-γ
	Type III	IFN-λ1 (IL-29)
		IFN-λ2 (IL-28A)
		IFN-λ3 (IL-28B)
Other cytokines (uncategorized)		IL-3
		IL-6
		IL-11
		IL-14
		IL-32
		IL-34
		TGFβ
		TNFα

Table E2. Cytokines and their receptors, transgenic mice, and human polymorphisms and mutations

	Phenotype of cytokine KO mice	Phenotype of receptor chain KO mice	Phenotype of certain transgenic	Phenotype of human polymorphisms & mutations
IL-1a, IL-1b	Resistance to fever induction, impaired acute-phase response, increased susceptibility to infections	Normal vigor, no overt phenotype	IL-1α transgenic mice develop a severe polyarthritic phenotype; overexpression of IL-1α in basal keratinocyte shows spontaneous inflammatory skin lesions	Polymorphisms associated periodontal diseases
IL-1ra (antagonist)	High susceptibility to develop collagen-induced arthritis, autoimmunity, arteritis and chronic inflammatory polyarthropathy	Normal vigor, no overt phenotype	Transgenic overexpression resulted in protection from collagen-induced arthritis, with increased locomotion and decreased habituation, in an anxiolytic effect, but did not influence motor performance; the febrile response elicited by IL-1β was abolished in IL-1ra-overexpressing animals;	Polymorphism associated with ulcerative colitis, lupus erythematosus, osteoporosis and viral infections
IL-2	Reduction of polyclonal T-cell responses, changes of the isotype levels in serum Igs, absent of secondary antiviral T-cell responses, delayed T helper response and reduced NK cells activity	Enlargement of peripheral lymphoid organs associated with polyclonal T and B cell expansion, developing of lymphoproliferative and autoimmune disorders, such as hemolytic anemia and inflammatory bowel disease	Transgenic mice show Treg cells deficiency; transegenic expression of IL-2 in pancreas resulted in a massive inflammatory response directed at beta cells, leading to diabetes	Development of X-Linked severe combined immunodeficiency (XSCID)

IL-3	Abnormal seminal vesicle development, hydrocephaly, reduced number of mast cells and basophils and impaired immunity in response to parasites	Growth, development, and longevity; diminished immunity to parasites (reduced numbers of mast cells), reduced expansion and accumulation of eosinophils in the lung, and inhibition of airway hyperresponsiveness, mucus hypersecretion and IgE-production.	Transgenic mouse expressing antisense IL-3 RNA: death after 3-6 month of age due to pre-B-cell lymphoproliferative syndrome or neurologic dysfunction	Ser27Pro: protective effect on the development of asthma
IL-4	Severe trouble on Th2 differentiation, decreases in IgE and IgG1 serum levels	Severe trouble on Th2 differentiation, decreases in IgE and IgG1 serum levels	Mice with transgenic overexpression of IL-4 show allergic airways inflammation and remodeling; they develop autoimmune-type disorders resembling human lupus nephritis and have altered homeostasis in the skin with an increased number of mast cells and Langerhans cells; transgenic renal IL-4 expression leads to progressive glomerulosclerosis	Development of X-Linked severe combined immunodeficiency (XSCID)
IL-5	Reduced numbers of blood and bone marrow cells and eosinophils in the airways and IgA+ cells in the lamina propria; resistance to induction of experimental asthma	IL-5Rα -/-: Low IgM and IgG3 serum concentrations.	IL-5 transgenic mice show prolonged wound healing, due to increased eosinphilic invasion into the wound areas	IL-5 polymorphisms are associated with atopic bronchial asthma and severity of the disease

IL-6	Normal (viable, fertile), impaired regulation of T cell trafficking, reduced number of thymocytes and peripheral T cells, abnormalities in acute phase response, resistance to the induction of a number of experimental autoimmune conditions	IL-6R: decreased production of serum amyloid A, ⅓ less T cells gp130 -/- embryos:† 12.5 days p.c., decreased number of pluripotential and hematopoietic progenitors in liver, decreased number of T cells in the thymus	IL-6 transgenic mice show increase of IgG1, monoclonal transplantable plasmacytoma, growth and skeletal abnormalities	IL-6 promoter polymorphism: risk of Kaposi sarcoma in HIV-infected cells, breast cancer and squamous cell carcinoma, low bone mineral density, juvenile rheumatoid arthritis;
IL-7	High lymphopenia, impaired transition to Pre-B cells, reduction of B cell numbers in thymus and spleen	Reduction in CD8 single positive T cells, regulatory T cells, and natural killer T cells in thymus; increase in B cells, γδ T and dendritic cells in thymus.	T and early B cells expansion, lymphoproliferative skin disorders, chronic colitis	X-Linked severe combined immunodeficiency (XSCID); polymorphisms associated to the risk of several inflammatory and autoimmune disease
IL-8	Impaired neutrophil infiltration but normal function	CXCR2-/-: increased susceptibility to various pathogens; impaired wound healing; impaired angiogenesis; neurological defects; altered growth of induced and implanted tumors	Excessive accumulation of neutrophils, decreased L-selectin expression on circulating neutrophils	IL-8 -251 (IL-8 promoter region): AA genotype increases the risk of atrophic gastritis and gastric cancer due to elevated IL-8 levels and neutrophils infiltration; CXCR1: M300R and R142C: reduced efficiency of HIV-infection due to reduced CD4 expression

IL-9	Mucus overproduction, excessive mast cells proliferation, complete inhibition of allergic airways inflammation and remodeling	Reduction of the number of thymocytes, critical role in early T cell development	Development of thymic lymphomas, asthma, intestinal mastocytosis and increased susceptibility to intestinal anaphylaxis	X-Linked severe combined immunodeficiency (XSCID), Hodgkin's disease, large cells anaplastic lymphomas
IL-10	Mice have growth retardation, anaemia and suffer from chronic enterocolitis. They demonstrate elevated Th1 responses leading to accelerated clearance of infections. Elevated Th2 responses leading to exaggerated allergic response.	IL-10R2-/- mice grow normally and are fertile but develop chronic colitis and splenomegaly after 12 weeks of age.	IL-10 overexpression results a defect in alpha/beta T cell maturation; Transgenic overexpression in the Lung causes mucus metaplasia, tissue Inflammation, and airway fibrosis	IL-10 polymorphisms lead to Inflammatory bowel disease, tuberculosis, cancer, allergies and a number of autoimmune disorders
IL-11	No obvious abnormalities	IL-11Rα -/-: increased trabecular bone volume, associated with low bone resorption and formation, and decreased osteoclast numbers; infertility in females due to abnormal development of the placenta	Airway hyperresponsiveness and remodeling	IL-11 polymorphism is associated with colitis
IL-12 (p35/p40)	P40 KO: immunocompromised, higher susceptibility to intracellular pathogens; P35 KO: impaired Th1 cells response and higher susceptibility to EAE and CIA	No obvious developmental abnormalities, impaired IFN-g secretion, Th1 differentiation, and NK cytolytic activity which results in higher susceptibility to intracellular pathogens	p40 transgenic mice develop inflammatory skin lesions, show decreased Th1 response, increased Th2 response, and an increased susceptibility to malarial infection	Psoriasis, susceptibility to poorly pathogenic mycobacterial and salmonella infection

IL-13	Decreased levels of IL-4, IL-5 and IL-10	up-regulation of IL-13Rα2 and IL-13, higher amount of CD4+ Th2 cells, increase of frequency of eosinophils in granuloma, decrease in severity of hepatic fibrosis, decrease in IgE serum levels	IL-13 transgene overexpression in the lung induces eosinophil-rich inflammatory cell infiltration, airway hyper-reactivity, and remodeling of the airway	IL-13 polymorphism is associated with bronchial asthma
IL-14	-	Defects restricted to appendicular skeleton	Hypergammaglobulinemia (IgG, IgA and IgM autoantibodies), CDS-Expressing B-Cell Lymphomas	SLE and Sjörgen's syndrome
IL-15	Reduced numbers of NK, NK T, and CD8+ T-cells, almost a total lack of memory CD8+ T-cells	Reduced numbers of NK, NK T, and CD8+ T-cells, almost a total lack of memory CD8+ T-cells	Increase of CD8+ T-cells and lymphomas, inhibition of IL-2-induced AICD, inhibition of allergic inflammation in asthma model, elimination of colon-carcinoma cells	X-Linked severe combined immunodeficiency (XSCID)
IL-16	No overt unstressed phenotype, although the yield of T cells from spleens of mature knockout mice is ~70% of the total of wild-type mice	-	Enhanced inflammation and airway mucous after RSV infections; cardiac overexpression induces cardiac fibrosis and increased macrophage infiltration	Crohn's disease, CC genotype is associated with contact dermatitis
IL-17A	Profound defects in host protection, resistance to several inflammatory diseases	Profound defects in host protection, resistance to several inflammatory diseases, increased haemopoietic toxicity	Inflammation and destruction of the tissue, neutrophilia	IL-17A polymorphisms are associated with susceptibility to IBD development in Koreans, coronary artery disease and gastric cancer
IL-17C	Lower susceptibility to EAE	Lower expression of genes encoding antibacterial molecules, greater bacterial burden, barely mortality during infection	IL-17C overexpression in keratinocytes promotes psoriasis skin inflammation	-

IL-17F	Profound defects in host protection, enhanced Th2 cytokine production and eosinophil function, defective airway neutrophilia in response to allergen challenge	Profound defects in host protection, resistance to several inflammatory diseases	Pathological phenotype in lung	SNP (His161Arg) is associated with protection against asthma and chronic fatigue syndrome, Behcet's disease
IL-18	Increased susceptibility to *L. major* infection accompanied by decreased Th1 cells response higher susceptibility to viral infections with impairment of NK cells activity	Impaired Th1 and NK cell development	Severe hepatic injury, increased production of both Th1 and Th2 cytokines	Polymorphisms linked to atopy and allergen sensitization
IL-19	Normal phenotype and no developmental abnormalities; epidermal hyperplasia in response to intradermal IL-23 treatment; higher susceptibility to experimental acute colitis induced by DSS; increased macrophage infiltration of the colonic mucosa and impaired B cell recruitment.	-	IL-19 transgenic mice have been reported to have no overt skin phenotype	Polymorphims in the IL-19 gene have been associated with psoriasis
IL-20	No knockouts described	IL-20R2-/- mice are unresponsive to skin alterations induced by intradermal IL-23 injection	IL-20 transgenic mice show skin abnormalities and death within a few days after birth; asthmatic mice overexpressing IL-20 manifest increased fibronectin and smooth muscle expression in	Polymorphims in the *IL-20* gene have been associated with psoriasis
IL-21	Reduced numbers of Th17 cells, reduced EAE progression	Reduced serum IgG1 levels, increased IgE levels, reduced numbers of Th17 cells, reduced Th2 responses, reduced EAE progression	CD8+ memory T cell accumulation, elevated serum IgM and IgG1	IL-21 polymorphism is associated to SLE

IL-22	Defects in host protection, increased intestinal epithelial damage		Transgenic mice over-expressing IL-22 have an aberrant skin phenotype that resembles psoriasis; liver over-expression promotes hepatocyte survival and proliferation but increases susceptible to tumor development	Viral clearance, anti viral defense
IL-23(p19+p40)	p40 KO: immunocompromised; p19 KO: can still generate Th1 cells and IFN-g, defect in DTH response, resistant to developing EAE and CIA	No obvious developmental abnormalities, impaired IFN-g secretion, Th1 differentiation, and NK cytolytic activity which results in higher susceptibility to intracellular pathogens	p40: inflammatory skin lesions p19: systemic inflammatory diseases	Crohn's disease, ulcerative colitis, psoriasis, ankylosing spondylitis and myocardial infarction, psoriasis, arthritis
IL-24	Epidermal hyperplasia	-	Epidermal hyperplasia, neonatal lethality and abnormal keratinocyte differentiation	IL-24 polymorphisms are associated with metabolic and cardiovascular risk factors
IL-25	Constant expression of Th2 cytokines and higher levels of IgE, increases in mast cells in parasitic infections	Lack of production of IL-5 and IL-13 by splecnocytes, lower number of eosinophils, neutrophils, lymphocytes	Splenomegaly, lymphadenopathy and increases in eosinophils and B-cells in the periphery, growth retardation and pronounced inflammations of organs, Th2-like reactions in the lung	-
IL-26	-	-	-	Polimosphism associated with protection from multiple sclerosis and rheumatoid arthritis
IL-27 (p28+EBI3)	EBI3 KO: early defect in Th1 cell response during L.Major infection, resistant to oxazolon induced colitis	gp130 KO: severe developmental defects, WSX1:increased Th1, Th2 or Th17 cell response in several models of infection and inflammation	Transgenic mice over-expressing IL-27p28 reveal defective thymus-dependent B cell responses, inability to form germinal centers, lack of class switching and affinity maturation; aberrant inflammatory response in the GI tract	COPD, asthma

IL-28A/B/IL29 (IFNd family)	-	IL28Rα -/- mice exhibit no altered virus susceptibility, but IFNAR1 -/- IL28Rα -/- mice are hypersensitive to a strain of influenza A virus that is normally nonpathogenic even in mice lacking only type I IFN receptors	-	IL-28 polymorphisms are associated with hepatitis C virus susceptibility
IL-31	-	Enhanced Th2-type responses, granuloma formation, accelerated worm expulsion, enhanced response to OSM	Alopecia, chronic pruritus, skin lesions, conjunctivitis and swelling around eyes, inverse T B cell ratio	Ashtma and atopic dermatitis
IL-32	-	-	IL32γ transgenic mice show increased level of TNF-a, IL-1, IL-6 in response to LPS, increased collagen-induced arthritis, increased inflammatory cell infiltration, vascular leakiness and tissue damage	IL-32 polymorphisms are associated with the risk of epithelial cell derived thyroid carcinoma
IL-33	Attenuated eosinophilic pulmonary inflammation in OVA-induced asthma model; attenuated eosinophilic pulmonary inflammation in protease-induced asthma model which is independent of T cells and B cells; resistance to LPS-induced septic shock	Altered antigen specific Th2 responses, lack of pulmonary granuloma formation in the lung, absence of endotoxin tolerance	Transgenic mice develop spontaneous pulmonary inflammation; skin-specific IL-33 overexpression activates ILC2 and elicits atopic dermatitis-like inflammation	Asthma and IBD
IL-35	No overt signs of autoimmune disease or developmental abnormalities	-	IL-35 depleted regulatory T cells failed to suppress colitis in RAG knockout mice after T cell transfer; the ectopic expression of IL-35 in the pancreas could prevent the development of type I diabetes	Polymorphisms in p35 and EBI3 is associated with increased susceptibility to asthma, atopic dermatitis, allergic rhinitis and celiac disease

IL-36	-	Severe inflammation phenotype and neonatal lethality	Transgenic expression of IL-36α in basal keratinocytes resulted in cutaneous inflammation sharing some features with psoriasis	Pustular psoriasis
IL-37	-	-	Protection from LPS-induced shock and from concanavalin A induced hepatitis, lower serum and tissue concentrations of IL-2, IL-4-IL-6, IL-9, IL-12, IFNγ; lower LPS-induced DCs activation.	IL37 gene variants are associated with the susceptibility to autoimmune thyroid disease
IL-38	-	-	-	IL-38 polymorphism rs3811058 is associated with ankylosing spondylitis in Taiwanese Chinese and psoriatic arthritis in a Caucasian population; the same SNP and also rs7570267 are significantly associated with rheumatoid arthritis in a Korean population
IFN-α, -β	IFN-β knockout mice are more susceptible to EAE than their wild-type littermates; they develop more severe and chronic neurological symptoms with more extensive CNS inflammation and demyelination	No overt anomalies; incapacity to cope with viral infections; higher vulnerability to develop autoimmune disease of the central nervous system	IFN-β transgenic mice develop male sterility and show enhanced viral resistance; transgenic expression in β-cells leads to functional alterations in islets, impaired glucose-stimulated insulin secretion and other features of a prediabetic state	IFNAR1 polymosphism affects susceptibility to chronic HBV infection

IFN-γ	Defects in TH1 cytokine induced functions, susceptibility to intracellular pathogens, tumor development, enhanced EAE	Defect in resistance to bacterial, viral and parasitic infections	Localized site inflammation, lymphocyte infiltration, severe tissue destruction, severe deficiency of NK cells and lower numbers of BM cells; epidermial overexpression leads inflammatory skin lesion, dermatitis, hair hypopigmentation and hair loss; overexpression in the central nervous system causes primary demyelination	Susceptibility to pulmonary tuberculosis, multiple sclerosis, myasthenia gravis and arthritis manifestations
TGFβ	TGFβ1 KO: 50% embryonic lethality and multiorgan autoimmunity, increased T cells activity and cytokine secretion, increased apoptosis, decreased regulatory T cell number and their suppressive function; TGFβ 2 and TGFβ 3 KO: perinatal lethal but no signs of autoimmunity	TGFβ Receptor I conditional knockout mice develop spontaneous squamous cell carcinoma in periorbital and/or perianal regions	Overexpression of TGFβ1 inhibits skin development	Asthma, allergic rhinitis, food allergy, eczema, allergic rhinitis, and eosinophilic gastrointestinal disease increased cancer risk, aortic aneurysm, aortic dissection, intracranial aneurysm, subarachnoidal hemorrhage
TNFα	Impaired defense against bacterial and viral infections, impaired lymph node follicle and germinal center formation and absence of follicular dendritic cells; higher more susceptibility to spontaneous tumor development	Impaired defense against bacterial and viral infections, impaired lymph node follicle and germinal center formation and absence of follicular dendritic cells	Transgenic mice over-expressing human TNFR2 spontaneously develop SIRS; Knock-in mice expressing a mutated non-sheddable TNFR1 show enhanced susceptibility to inflammatory diseases.	Increased risk of allergic diseases

IL-1

Discovery and structure

IL-1, was originally termed as human leukocytic pyrogen, a protein inducing fever. [1, 2] After cloning of IL-1β cDNA, it was demonstrated that recombinant IL-1β produced fever in humans. [3] In the same year, two cDNAs for IL-1 were reported and its cloning resulted in the expression of two related proteins, termed IL-1α and IL-1β. [4] Now, about 25 years later, 11 members of the IL-1 family were found. In this review, we will concentrate on IL-1α and IL-1β and the IL-1Ra.

Genes for IL-1α, IL-1β and IL-1Ra are closely associated in the region of 2q12-q21 of human chromosome 2. Human IL-1α and β share low sequence homology and are synthesized as 31 kDa, variably glycosylated pro-cytokines that share 25% amino acid identity across their entire precursor structure, and 22% amino acid identity over their mature segments. [5] The mature forms of these two cytokines have a single beta-trefoil domain that is shared with fibroblast growth factors. [6]

Receptor and signaling

IL-1 receptors (IL-1Rs) belong to the Toll-IL-1-receptor (TIR) superfamily, which are defined by an intracellular TIR domain that initiates the signaling cascade. Regarding the extracellular domains TIR receptors can be divided into a group containing a leucine-rich repeat motif and into another group, which is characterized by an Ig-like domain. TIRs belong to the group with the leucine-rich repeat motif, whereas the Ig domain subgroup includes the IL-1Rs. IL-1α and IL-1β exert similar effects by binding to the IL-1 type I receptor (IL-1RI). The binding of IL-1α and IL-1β to the IL-1 type II receptor (IL-1RII), does not lead to signal transduction as IL-1RII acts as a decoy receptor for both of these molecules. [7] Two distinct IL-1R binding proteins, plus a non-binding signalling accessory protein have been identified. [8,9] Both IL-1Rs contain a ligand-binding domain, which is composed of three Ig-like domains. In addition, each receptor has an N-terminal signal peptide and a single membrane-spanning region. The main difference between IL-1RI and IL-1RII is found in the intracellular domain, which is extremely short in IL-1RII (29 amino acids) compared to IL-1RI (213 amino acids). In contrast to IL-1RI, IL-1RII is unable to

complex with IL-1 accessory protein (IL-1R-AcP), which is necessary for signal transduction. Therefore, the functional role of IL-1RII is the avoidance of the interaction between IL-1 and IL-1RI. The decoy receptor IL-1RII acts as a natural inhibitor of IL-1 activity, a function complementary to that of IL-1Ra, which is an endogenous inhibitor of IL-1α and β and binds competitively to the IL-1RI without activating it. The extracellular domain of IL-1RI consisting of 319 amino acids is responsible for ligand binding and interacts with similar affinity either with agonist proteins IL-1α and IL-1β or with the antagonist protein IL-1Ra.

In addition, pro-IL-1α is binding with high affinity to IL-1RI, but there is no binding of pro-IL-1β. After binding of ligands to the IL-1R1 membrane receptor the approximation of IL-1R1 and IL-1AcP is necessary for initiation of signalling, which involves the recruitment of adaptor molecules such as MyD88 and activation of IL-1R-associated kinases (IRAK), leading to activation of nuclear factor NF-κB and mitogen activated protein kinase (MAPK)-regulated transcription factors such as c-jun n-terminal kinase (JNK) and p38. [10]

Cellular sources and targets

Macrophages, monocytes, DCs, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts and synovial lining cells are the main sources of IL-1. Whereas the precursor of IL-1α is constitutively expressed in healthy conditions in nearly all human cells, IL-1β is mostly undetectable in cells from healthy individuals. IL-1β is mainly expressed by monocytes, macrophages and dendritic cells. Recent findings have shown, that during influenza-infection, IL-1β can also be produced in large quantities by infected lung fibroblast cells and human pulmonary microvascular endothelial cells. [11] The IL-1RI is predominantly expressed on T cells, fibroblasts, epithelial and endothelial cells and is often co-expressed with IL-1RII. Cell activation for example by stimulation of membrane-bound TLRs leads to translation of the precursors pro-IL-1α and pro-IL-1β. Both proteins, IL-1α and β, are synthesized as leaderless secretory 31 kDa precursors. However, there are fundamental differences in relation to localization, maturation and secretion of the two proteins. Pro-IL-1α is already fully biologically active in contrast to pro-IL-1β, which

has no biological activity until it is processed by inflammasome and caspase-1. [12] Calpain processes pro-IL-1α into mature IL-1α, which remains intracellular or is membrane-associated for the main part and is mostly not secreted. IL-1α at the cell surface membrane can activate adjacent cells bearing IL-1RI. Only a small part of pro-IL-1α is cleaved by calpain into the mature 17kDa IL-1α form and the 16 kDa N-terminal cleavage product. [13] IL-1α is only rarely found in the extra-cellular biological liquids or in the circulation. [14] Activation of IL-1β usually occurs as a two-step process. First, transcription of *IL1B* mRNA is induced and it is translated as the 31-kDa IL-1-precursor protein. This process can occur after the activation of pattern recognition receptors such as Toll-like receptors (TLRs) or after the release of alarmins such as IL-1α or TNFα that occurs after cell death. Mature IL-1β remains dispersed in the cytosol until a second stimulus drives processing and release of the active form. Next, for the generation of the 17-kDa mature form of IL-1β a proteolytical step is necessary, which might be achieved in inflammasome-dependent and -independent mechanisms.[15] In monocytes, macrophages and DCs, for this intracellular processing step of IL-1β, the IL-1β-converting enzyme (also known as caspase-1) is needed. Caspase-1 is a part of a complex of intracellular proteins called inflammasome. [16] Inflammasomes are large, cytosolic multiprotein complexes. They contain cytoplasmic sensor molecules such as NLRP3, AIM2, NLRC4, NLRP1, activation of which leads to the rapid polymerization of the common adaptor protein called apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC, also known as PYCARD). ASC forms large filamentous scaffolds, which are referred to as ASC specks, that recruit and activate caspase-1, resulting in the maturation of interleukin (IL)-1β and IL-18. Potassium efflux, calcium influx, lysosomal damage, mitochondrial and other reactive oxygen species, mtDNA are all involved in different signaling pathways of various inflammasome activation upon variety of infectious and non-infectious stimuli, leading to activation of caspase-1 and processing of IL-1β and IL-18 precursors into their mature forms.[17] In resting cells pro-caspase-1 is bound to an inhibitor molecule, which prevents its activation. Other mechanisms have been also recently described to control excessive inflammasome activation and mature IL-1β release including autophagy,[18] omega-3 fatty acids,[19]

PGE_2, [20] and cAMP.[21] Non-inflammasome dependent mechanisms of IL-1β proteolysis involve neutrophil-derived serine proteases, in particular proteinase-3 (also known as myeloblastin), but also including neutrophil elastase, cathepsin G and granzyme A.[22, 23] Caspase-8 might also induce the processing of mature IL-1β in response to TLR3 and TLR4 stimulation. [24]

Role in immune regulation and cellular targets

IL-1 is a master cytokine in inflammation and plays an important role of the innate immune system, which regulates functions of the adaptive immune system. IL-1α and β are both potent pro-inflammatory proteins and have diverse potentiating effects on proliferation, differentiation and function of diverse non-adaptive as well as specific immunocompetent cells. [25] Already 20 years ago, it was described that human IL-1 is one of the mediators responsible for the acute-phase protein response of the liver in inflammation. [26] Intravenously administered recombinant IL-1 is acting as an endogenous pyrogen and induces a rise of body temperature in rabbits. [27] The balance between IL-1 and IL-1Ra in local tissues influences the possible development of inflammatory diseases and plays an important role in the severity of many diseases. In the presence of excess amount of IL-1 or the reduced production of IL-1Ra, inflammatory and autoimmune diseases may develop in many organs such as joints, lungs, central nervous system, gastrointestinal track or blood vessels.

IL-1β promotes the differentiation of human naive CD4+ T cells into Th17 cells. [28] In this context, it is described that Th17 cell differentiation is regulated via differential expression of IL-1RI, which is controlled by IL-7 and IL-15.[29] The importance of IL-1β for the induction of IL-17 was also demonstrated on T cells, which produce IL-17 after stimulation with IL-1β in combination with IL-23. [30] IL-17 is shown to play a key role in many autoimmune disorders, such as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematous, and inflammatory bowel disease as well as in allergy and asthma. [31] Recently, it was shown that IL-1β promotes Th17 responses from CD4+ T cells in chronic intestinal inflammation. [32] Interestingly, commensal-induced IL-1β is critical for Th17 differentiation in the gut. [33] In addition, it was demonstrated that IL-1β is essential in candida albicans-induced Th17 differentiation demonstrating

its role as a pro-inflammatory regulator of Th17 cells. [34]

Recently, it was shown, that IL-1β induced by gut microbiota can promote development of IL-10-producing regulatory B cells in spleen and mesentheric lymph nodes of mice. Also it was observed that mice having B cells deficient in IL-1 receptor 1 develop stronger arthritis symptoms, due to impaired response towards IL-1β.[35]

Also IL-1 is acting as a major inflammatory mediator, it has been implicated as a regulator of bone marrow hematopoietic stem cells and progenitor cells. [36] It was shown that IL-1RI-deficient mouse embryos show an increased myeloid differentiation suggesting that IL-1 is an important homeostatic regulator at the earliest time of hematopoietic stem cells. [37]

IL-1β induces synthesis of chemokines, including IL-8, which is a potent neutrophil chemoattractant. [38] Neutrophils can enhance the inflammation by inducing pro-inflammatory cytokines and release of neutrophil granule enzymes, which are involved in tissue damage. [39]

Role in host defence or other immune regulatory conditions

Activated macrophages and monocytes produce IL-1α and β, which belong to the key players in the innate immune response. They have important functions in the coordination of local and systemic inflammation by causing inflammation and inducing the expression of other pro-inflammatory genes like cyclooxygenase type II, inducible nitric oxide synthase and other cytokines or chemokines. Moreover, IL-1β activates local endothelium to induce vasodilation, which results in an increase of the permeability of blood vessels. Consequently serum proteins and leukocytes can be recruited to the site of infection. In addition, IL-1β activates hepatocytes to produce acute phase proteins, which are important to activate and opsonize pathogens for phagocytosis by macrophages and neutrophils. IL-1β is also a key inducer of antimicrobial proteins, for example beta defensin, which plays a role in mucosal defense in the lungs during first pathogen contact. [40] IL-1β is able to enhance antigen-mediated expansion of in-vitro primed T_H1, T_H2 and T_H17 cells. [41] Others showed that IL-1β especially induced T_H17 cells. [42] IL-1 signaling via MyD88 is necessary in early differentiation stages of these cells, while it gains even more importance together with IL-23 in expansion of committed T_H17 cells. [43] Similar to the

effect on CD4+ T cells, IL-1β was also seen to enhance expansion, effector and secondary responses as well as influencing tissue-localization of CD8+ T cells. [44]

IL-1β plays a major role in a wide range of autoimmune and inflammatory diseases. For example, IL-1β is implicated in rheumatoid arthritis, which is a chronic inflammatory disease characterized by progressive joint destruction and systemic manifestations. In this context, IL-1 was first described as a factor released from activated chondrocytes leading to proteoglycan degradation. [45] Later, IL-1 could be measured in the local inflammatory environment and was correlated with RA disease activity. [46] In experimental animal models of arthritis, injection of neutralizing antibodies to IL-1 suppressed cartilage proteoglycan synthesis and reversed synovial inflammation in mice in contrast to injection of recombinant IL-1 into mouse knees, which stimulated proteoglycan synthesis and leukocyte infiltration. [47,48] IL-1α transgenic mice developed a severe polyarthritic phenotype characterized by accumulation of macrophages, hyperplasia of the synovial lining layer and destruction of cartilage. [49] Because of the wide range of experimental data supporting the role of IL-1 in rheumatoid arthritis, clinical trials with agents blocking IL-1 have been carried out (described below in section IL-1Ra). Furthermore, IL-1β, as an end product of an excessive NLRP3 inflammasome activation, due to the gain of function mutations in the *NLRP3* gene is responsible for symptoms in cryopyrin-associated periodic fever syndromes (CAPS), including familial cold-induced autoinflammatory syndrome, Muckle–Wells syndrome, and neonatal onset multisystem inflammatory disorder (NOMID).[50]

IL-1 is also important in the pathogenesis of the inflammatory bowel disease (IBD), which covers a group of disorders, in which the intestines become inflamed probably as a result of an autoimmune disorder. In mucosal biopsies higher IL-1 mRNA levels were present in active colitis samples than in samples with inactive colitis and non-inflammatory controls. [51] The correlation between tissue levels of IL-1 with the degree of mucosal inflammation suggests that IL-1 is one of the critical mediator if intestinal inflammation in IBD. In experimental animal models, blocking IL-1 in immune complex-induced colitis in rabbits markedly reduced inflammatory cell infiltration and necrosis in the colon, whereas neutralization of IL-1Ra led to prolonged intestinal

inflammation and increased the mortality. [52]

Inflammation plays an important role in the development and progression of atherosclerosis where the chronic inflammation mediated by IL-1 has a recognized role. Importantly, IL-1 KO or IL-1Ra KO mice develop less atherosclerosis. [53] Although current interventions in human patients are mainly focused on IL-1β, it was shown recently, that IL-1α is actually the main driver of vascular inflammation. [54] In humans, an association between IL-1Ra gene polymorphisms and the severity of coronary disease has also been identified.[55] IL-1 has also important functions in many other diseases including osteoarthritis, chronic obstructive pulmonary disease, multiple sclerosis or Alzheimer's disease.

Interestingly, two neutralizing mAbs were designed, developed and registered for IL-1 neutralization, namely Canakinumab and Rilonacept, and are used in clinical practice for treatment cryopyrin-associated periodic syndromes. [56-58] Canakinumab is a human mAbs targeting selectively IL-1β. [59, 60] In contrast Rilonacept (also known as IL-1 Trap) is a dimeric fusion protein consisting of human IL-1R (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) linked with Fc region of human IgG1 that neutralize IL-1.[61] In addition, IL-1 neutralizing antibodies are tested in clinical trials as a possible treatment for systemic juvenile idiopathic arthritis, [62] gout, [63, 64] diabetes, rheumatoid arthritis and cardiovascular disease [65] and Deficiency of the Interleukin-1 Receptor Antagonist (DIRA). [66]

Role in allergic diseases

Although IL-1 has major functions in a wide range of autoimmune diseases, it is also implicated in the inflammatory process of allergic diseases. Atopic dermatitis patients have defects in innate immune responses and are predisposed for skin infections with *Staphylococcus aureus* resulting in disease aggravation. IL-1 pathways are implicated in the host response to *Staphylococcus aureus*. It has been shown that atopic dermatitis patients have an increased ratio of IL-1Ra to IL-1α in the *stratum corneum*, which would have an inhibitory effect on IL-1-mediated actions. [67] The importance of IL-1 for the *Staphylococcus aureus* defense is also demonstrated in cutaneous infection model in IL-1R deficient mice showing larger skin lesions,

higher bacterial counts and lower neutrophil numbers. [68] In asthma patients, IL-1β is necessary for the differentiation of Th17 cells, [69] which are increased in airways of asthma patients. [70] In addition IL-1β induces airway neutrophilia and increases airways responsiveness selectively to bradykinin in the rat. [71] IL-1 from bronchial epithelial cells, which is induced by double-stranded RNA, plays an important role for the activation of Th2 cytokine production by mast cells in the airways. [72]

IL-1 in mice and human mutations

Mice deficient in IL-1α, or IL-1β or doubly deficient in IL-1α and IL-1β show no different phenotype compared to the same strain wild-type mice indicating that IL-1 is not essential for normal embryonic development and postnatal growth. In contrast, when local or systemic inflammation is induced IL-1 deficiency reduced in inflammatory response and increased susceptibility to infections, whereas IL-1β plays a greater role in inflammation than IL-1α. Fever development upon injection with turpentine was suppressed in IL-1β as well as IL-1α/β deficient mice, but not in IL-1α deficient mice indicating that IL-1β but not IL-1α is crucial in febrile responses. [73] In human, polymorphisms in IL-1 gene cluster can be associated with numerous diseases, such as gastric carcinoma[74, 75], ankylosing spondylitis [76] and Graves' disease. [77]

IL-1 receptor antagonist

Discovery, structure, receptor and signaling

IL-1Ra, which was discovered in 1984, is also synthesized and released in response to the same stimuli that drive IL-1 release. Because IL-1Ra lacks the IL-1R-AcP interacting domain, its binding to IL-1RI results in inhibition of the IL-1 signaling cascade. Consequently, IL-1Ra acts as a physiological inhibitor of IL-1 by silencing IL-1-dependent cell activation and blocks the activity of both, IL-1α and IL-1β. IL-1Ra can also bind to IL-1RII suggesting that the inhibitory activity of IL-1Ra is depending on the balance between IL-1RI and IL-1RII. [78] Until now, four isoforms of IL-1Ra are identified, from which three are located intracellularly and one has a signal peptide and is generally secreted without requiring maturation in the ER-Golgi exocytic pathway. The intracellular isoforms could be detected in monocytes, fibroblasts,

endothelial cells, keratinocytes and other epithelial cells whereas the originally described isoform of IL-1Ra is secreted from monocytes, macrophages, neutrophils and other cells. [79]

Role in immune regulation and cellular targets

IL-1Ra is neutralizing the effects of IL-1α and IL-1β. Complete inhibition of IL-1 requires 10 to 100 fold molar excess of IL-1Ra over IL-1. As a drug for therapeutic applications a nonglycosylated recombinant form of human IL-1Ra, called Anakinra, is available that competitively inhibits IL-1 by binding to IL-1RI. Anakinra binds IL-1 receptors with an affinity nearly equal to that of IL-1 and operates in the same manner like the endogenous IL-1Ra. [80] *In vitro*, it has been demonstrated that Anakinra antagonizes IL-1-induced prostaglandin E2 secretion, production of metalloproteinases and the proteoglycan degradation. [81] In addition, IL-1-induced stimulation of hyaluronic acid was inhibited by Anakinra in a dose-dependent manner in human synovial cells and Anakinra reversed the decrease in proteoglycan synthesis induced by IL-1.[82] Intravenous injection of IL-1Ra into rabbits given an intraarticular injection of recombinant IL-1β inhibits leukocyte infiltration into the synovial lining and joint cavity and also blocks the ability of IL-1 to cause loss of proteoglycan from articular cartilage. [83] Recently, it was demonstrated that IL-1Ra, derived from hepatocytes, plays also an important role in the resolution of hepatic damages. [84]

Role in host defense or other immune regulatory conditions

The fact that IL-1Ra gene deficiency causes autoimmunity and joint-specific inflammation suggests that the balance between IL-1 and IL-1Ra is important in maintaining the normal physiology of the joints and homeostasis of the immune system.[85] Polymorphisms of the IL-1Ra gene, which can lead to changes in the IL-1Ra and IL-1 balance, are associated with susceptibility and progress of a variety of diseases, such as ulcerative colitis, lupus erythematosus, osteoporosis and viral infections. [86]

Anakinra, which shows an excellent safety record, is administrated as a once-daily subcutaneous injection. Anakinra is efficient as mono therapy for the treatment of patients with rheumatoid arthritis. [87] In addition, Anakinra treatment has been

reported to be effective in some patients with systemic-onset juvenile idiopathic arthritis or adult-onset Still disease. Lequerre et al. showed that therapy with Anakinra was effective in most patients with adult-onset Still disease but less than 50 % of patients with systemic-onset juvenile idiopathic arthritis achieved a marked improvement. [88] A recent study demonstrates that anakinra was consistently efficacious in the treatment of adult-onset Still disease over the long term. [89]

Anakinra is also evaluated as a treatment option in patients with cardiovascular disease. IL-1 inhibition by administration of Anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis and is associated with reduction of nitrooxidative stress and endothelin. [90] An animal study with mice demonstrated that administration of Anakinra within 24 hours of acute myocardial infarction significantly ameliorates the remodeling process by inhibiting cardiomyocyte apoptosis. [91] These results suggest that Anakinra could be useful to prevent postischemic cardiac remodeling and heart failure.

Depletion of granulocytes and monocytes by selective apheresis is one treatment opportunity of ulcerative colitis. The mechanism of clinical efficacy associated with this therapy could be explained by the release of IL-1Ra and the increase of IL-1Ra in the adacolumn outflow during therapy. [92] Moreover, it is well accepted that patients with inflammatory bowel disease have a decreased ratio of IL-1Ra/IL-1β in their colonic mucosal tissue. [93] In animal models it has been suggested that exogenous administration of IL-1Ra have a therapeutic benefit in experimental colitis. Regarding the beneficial effects of Anakinra in patients with rheumatoid arthritis, further investigations of this mode of therapy in inflammatory bowel disease is warranted.

Recently, it was shown in an animal model of type 1 diabetes that blocking of IL-1 with Anakinra early in the disease progression can prevent islet autoimmunity triggered by virus infection. [94]

IL-1Ra in allergic diseases

Until now, there is some evidence that IL-1Ra could be involved in the pathogenesis of atopic dermatitis and asthma. Like described above, IL-1β is detected in the airways and contributes to the changes in the airways. Therefore, inhibition of IL-1β by IL-1Ra can reduce local inflammation and airway

hyperresponsiveness. In this context, it was demonstrated that variants in the IL-1Ra gene are associated with asthma and contribute to the pathology of asthma.[95] After treatment of antigen-sensitized guinea pigs with IL-1Ra the bronchial hyperreactivity and the leukocyte influx into the BAL decreased. [96] In a phase one clinical study, IL-1Ra has reduced inhaled LPS-induced airway neutrophilia as a candidate for the treatment of neutrophilic asthma. [97]

IL-1Ra in mouse models

Mice deficient in IL-1Ra have low litter numbers and exhibit growth retardation in adult life. [98] In addition, IL-1Ra KO mice spontaneously developed inflammation in constitutively stressed artery walls suggesting that IL-1Ra is required to prevent the development of lethal arthritis. [99] IL-1Ra KO mice also spontaneously developed chronic inflammatory polyarthropathy, which was similar to human rheumatoid arthritis and was characterized by the over-expression of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α in the joints. [85]

IL-2

Discovery and structure

Morgan et al. and Gillis et al. demonstrated 30 years ago that cultured media of activated T cells contain mediators that induce the proliferation of antigen-activated T cells. [100, 101] Already in 1965, Kasakura et al. and Gordon et al. found a soluble mitogenic factor for lymphocytes in the culture media of mixed leukocytes. [102, 103] In the ensuing years, it had become clear that a single protein was responsible for this effect, and this T cell growth factor (TCGF) has been called IL-2.

IL-2 is a monomer of 15.5 kDa and consists of 133 amino acids. It is a member of the four α-helix bundle cytokine family. These family members (IL-2, interferon and IL-10 subfamilies) are characterized by antiparallel juxtaposed helices A, C, B, D, and two long end-to-end loops, loop AB and CD, which are connected by a short β-sheet packed against helices B and D. [104]

Receptor and signaling

The IL-2R consists of three subunits, the ligand specific α chain IL-2Rα (CD25, originally called Tac for T activation), the β chain IL-2Rβ (CD122), which is also part of the IL-15 receptor complex, and the common γc (CD132), which is shared by IL-4, IL-7, IL-9, IL-15, and IL-21. IL-2Rα (consists of two sushi domains, see also IL-15Rα). [105] IL-2Rα and IL-2Rβ are important for cytokine binding, whereas IL-2Rβ and γc are involved in signal transduction. All three subunits are required for the formation of the high-affinity IL-2R (Kd ~ 10^{-11} M). The IL-2Rβ/γc complex is expressed at low levels on resting T cells (and on NK cells). Binding of IL-2 to this complex (Kd ~ 10^{-9} M) induces cell growth Upon T cell activation, IL-2Rα is rapidly induced and thereby building the high affinity quaternary complex reducing the concentration of IL-2 needed for growth stimulation. IL-2Rα is found on subsets of developing pre-T and pre-B cells, but because these cells lack γc, they do not respond to IL-2. Also the development of T and B cells in young IL-2Rα-deficient mice is normal before their accompanying severe autoimmunity disrupts lymphocytes development. Additionally, IL-2Rα is prominently found on natural CD4+ FOXP3+ Treg cells, the commonly known CD4+ CD25+ Treg cells. [106, 107] IL-2 receptor signaling is essential for the development of Klrg1+, marks a unique Treg subset, terminally differentiated Treg. [108]

Binding to IL-2Ra alone with low affinity (Kd ~ 10^{-8} M) does not lead to a detectable biologic response, but promotes association with IL-2Rb and g chains. The quaternary complex (IL-2, IL-2Ra, IL-2Rb, gc) induces IL-2 signaling that results in the activation of multiple signal transduction pathways, including the JAK/STAT, Ras/MAPK, and PI 3-kinase/Akt signaling pathways. Chronic T cell stimulation leads to a shedding of IL-2Ra, which is a marker for strong antigenic stimulation. IL-2 is required for human plasma cell generation to initiate the differentiation and proliferation by enhancing MAPK-ERK signaling. [109]

Although individual IL-2R subunits are widely distributed on many different cell types, only two major cell subsets readily coexpress all three subunits, which are required for the high affinity IL-2R, namely CD4+ FOXP3+ Treg cells and activated conventional CD4+ and CD8+ T cells. Treg cells and antigen-activated T cells

represent the main population of cells poised to respond to IL-2 in vivo. *Aiolos,* a transcription factor, is upregulated in T lymphocytes leads to silencing of the gene encoding IL-2. This acts as a cell-intrinsic safeguard mechanism for the differentiation of helper T cells into the Th17 subset. [110]

Cellular sources and targets

IL-2 is mainly produced by CD4+ and CD8+ T cells after activation by antigens/TCR and costimulation. IL-2 production is transient, a peak secretion occurs after 8 to 12 hours after stimulation. IL-2 is also produced by Mast cells and promote Treg expansion which contribute to suppression of allergic inflammation. [111] To a lesser extend also activated DCs, NK, NKT cells and innate lymphoid cells (ILCs)[112] produce IL-2, however, the biological relevance of this is not known yet. Target cells of IL-2 include CD4+, CD8+ T cells, NK, B cells and ILCs. $CD8^+$ T cells, rather than $CD4^+$ T cells produce IL-2 required for generation of helper T cell-dependent memory $CD8^+$ T cells. [113] Tregs reduce IL-2 exposure $CD8^+$ T cells and this is crucial step to generate functional $CD8^+$ T memory cells. [114]

Role in immune regulation and cellular networks

IL- 2 is a central player for T cell-dependent immune responses. Activation of T cells through TCR and costimulatory molecules such as CD28 induce production of IL-2 and expression of IL-2R. The binding of IL-2 to its receptor subsequently drives extensive clonal expansion and effector T and B cell development.

Role in host defense or other immune regulatory conditions

IL-2 is an essential growth factor for T cells, however repeated activation of CD4+ T cells with IL-2 makes these cells sensitive to Fas-induced apoptosis (AICD) and contributes thereby to the termination of a persistent immune response. IL-2 is also essential for the development of Treg cells, which provides another mechanism to abate the immune response. [115] IL-2 promotes also the proliferation and differentiation of NK cells and enhances their cytolytic functions. In addition, Treg cells restrain IL-2-dependent NK cell cytotoxicity and proliferation. [116-118] Since NK cells only express the IL-2Rb/gc complex (they do not express IL-2Ra), high amounts of IL-2 are necessary for their stimulation. However, IL-12 induction of IL-2Ra (CD25) plays role high-affinity IL-2 receptors on NK cells. [119] IL-2 acts on B cells as a growth

factor and as a stimulus for antibody synthesis. IL-2 induces proliferation and cytokine production by ILCs. [112, 120, 121]

Functions as demonstrated in IL-2-deleted mice, receptor-deficient mice, human mutations and the clinical use

IL-2-deficient mice are normal with regard to thymocyte and peripheral T-cell subset composition, but a dysregulation of the immune system is manifested by reduced polyclonal *in vitro* T-cell responses and by dramatic changes in the isotype levels of serum Igs. [122] Nevertheless, the IL-2 deficiency model evaluating the costimulatory signals in T cell induction showed that secondary antiviral T cell responses were absent unless IL-2 was given in vivo. Primary and secondary cytotoxic T cell responses against vaccinia and lymphocytic choriomeningitis virus were within normal ranges, B cell reactivity to vesicular stomatitis virus was not impaired, T helper cell responses were delayed, but biologically functional and NK cell activity was markedly reduced. [123] IL-2 influence developing $CD4^+$ T effector cells and choose a T follicular cells fate in vivo using influenza model. [124] IL-2 has a negative effect for regulating T follicular cells via STAT5. [125] Substantial expansion antigen-activated T cell clones can occur without IL-2. [124-126] Additionally mutation in STXBP2 that causes familial hemophagocytic lymphohistiocytosis disease prevents IL-2 induced NK cell cytotoxicity. [127]

IL-2Rα chain deficient mice has demonstrated that this receptor chain is essential for the regulation of both the size and content of the peripheral lymphoid compartment. Young mice that lack IL-2Rα had phenotypically normal development of T and B cells, but adults developed massive enlargement of peripheral lymphoid organs associated with polyclonal T and B cell expansion. [128] Older IL-2Rα-deficient mice also develop autoimmune disorders, including hemolytic anemia and inflammatory bowel disease, which was also shown in IL-2-deficient mice. [129, 130]

It was quite surprising that the resulting phenotype of mice deficient in IL-2 or in the α or β chain of its receptor was not immunodeficiency, as predicted, but rather a very serious lymphoproliferative and autoimmune disorder. [122, 131, 132]

The unexpected observation that deficiency of IL-2 or of the α- or β- chain of IL-2R results not in immunodeficiency, but in autoimmune disease can be explained by

failure of AICD in T cells and by a defect in CD4+CD25+ FOXP3+ Treg cell production. [133] Even though IL-2 and IL-15 share two of three receptor units (IL-2Rβ and γc) IL-15- and IL-15Rα-deficient mice have no autoimmune deficiency and contain a normal number of FOXP3+ Treg cells, which indicates that IL-2 is the critical cytokine for Treg cells. IL-15 and IL-2 induced similar signals, and the cytokine specificity of IL-2Rα versus IL-15Rα determined cellular responsiveness. [134]

Thymus-restricted transgenic expression of IL-2Rβ can restore functional CD4+CD25+ Treg cells, suggesting that IL-2 signaling in the thymus is critical for the development of Treg cells. [135] Abrogation of CD40-CD154 signaling impedes the homeostasis of thymic-resident Tregs to reduced intrathymic cytokine particularly, by altering the levels of IL-2. [136]

In an IL-2Rα deficient patient an immunodeficiency has been described, characterized by decreased number of peripheral T cells, abnormal proliferation, but normal B cell development, and extensive lymphocytic infiltration of accompanied by tissue atrophy and inflammation. Although mature T cells were present, the absence of CD25 affected the differentiation of thymocytes. [137]

Humans with a mutation in the common gamma chain γc (as mentioned above this includes defect signaling of IL-2, -4, -7, -9, -15, -21) suffer from X-linked severe combined immunodeficiency (XSCID) 1, a disease characterized by the absence of T and NK cells and the presence of nonfunctional B cells. Since IL-2Rα is continuously expressed by malignant T cells of patients with leukemia, autoimmunity and organ transplant rejections, but not expressed by any resting T and B cells except Treg cells; it is an interesting target for therapeutic interventions. [138] Antagonistic IL-2Rα mAbs (anti-Tac / daclizumab, basiliximab) are effective in preventing rejections of organ transplants. The administration of these antibodies blocks the interaction of IL-2 with IL-2R and leads to cytokine deprivation and death in IL-2-dependent cells. In addition, administration of daclizumab alone has been shown to be useful for the treatment of T-cell-mediated autoimmune diseases associated with abnormalities of the IL-2/IL-2R system. In particular, daclizumab provided an effective therapy for patients with non-infectious uveitis. [139] IL-2 itself (proleukin) is therapeutically used as an immune adjuvant in certain types of lymphoproliferative diseases and cancers, but

severe dose-limiting toxicity has restricted its effectiveness in the clinic. On the other hand, recombinat protein combining IL-2 and Diphtheria toxin (Denileukin diftitox) was designed and approved for treatment of cutaneus T-cell lymphoma (CTCL).[140] Interestingly, recent findings suggested that low-dose IL-2 therapy has less side effects and has possibility to be a new therapeutic way for autoimmune and inflammatory diseases. [141] Another approach IL-2/S4B6 mAb complexes therapy showed successful organ transplantation via increasing 10 to 20 fold Tregs numbers in mice without any other immunosuppressive agents. [142] [143] Moreover, IL-2 associated drugs were tested in clinical trials as a possible treatment of cancer[144, 145], multiple sclerosis, type I diabetes [146], thrombocytopenia, ulcerative colitis, Sjögren's syndrome, different autoimmune and inflammatory diseases. [66, 141]

IL-3

Discovery and structure

Human IL-3 was first identified by screening a human cDNA library, using gibbon IL-3 cDNA as a hybridization probe. [147] The human IL-3 gene is encoded on the long arm of chromosome 5 in close proximity to the IL-5 and GM-CSF gene, indicating a common ancestral relationship. IL-3 is a 15.1 kDa monomeric, N-glycosylated protein, consisting of 152 amino acids. The crystal structure of IL-3 reveals four alpha-helices in an up-up-down-down anti-parallel conformation, linked by long overhand loops. [148] This four-alpha helical bundle motif is highly similar to the structure of GM-CSF and to the IL-5 homodimer.

Receptor and signaling

Besides the functional structure, IL-3, IL-5 and GM-CSF also share the common receptor subunit beta chain (CD131), resulting in partially overlapping functions of these hematopoietic cytokines. The beta chain forms a heterodimer together with the cytokine-specific receptor alpha (IL-3Rα, CD123) upon cytokine binding. [149] IL-3Rα [150] is a transmembrane molecule, it binds the antiparallel first and third loop of IL-3 and initiates the signaling via its cytoplasmic domain. The beta chain interacts with a distinct domain of IL-3, which allocates around a conserved glutamate residue and completes the signal transductions via its long cytoplasmic tail. The glycans on the

beta chain were shown not to be relevant for ligand-binding and receptor activation, but may still have some regulatory functions. [151] Functional and structural studies on the GM-CSF/IL-3/IL-5 receptor family have been recently thoroughly reviewed by Broughton et al. [152]

Upon binding of IL-3 to its heterodimeric receptor, three principal signaling pathways are activated: the Janus kinase (JAK) / signal transducer and activator of transcription (STAT) pathway, the mitogen-activated protein kinase (MAPK) pathway, and the phosphatidylinositol 3-kinase (PI3-K) pathway.

The first event in the JAK / STAT pathway is the phosphorylation of the receptor associated kinases JAK2 and JAK1. Activated JAK2 and JAK1, in turn, phosphorylate the beta chain on six critical tyrosine residues that serve as binding sites for STAT1 and STAT5. STAT family members bind to the receptor complex via their SH2 domains, become tyrosine phosphorylated, and dimerize. STAT1 and STAT5 homodimers are able to translocate to the nucleus and bind to specific enhancer sequences in the promoter region of activated genes.

The MAPK pathway leads to the sequential activation of Ras, Raf-1, and MEK, resulting in ERK, JNK, and p38 signaling cascades. ERK eventually activates c-Fos and c-Jun that form the heterodimeric transcription factor AP-1. Beside the induction of proliferation the activation of the MAPK pathway inhibits apoptosis of target cells. The expression of anti-apoptotic factors such as Pim1, cIAP2, Mcl-1, and Bcl-XL becomes upregulated in response to IL-3, [153] while the activity of the pro-apoptotic factor BAD is inhibited.

The PI3-K pathway is initiated by protein kinase A, which phosphorylates the beta chain resulting in the recruitment and activation of PI3-K. PI3-K regulates multiple cellular processes such as proliferation, growth and cell size, rearrangement of the cytoskeleton and apoptosis via the second messenger phosphatidylinositol 3,4,5-triphosphate (PIP3).

Several negative feedback mechanisms have been described that down-regulate the IL-3 signaling: cytosolic tyrosine phosphatases such as SHP1 control the level of ligand-induced phosphorylated proteins. Members of the suppressor of cytokine signaling (SOCS) family are able to inactivate JAKs, block the binding of STATs to

the IL-3R or induce the ubiquitination and the subsequent proteasomal degradation of signaling molecules. Moreover protein inhibitor of activated STAT (PIAS) 1 binds activated STAT1 and inhibits its binding to the DNA. Finally, endocytosis and degradation of the IL-3 receptor terminates cytokine signaling. As IL-3, IL-5, and GM-CSF all signal via beta chain, these down regulation processes prevent the cell from being further activated by any other beta chain-engaging cytokines.

Cellular sources and targets

IL-3 is expressed by T cells, macrophages, stromal cells, NK cells, mast cells, and eosinophils. Recently, its expression in basophils has been shown upon IgE dependent activation. IL-3 drives basophils development and thus can act in an autocrine manner enhancing activation.[154] Its transcription is regulated by two NFAT-dependent enhancers that have distinct tissue-specific activity. [155] While the first enhancer located 14 kb upstream of the IL-3 gene functions only in a subset of T cells, the second is induced in both T cells and mast cells.

IL-3Rα is expressed on bone marrow stem cells, megakaryocytes, monocytes, granulocytes, T regulatory and endothelial cells,[152]. While the IL-3Rα transcript expression is low in unstimulated blood eosinophils, its expression is significantly increased after stimulation with IL-3, IL-5, or GM-CSF. [156]

Role in immune regulation and cellular networks

IL-3 is a multi-lineage hematopoietic growth factor, acting rather on early stages of hematopoiesis than on late differentiation and maturation processes. In synergy with other cytokines IL-3 plays an important role in the differentiation and growth of various cell lineages.

In combination with erythropoietin, IL-3 induces erythroid lineages whereas it synergizes with GM-CSF or G-CSF to induce the granulocyte-macrophage lineage. This effect was inhibited by the presence of CD4+ CD25+ FOXP3+ Treg cells. IL-3 together with TNF-α leads to short-term proliferation of CD34+ progenitor cells and the differentiation of DCs and Langerhans cells. Moreover it supports the effect of stem cell factor (SCF) on the proliferation of mast cell precursors and enhances the IL-2 induced proliferation and differentiation of B cells. Beside its function as a hematopoietic growth factor, IL-3 is responsible for positively regulating the

expression of C-type lectin receptors (CTLR) in macrophages, leading to a more efficient antigen uptake and phagocytosis[157] and for the activation and survival of different mature cell types, including basophils.

The effects of IL-3 are not limited to hematopoietic cells as IL-3 is able to directly stimulate pro-inflammatory reactions such as eosinophils degranulation or histamine, IL-4 and IL-6 release from basophils. Moreover it plays a role in neurodegeneration processes of the central nervous system as shown by experiments with microglial cells. In fact, microglial cells secrete and respond to IL-3 and are the only cells in the brain that express the beta chain, suggesting that IL-3 acts in an autocrine manner. Their stimulation with IL-3 *in vitro* leads to proliferation and the generation of multinucleated giant cells. IL-3 was as well detected post-mortem in the brain of patients with Alzheimer's disease, and associated with brain volume upon genetic variation of promoter region, indicating a clinical relevance of the effects observed *in vitro*. [152, 158, 159]

Role in allergic disease and other pathologic conditions

In vitro data suggests a role for IL-3 in allergic diseases by preventing the apoptosis of basophils via PI3-K; but only little effects on basophil survival have been observed *in vivo*. [160] Upon stimulation with IL-3, basophils upregulate the activation markers CD69 [161] and CD203c, [162] and show enhanced mediator release in response to Fc epsilon receptor crosslinking. Further IL-3 stimulation of basophils leads to the expression of retinaldehyde dehydrogenase-II, which generates retinoic acid. This vitamin A metabolite regulates diverse functions of immune and resident cells; among others it skews the differentiation of naïve T cells towards a Th2 or Treg phenotype. Notably, neither constitutive nor inducible retinaldehyde dehydrogenase-II expression has been detected in any other myeloid, lymphoid, or DC type.[163] More recently, IL-3 has been shown to trigger amphiregulin production in basophils, which could contribute to tissue remodeling in type 2 immune responses.[164] In eosinophils IL-3 induces the surface expression of HLA-DR and the costimulatory molecule B7.2 (CD86). IL-3 treated eosinophils are therefore able to present antigenic peptides and support antigen-specific T cell proliferation in allergic and parasitic diseases. [165] Furthermore, the expression of the eosinophilic activation molecule CD48 is

enhanced by IL-3 and allergen challenge. Crosslinking of CD48 on the surface of eosinophils triggers the release of granule proteins thereby promoting allergic inflammation. [166] Stimulation of monocytes with IL-3 and GM-CSF leads to increased expression of HLA-DR, CD14, IL-1 alpha, and integrin CD18, which mediate cell adhesion. Interestingly, DCs, which differentiated in the presence of IL-3 and IL-4, show decreased IL-12 production and preferentially induce Th2 responses.[167] Thus, IL-3 is a potential target in the development of strategies to modify the balance of different T helper cell subsets.

In allergic asthmatic airways basophils are activated through TSLP release. Basophils in turn produce TSLP, generating a positive feedback loop which is IL-3 dependent.[168]

A role of IL-3 for pathological bone resorption and rheumatoid arthritis was already suggested in early studies, showing that IL-3 can regulate osteoclast differentiation in vitro[169, 170]. More recently IL-3 was shown to reduce TNF-α induced bone resorption[171], to possess anti-inflammatory properties and to trigger the formation T regulatory cells[172].

Several malignant tumors have been shown to secrete hematopoietic cytokines and increased concentrations of IL-3 were observed in sera of cancer patients. IL-3Rα has been detected on several cancer cell lines and IL-3 stimulation induced the proliferation of hematopoietic and non-hematopoietic cancer cells derived from colorectal adenocarcinomas, bladder, and lung cancers. While under healthy conditions B cells do not express IL-3Rα, it is found on the surface of B cells in 40 % of patients with B cell acute lymphocytic leukemia or acute myeloid leukemia. In these patients the increased expression of IL-3Rα is accompanied by enhanced blast proliferation, increased cellularity and poor prognosis. [173] As IL-3Rα is overexpressed on acute myeloid leukemia blasts compared to normal hematopoietic cells, it might serve as a target for therapy. Cytotoxic diphtheria toxin-IL-3 fusion proteins were shown to specifically kill acute myeloid leukemia cells in mice. [174] Additionally, toxin-IL-3 and recombinant human IL-3 were tested in clinical trials as possible treatments for breast neoplasms, leukaemia, myelodysplastic syndromes, blastic plasmacytoid dendritic cell neoplasm, HIV infections and cytopenias. [66]

Functions as demonstrated in IL-3-deficient mice, receptor-deficient mice and transgenic models

Mice deficient in the IL-3 gene or the IL-3Rα do not show altered basal hematopoiesis, growth, development, or longevity. [175, 176] However, IL-3 knockout mice have reduced numbers of mast cells and basophils and impaired immunity in response to parasites such as *Stronglycoides venezuelensis*. [177] These findings are supported by the observation that upon infection of mice with the gastrointestinal parasite *Nippostrongylus brasiliensis* activated T cells secrete IL-3, which enhances basophils production.[160]

Inhibition of IL-3, IL-5, and GM-CSF signaling in beta chain-deficient mice demonstrates an essential role for hematopoietic cytokines in the regulation of Th2 immunity and allergic airway inflammation. In a mouse model of allergic airway inflammation beta chain-deficient mice showed reduced expansion and accumulation of eosinophils in the lung, inhibition of airway hyperresponsiveness, mucus hypersecretion and IgE-production. Th2 cells in the lung of allergen-challenged animals had diminished ability to proliferate, secrete cytokines and migrate. [178] A natural occurring mutation in the IL-3 gene (Ser27Pro) was shown to have protective effects on the development of asthma. [179]

IL-4

Discovery and structure

IL-4 was discovered in 1982 and originally designated B cell growth factor-I (BCGF-I) or B cell stimulating factor-I (BSF-I).[180] It is a monomer of 15 kDa and consists of 129 amino acids. It is a member of the four α-helix bundle cytokine family. These family members are characterized by antiparallel juxtaposed helices A, C, B, D, and two long end-to-end loops, loop AB and CD, which are connected by a short β-sheet packed against helices B and D.[104, 181]

Receptor and signaling

There are two types of IL-4 binding receptors: the type I IL-4R, which predominates in hematopoietic cells and which is responsible for IL-4 signaling in T cells, and the type II IL-4R, which is expressed on both hematopoietic and non-

hematopoietic cells, but not on T cells.[182] Both types have the IL-4Rα chain in common. Type I IL-4R binds IL-4 exclusively and consists of IL-4Rα (CD124) and the common γc (CD132), which is also a receptor for IL-2, IL-7, IL-9, IL-15, and IL-21. Type II IL-4R binds IL-4 and also IL-13 and consists of the IL-4Rα chain and the IL-13Rα1 chain. Binding to these receptor complexes promotes activation of members of the Janus family of protein kinases (Jaks), which are constitutively associated with IL-4Rα (Jak1), the γc chain (Jak3) and the IL-13Rα1 chain (Tyk2 or Jak2).[181] Whereas the signals of the type II IL-4R are transduced by signal transduction and activator of transcription (STAT3), the signals of the type I IL-4R are transduced by the transcription factor STAT6.

Cellular sources and targets

The main sources for IL-4 are Th2 cells and ILC2 cells. IL-4 is additionally produced by basophils, eosinophils, mast cells and by a specialized subset of T cells, which express NK1.1 and appear to be specific for CD-1 (NK T cells). Also γ /δ T cells produce IL-4, and mice lacking these cells fail to develop IL-4-dependent airway hypersensitivity. Main target cells for IL-4 are T and B cells.

Role in immune regulation and cellular networks

IL-4 plays a central role in the differentiation of antigen-stimulated naive T cells into Th2 cells.[183, 184] IL-4 has a variety of other effects in hematopoietic tissues. It increases the expression of class II MHC molecules in B cells, enhances expression of CD23, induces IgE class switch, up-regulates the expression of the IL-4R, and, in association with LPS, allows B cells to express Thy 1. It also acts as a co-mitogen for B cell growth. Although not a growth factor by itself for resting lymphocytes, it can substantially prolong the lives of T and B lymphocytes in culture. IL-4 has also an important role in tissue adhesion and inflammation. It acts with TNF-α to induce expression of vascular cell adhesion molecule-1 (VCAM-1) on vascular endothelial cells, and it down-regulates the expression of E-selectin. IL-4 plays a role in *in vitro* differentiation of myeloid DCs in combination with GM-CSF.[180, 185-189]

In keratinocytes IL-4 upregulate, chemokine for eosinophils, CCL26. In addition, IL-4 induces Stat6 nuclear translocation and stimulates phosphorylation of Jak1 and Jak2, but not Tyk2 and this may provide an explanation for the pathogenesis of

atopic dermatitis.[190] In allergic skin, inflammaotry monocytes acquire an anti-inflammatory M2-like phenotype in response to basophil-derived IL-4 and exert an anti-inflamatory function.[191] IL-4 induces differentiation of stem/precursor cells into fibroblast-like cells that demonstrate a more fibrogenic phenotype, which is due to reduced expression of miR-155.[192] Although murine DCs could be obtained by culturing monocytes with GM-CSF alone, both GM-CSF and IL-4 are indispensable for the differentiatin of human monocyte-dirived DCs.[193] These cell retain the ability to polarize Th1 responses.

Role in host defense or other immune regulatory conditions and allergy

IL-4 has a central role in the regulation of allergic conditions. It is the major stimulus for the Th2 development and suppresses the Th1 development. Furthermore IL-4 is important in the control of Ig class switching. It determines that human B cells switch to IgE and IgG4 and mouse B cells to IgE and IgG1. IL-4 plays a major role in the development of protective immune responses to helminthes, *Leishmania major* and other extracellular parasites.[194] IL-4 attenuates Th1-associated chemokine expression and lymphocyte recruitment and limits pathogen clearance.[195] In chronic rhinosinusitis patients epithelial cell integrity is disrupt after IL-4 *in vitro* indicates a possible role in the pathogenesis of those patients.[196] IL-4 suppress IL-10 induced by innate signals and therefore may promote chronic allergic diseases.[197]

IL-4 decrease the expression of multiple genes associated with innate defense including genes in the epidermal differentiation complex (EDC) that regulate epidermal barrier function. IL-4 plays an important role in regulating epidermal homeostasis and innate barrier function.[198]

Functions as demonstrated in IL-4-deleted mice, receptor-deficient mice and human mutations

IL-4 and IL-4Rα KO mice have severely compromised Th2 differentiation, and even though the T and B cell development is normal, the serum levels of IgG1 and IgE are strongly reduced.[199] The IgG1 dominance in a T cell-dependent immune response was lost, and IgE was not detectable upon nematode infection.[199, 200]

IL-4 deficiency also limits the development of follicular Th cells and prevents germinal center formation in immunized neonates.[201] IL-4Rα and Stat6 transgenic mice show, that IL-4R signaling induces AHR through direct effects on more than one cell type and leave open the possibility that AHR development is promot by direct IL-4 signaling of smooth muscle cells. In mice that express IL-4Rα only in smooth muscle and in mice that have selectively deleted IL4Rα from smooth muscle show that selective smooth muscle expression of IL-4R is sufficient for cytokine-dependent induction of AHR.[202]

Mice lacking IL-4Rα induced alternative activation of macrophages are not protected against allergic airway disease.[203] In addition, $CD4^+$ T cell specific deletion of IL-4Rα attenuates neonatal RSV infection induced Th2 responses upon reinfection.[204] In a quadruple IL-4/5/9/13 KO model complete inhibition of allergic airway inflammation and remodeling has been shown.[205]

In F709 mice, in which the IL-4Rα immunoreceptor tyrosine-based inhibitory motif is inactivated, augmented IL-4Rα signaling confers increased intestinal permeability and dramatically enhanced sensitivity to food allergens. Unlike anaphylaxis to injected antigens in F709 mice is solely IgE dependent.[206] In lymph nodes of reporter mice follicular helper T cells (T_{FH} cells) produce IL-4 but not IL-13, in contrast tissue type 2 helper T cells (Th2 cells) produce both cytokines.[207] Production of IL-4 and specific IgE/IgG1 antibodies correlate with aversion to antigen induced by food allergy in BALB/c mice.[208]

In mice with genetically altered *Il4* and *Il13* loc, that allow detection of cytokine expression by individual cells *in vivo*, follicular helper T cells (T_{FH} cells) and basophils produced only IL-4 *in vivo* and do not have high expression of GATA-3.[207] Humans with a mutation in the common γc (as mentioned above this includes defect signaling of IL-2, -4, -7, -9, -15, -21) suffer from X-linked severe combined immunodeficiency (XSCID) 1, a disease characterized by the absence of T and NK cells but the presence of nonfunctional B cells.

Clinical use

IL-4 inhibits the production of inflammatory cytokines (IL-1, IL-6, TNF-α) and is therefore interesting for the treatment of inflammatory and autoimmune disease such

as allergy/asthma, insulin-dependent diabetes mellitus.[181, 209] In fact, soluble recombinant human IL-4 receptor (Pitrakinra) and Humanized blocking mAbs specific for IL-4 (Pascolizumab) were tested in clinical trials for treatment of asthma and tuberculosis. [209, 210] There are also some evidences that IL-4 might be useful in the treatment of certain tumors. IL-4 can have negative or positive effects on the control of tumor growth, depending on the type of effector cell mediating the tumor clearance and the type of tumor cell model analyzed.[211] Furthermore, IL-4 may play an important role in the pathogenesis of chronic lymphocytic leukemia disease by preventing death and proliferation of the malignant B-cells.[212]

The pharmacogenetic investigation of the inflammatory IL-4/IL-13 pathway in patients with moderate-to-severe asthma demonstrates a significant pharmacogenetic interaction between anti-IL-4 receptor α therapy and IL4RA gene variation, identifying an asthma subgroup that is more responsive to therapy with this antagonist.[213, 214]

IL-5

Discovery and structure

IL-5 was described for the first time as an eosinophil- and B-cell growth factor in 1987. It is a hematopoietic cytokine that is encoded on chromosome 5q23.3-q31.1. Like IL-3 and GM-CSF, it belongs to a group of short chain 4-α-helical bundle proteins that shares the β-receptor chain for signaling.[215] The structure is characterized by 4-helices with anti-parallel conformation. In contrast to IL-3 and GM-CSF, IL-5 consists of a pair of identical 4-α-helical bundles that share the 4th helix of one chain.[216]

Receptor and signaling

IL-5 binds to a heterodimeric receptor that has been defined by Tarvernier et al in 1991.[215] It consists of the specific receptor alpha unit and the β-chain it shares with IL-3 and GM-CSF.[215] Upon binding to the alpha receptor subunit, recruitment of the β chain takes place. IL-5Rα is encoded on chromosome 3 and characterized by an extracellular domain with a proximal WSXWS motif and a homology module containing 2 fibronectin type III domains with paired cysteine residues membrane

distal.[217] Both motifs are highly conserved. The β chain R shows a similar structure, but is generally larger with a longer extracellular and intracellular tails. The extracellular part of the β chain unit consists of 2 homology modules containing 2 fibronectin type III domains with paired cysteine residues membrane distal. The membrane proximal cytoplasmatic proline rich sequence motif is vital, both for IL-5αR- and ß chain-signal transduction, while the carboxyterminal region of the IL5Rα is involved IL-5-induced IgH-class switch recombination.[218] The crystal structure of dimeric IL-5 in complex with the IL-5Rα extracellular domains was recently described: IL-5Rα sandwiches the IL-5 homodimer by three tandem domains. The authors have also confirmed in protein photo-cross-linking experiments that the IL-5 and IL-5Rα interact with each other in vivo in the same manner as that in the crystal structure.[219]

IL-5 signaling takes place via the JAK/STAT[220], MAPK[220, 221] and the PI3 kinase pathways.[222] JAK/STAT phosphorylation of JAK 1 and JAK 2 after hetero-dimerization of the receptor results in STAT 1 and STAT5 activation and is considered to play an important part in IL-5 induced proliferation and differentiation. With regard to the MAPK pathway actions are induced via ERK and TCF ultimately increasing cytokine induced proliferation and preventing apoptosis of eosinophils by upregulation of genes encoding for bcl-2 and bcl-x.[223] In addition, the JNK pathway was reported to be affected by IL-5. PI3K mediated signaling via AKT/PKB was been linked to inhibition of apoptosis via IL-5. Recently, Oct-2 has been shown to facilitate differentiation of B-cells to plasma cells by upregulation of the IL-5R.[224]

Several negative regulators are considered to play an important role: SHP-1 down-regulates common β receptor-activation and CIS negatively influences STAT5. In addition, SOCS1 is considered to be involved in negative feedback via a reduction of JAK 1 activity.[224]

Cellular sources and targets

IL-5 is mainly produced by Th2 cells, activated eosinophils and mast cells, but also by Tc2 cells, γδ T-cells, NK cells[225], NKT cells[226], CD4- ckit$^-$ CD3ε$^-$ IL-2Rα$^+$ in Peyers patches.[227] Type 2 innate lymphoid cell (ILC2) is an important source of both IL-5 and IL-13, not only in IL-25- or IL-33-induced allergic lung inflammation, but also in models of allergic asthma induce with OVA and HDM.[228] IL-5 may increase the

likelihood of B2 B-cells to differentiate into antigen producing plasma cells and synergizes with IL-4. In mice innate non-T IL-5–producing cells localized most abundantly in the lung and proliferated and upregulated IL-5 production in response to IL-25 and IL-33.[229]

The major target cells of IL-5 are eosinophils and, to a lesser extent, basophils and mast cells. Tregs (CD4+CD25+) express IL-5Rα.[230] Novel data demonstrate IL-5 receptor expression on neutrophils and monocytes in sepsis.[231] In mice, IL-5Rα is constitutively expressed on B-1 cells and up-regulated on B-2 cells upon stimulation.

Role in immune regulation and cellular networks

IL-5 secretion is mainly controlled via the transcription factor GATA-3 that also acts as a transcription factor for IL-4 and IL-13. IL-3, GM-CSF and IL-5 synergize for differentiation and function of myeloid cells. In general, IL-5 leads to growth, activation, mobilization, differentiation and survival of eosinophils.[223, 232] Moreover, IL-5 displays eosinophil chemotactic activity, increases eosinophil adhesion to endothelial cells and thereby enhances effector functions of eosinophils. However, the later effects are less pronounced. Eotoxin-2 seems to be crucial for IL-5 induced IL-13 production and AHR.[233]

Recently, interaction of eosinophils with fibroblasts has been described leading to proliferation and matrix production of the latter.[234] This suggests a role of IL-5 in remodeling and wound healing. Furthermore, there is some evidence that IL-5 links innate and adaptive immunity not only in terms of wound healing, but also in terms of IgM-mediated suppression of atherosclerotic plaque formation.[235]

IL-5–producing ILCs play a role in tumor surveillance through lung eosinophils and may contribute to development of novel immunotherapies for cancer.[229]

Tregs (CD4+CD25+) cultured with IL-4 and an autoantigen express Il-5rα. Treatment of experimental autoimmune neuritis with IL-5 markedly reduced clinical paralysis, weight loss, demyelination, and infiltration of CD4+ (Th1, Th17) and CD8+ T cells, as well as macrophages in nerves. Clinical improvement was associated with expansion of Tregs (CD4+CD25+FOXP3+) that expressed Il-5rα and proliferated only in response to specific autoantigen, that was further enhanced by IL-5.[230]

A potentially protective role for IL-5 in sepsis have been suggested; however, the loss of eosinophils in this disease presents a paradox. The protective effects of IL-5 were confirmed in humans, where IL-5 levels were elevated in patients with sepsis. Moreover, neutrophils and monocytes from patients expressed the IL-5 receptor. These data support a novel role for IL-5 on noneosinophilic myeloid populations, and suggest treatment with IL-5 may be a viable therapy for sepsis.[231]

Role in allergic disease and other pathologic conditions

IL-5 and its receptor drive allergic and inflammatory immune responses characterizing numerous diseases, such as asthma, atopic dermatitis, chronic obstructive pulmonary disease, eosinophilic gastrointestinal diseases, hyper-eosinophilic syndrome, Churg-Strauss syndrome and eosinophilic nasal polyposis.[236] IL-5 plays a central role in allergic asthma. Th2 cells, which secrete IL-5 recruit eosinophils and contribute to the induction of airway hyperreactivity. Recruitment of eosinophils in the lung is a key feature of asthma.[237] IL-5 levels, Th2 cells and eosinophils are increased in BAL and in biopsies of asthmatics. Moreover, IL-5 levels correlate with severity of the disease.[238] The IL-5Rα is already expressed in CD34+ cells. This particular subset increases upon allergen challenge and ultimately increases the number of mature eosinophils in the periphery.[239] Pulmonary ILC2s significantly contribute to production of the key cytokines IL-5 and IL-13 in experimental model of allergic asthma. In naive mice, lineage-marker negative ILC2s expressing IL-7Rα, CD25, Sca-1, and T1/ST2 (IL-33R) were present in lungs and mediastinal lymph nodes (MedLNs), but not in broncho-alveolar lavage (BAL) fluid.[228]

Toll-like receptor (TLR) 7 expression and antiviral responses can be negatively regulated by IL-5-induced airways eosinophilia. Targeting eosinophils could be an effective therapeutic approach for the prevention of asthma exacerbations. [240]

IL-5 and IL-17A are crucial for the maintenance of the specific-IgE secreting B cell function.[241] In experimental models, anti-IL-5 treatment suggested to be an effective treatment. The treatment of asthma with anti-IL-5 antibodies (mepolizumab, reslizumab) reduced blood eosinophilia and sputum eosinophils, but little or no effects on asthma symptoms were observed in the initial clinical trials.[242-244] However, recent studies reported significant reductions in exacerbation rates in refractory

eosinophilic asthma[245] and steroid dependent asthma with sputum eosinophilia.[246] Reslizumab is a humanized anti-IL-5 mAb that has been used successfully in the treatment of nasal polyps, reducing polyp size in half of patients studied; baseline concentrations of IL-5 in nasal secretions were predictive of response to reslizumab.[236]

Benralizumab (formerly MEDI-563) is a humanized anti-IL-5Rα mAb that binds with high affinity to the alpha chain of the IL-5R to block IL-5 function and induce apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC). By binding to the IL-5R, benralizumab targets the effector cells that are driven by IL-5 (eosinophils/ basophils) rather than the numerous cells that only produce IL-5. The product potently and efficiently depleted peripheral-blood eosinophils and their precursors to less than the limit of detection.[247]

Anti-IL-5 treatment also showed some promising effects in a subgroup of patients that suffer from hypereosinophilic syndrome (HES). Mainly patients with the lymphocytic variant are considered to profit from anti-IL5 therapy. In this subtype of HES expansion of T-cell subsets with aberrant surface marker expression ($CD3^+CD4^-CD8^-$, $CD3^-CD4^+$) secrete eosinophilopoietic cytokines including IL5. A corticosteroid sparing effect was observed over a time period of 36 weeks in patients receiving 750mg mepolizumab every 4th week.[248] In addition, Mepolizumab, Benralizumab and Reslizumab were tested in clinical trials for treatment of hypereosinophilic syndrome,[249] COPD, [250, 251] atopic dermatitis, asthma, [252-254] among others.

Functions as demonstrated in IL-5-deficient mice, receptor-deficient mice and transgenic models

IL-5-deficient mice do not show abnormal development, but they display difficulties to expel *Nippostrongylus brasiliensis* and have reduced numbers of blood and bone marrow cells and eosinophils in the airways and IgA+ cells in the lamina propria, compared with control mice.[255, 256]

Regarding asthma, IL-5-deficient mice show different onsets of the disease. Two different studies used different mice strains and showed that Balb/c mice lacking IL-5 expression failed to develop airway hyperresponsiveness (AHR) after allergen

challenge[256] whereas C57Bl/6 IL-5 deficient mice develop AHR to the same extent as wild type mice do.[257] The same effects seen in Balb/c mice were observed upon treatment with αIL-5 antibodies.[258] In accordance with these findings, topical overexpression of IL-5 resulted in AHR and increased eosinophil counts in the lung.[259] Leitch et al. recently reported that IL-5 over-expression leads to prolonged wound healing most likely due to increased eosinophilic invasion into the wound areas.[260] IL-5 Rα -/- mice display reduced numbers of B-1 cells and consequently low IgM and IgG3 serum concentrations. In addition, *A cantonesis* survived longer in IL-5Rα -/- mice. As expected, there was no eosinophilia in response to IL-5.

IL-6

Alternative names: IFNB2 (Interferon beta 2); B-cell differentiation factor; BSF2 (B-cell stimulatory factor); HSF (hepatocyte stimulatory factor); HGF (hybridoma growth factor)

Discovery and structure

IL-6 was originally discovered as a B-cell differentiation factor [261] with IFNb2 activity. Further investigations revealed that IL-6 does not show any INF activity, but this factor has been demonstrated to be a multifunctional pleiotropic cytokine that regulates immune response, acute phase response, hematopoiesis, and inflammation. The human gene of IL-6 (*IL6*) is located on the short arm of chromosome 7 at position 21 (7p21) [262] [263], the murine IL-6 is located on chromosome 5.[264] Human and murine IL-6 contains five exons and four introns.

IL-6 is a member of the IL-6-type cytokine family, which also includes leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), oncostatin-M (OSM), IL-11, IL-31 and IL-35.[265] IL-6 mRNA spanning a length of 1.3kb is translated into a 212 amino acid precursor protein. After removal of a 28 amino acid signal peptide, IL-6- with two possible N-glycosylation sites (position 73 and 172) is secreted in different molecular masses of 19-26 kDa.[266] As member of the IL-6 cytokines, IL-6 has a helix bundle structure consisting of four long α-helices.

Receptors and signaling

IL-6 signals through a cell- surface signaling complex composed of IL-6, IL-6a-receptor (CD126) and the signal-inducing component gp130 (CD130). IL-6R is a member of a cytokine receptor family characterized by four conserved cysteine residues in the N-termini and a Tryptophan-Serine-X-Trytophan-Serine motif located above the transmembrane domain. First, IL-6 binds to its low- affinity a-receptor unit, an 80kDa glycoprotein. Two forms of the 80kDa receptor are known: the transmembrane form and a soluble form. When IL-6 binds to the transmembrane form containing a short intracytoplasmic region, the signaling receptor unit gp130 is recruited. The IL-6R is also secreted as a soluble form (sIL-6R).[267] Upon binding to IL-6, sIL-6R associates with gp130 to trigger several cellular steps termed "IL-6 *trans*-signaling". It has been shown that the soluble interleukin 6 receptor plays a key role in the regulation of IL-6 responses. Besides IL-6 other cytokines of the IL-6 family such as leukemia inhibitory factor and ciliary neurotrophic factor use signaling through gp130. This explains why these cytokines share many biological activities although the factor themselves are not related to each other.

Gp130 is expressed ubiquitously in tissues [268], whereas the expression of the IL-6a-receptor subunit is limited and predominantly confined to hepatocyte and leukocyte subpopulations. The interaction of IL-6 with its receptor leads to a complex consisting of two IL-6 molecules (homodimer), two IL-6 receptor proteins and two gp130 signaling units. Upon dimerization of gp130, intracytoplasmic JAK tyrosine kinases induce tyrosine phosphorylation and the recruitment of STAT3.[269] The following dimerization and translocation of STAT3 to the nucleus induces gene expression e.g. for acute-phase protein synthesis in hepatocytes. The negative feedback mechanism of this signaling pathway is regulated by the suppressors of cytokine signaling (SOCS) proteins 1 and 3 and the protein inhibitors of activated STATs (PIAS). Recently, it was reported that binding of IL-6 receptor to epidermal growth factor receptor (EGFR) lead rephosphorylation of STAT3, which is not inhibited by SOCS3. EGFR-dependent sustained signal transduction of IL-6 would play crucial role in constituting chronic inflammation and cancer microenvironment.[270]

Cellular sources and targets

IL-6 is produced after stimulation by many different cells: T cells, B cells, granulocytes, smooth muscle cells, eosinophils, chondrocytes, osteoblasts, mast cells, glia cells and keratinocytes. Endothelial cells, fibroblasts and monocytes/macrophages triggered by various stimuli during systemic inflammation are the main source of this cytokine. Monocytes/ macrophages are driven by bacterial lipopolysaccharide, IL-1α, TNF-α, IFN-γ and GM-CSF to produce IL-6 whose release is inhibited by glucocorticoids. Human fibroblasts secrete IL-6 upon stimulation with IL-1α, bacteria/yeast, TNF-α and IFN-α. The main cellular targets are hepatocytes, leukocytes, T cells, B cells and hematopoietic cells.

Role in immune regulation and cellular networks

IL-6 is involved in a broad spectrum of biological activities, in humoral as well as in cellular defense, and acts on various target cells. IL-6 directs leukocyte trafficking and activation. Although studies with IL-6-deficient mice showed that neutrophil accumulation at sites of infection or inflammation is inhibited by IL-6[271], neutrophil clearance and the transition from neutrophil to mononuclear cell recruitment is driven by soluble IL-6R and the following IL-6 trans-signaling. [272] *In vitro* studies demonstrated that IL-6 trans- signaling suppresses the TNF-α or IL-1β induced control of CXCL1, CXCL8 and CXCL1 and increases chemokine secretion of CXCL5,CXCL6, CCL2 and CCL8.[272, 273] Besides the recruitment of neutrophils and mononuclear cells, it is evident that IL-6 regulates T cell infiltration by influencing chemokine secretion (CXCL10, CCL4, CCL5, CCL11 and CCL17) and chemokine receptor (CCR3, CCR4, CCR5 and CXCR3) expression on $CD3^+$ infiltrate. Additionally CD62 ligand, adhesion and the expression of ICAM-1 and VCAM-1 are also regulated by IL-6. IL-6 activation of STAT3 promotes T cell apoptosis.[274] Through the gp130 signaling of IL-6, human monocytes are driven to differentiate into a more macrophage phenotype which is eventually attributed to induction of the M-CSF receptor on monocytes.[275] As mentioned in the beginning, the cytokine IL-6 was first described as IFN-β2 and as B-cell stimulatory factor (BSF-2) stressing the function of IL-6 in the regulation of T cell proliferation and differentiation [276], as well as in the induction of B cells to produce Ig M,G and A.[277-279] Moreover, IL-6 plays an important role in the differentiation of stimulated B cells into plasma cells.[278] It has

also been demonstrated that IL-6 induces cytotoxic T cell differentiation by increasing the IL-2R expression and IL-2 production.[280] [281] IL-6 induces proliferation of thymocytes and is probably involved in the development of thymic T cells. TGF-β stimulates in presence of IL-6 the differentiation of naïve T lymphocytes into proinflammatory Th17 cells leading to autoimmunity and inflammation.[282]. Moreover, IL-6 can convert natural occurring Treg to Th17 cells [283]. Recently, it has been shown that IL-6 promotes NK cell expression of RORgt and IL-17 during toxoplasmosis [284]. Together with TGF-β, IL-6 is also shown to stimulate differentiation of Th22 cells with high IL-22 production [285, 286], and this subset is claimed to have a tissue-protective role [287]. IL-6 can synergize with IL-15 or IL-7 to stimulate TCR-independent proliferation and effector functions of $CD8^+$ T lymphocytes. [288] As a co-stimulant together with IL-3, IL-6 initiates the proliferation of multipotential hematopoietic cells. It has been reported that IL-6 shortens the G0 period of hematopoietic stem cells. Macrophage differentiation and megakaryocyte maturation are driven by IL-6. The cytokine acts efficiently on bone where it affects mainly osteoclastogenesis and bone resorption. It is also involved in the recruitment of mesenchymal vascular cells, neoangionesis *in vivo*, synovial fibroblast proliferation and cartilage degradation.[289] IL-6 is responsible for the initiation of the acute phase response in human hepatocytes.[290] Studies with recombinant IL-6 show an increase in protein synthesis of β-fibrinogen, α-1-antichymotrypsin, ceruloplasmin, haptoglobin, α1-acid glycoprotein, α1-antitrypsin, C-reactive protein, and complement factor B. IL-6 has also a negative inotropic effect on the heart. In neuronal cells, IL-6 induces the differentiation of PC12 cells, supports the survival of cholinergic neurons and leads to the induction of adrenocorticotropic hormone synthesis.

Role in host defense and autoimmunity

Since IL-6 has an important role in the regulation of the immune response, a deregulated production of IL-6 affects the pathogenesis of several autoimmune and inflammatory diseases. The first suggestion that IL-6 contributes to autoimmunity was observed in patients with cardiac myxoma. Cardiac myxoma cells produce IL-6 and the patients exhibit autoimmune symptoms.[291] Further studies indicate the involvement of IL-6 in autoimmune diseases, chronic inflammatory proliferative

disease, B cell malignancy, including systemic lupus erythematosus [292], Castleman's disease, pulmonary fibrosis [293], and plasmacytoma/multiple myeloma.[294] In some countries, humanized anti-IL-6 receptor mAbs (Tocilizumab) have already been approved for treatment of RA [295], Castleman's disease [296], and systemic juvenile idiopathic arthritis[297] treatment. Moreover, Tocilizumab has been tested in clinical trials for potential treatment in acute graft versus host disease, type 1 diabetes mellitus, dermatomyositis, ankylosing spondylitis[298], hemophagocytic lymphohistiocytosis, myocardial infarction and diabetic macular edema.[66] ~~In some countries, anti-IL-6 receptor monoclonal antibody (tocilizumab) have already approved for RA treatment. Further, recent randomized trial revealed that tocilizumab is effective for severe and persistent systemic juvenile idiopathic arthritis~~.[299] Some clinical studies for other autoimmune disorders are undergoing. IL-6 is required for experimentally induced autoimmune diseases such as type II collagen-induced arthritis [300] and antigen-induced arthritis [301], myelin oligodendrocyte protein- induced experimental autoimmune encephalomyelitis [302], and pristine-induced autoantibody production in mouse models.[303] There is some evidence that IL-6 could play a role in diabetes derived from an animal model for insulin-dependent diabetes mellitus. In psoriasis, it has been demonstrated that IL-17F is able to induce IL-6 production in human epidermal keratinocytes and in mouse skin and thus IL-17F/IL-6 axis may enhance inflammation of lesional skin in psoriasis.[304]

Role in allergic disease

IL-6 plays a role in the development of allergic diseases by increasing the number of the effector cells via the sIL-6R on one hand and by suppressing Treg cells and the initial stages of Th2 cell development via gp130 signals mediated by the membrane-bound IL-6R on the other hand. It was demonstrated that allergic patients have increased levels of sIL-6R in airways as compared with control subjects [305], and a recent study revealed that inhibition of IL-6R could be potential therapeutic target of certain type of asthma.[306] A study investigating molecular mechanisms of loss of allergen-specific T-cell unresponsiveness in human subjects reports tolerance breaking effects of IL-6, which is associated with a slight increase of proinflammatory cytokines.[307]

Functions in IL-6-deleted mice and receptor deficient mice

In general, IL-6-/- deficient mice of both sexes are viable and fertile and do not present any evident phenotype abnormality. More in detail, IL-6-/- deficient mice remain resistant to the induction of a number of experimental autoimmune conditions. They are not able to regulate T cell trafficking, which results in an impaired local chemokine secretion and reduced chemokine receptor expression. Mice homozygous for a targeted disruption of IL-6 show a normal development, whereas the number of thymocytes and peripheral T cells is reduced compared to the wild type. In IL-6 deficient mice, abnormalities in acute phase reaction during tissue damage and infection are observed. Gp130 deficient mice embryos die between 12.5 days postcoitum and term. Hypoplastic ventricular myocardium is observed 16.5 days postcoitum and later. The mutant embryos show a decreased number of pluripotential and committed hematopoietic progenitors in the liver and differentiated lineages such as T cells in the thymus.[308] IL-6R deficient mice are viable and fertile, have one third less T cells than wild-type mice, and the production of serum amyloid A is significantly decreased. IL-6-overexpressing transgenic BALB/c mice develop a massive increase of IgG1 and monoclonal transplantable plasmacytoma.[290]

IL-7

Discovery and structure

IL-7, also known as pre-B cell growth factor (PBGF) and lymphopoietin-1 (LP-1), was originally derived from bone marrow stromal cells and described as a mediator that alone could support the growth of B-cell progenitors. [309] It is a monomer of 25 kDa and consists of 152 amino acids. It is a member of the four α-helix bundle cytokine family. These family members are characterized by antiparallel juxtaposed helices A, C, B, D, and two long end-to-end loops, loop AB and CD, which are connected by a short β-sheet packed against helices B and D. [104]

Receptor and signaling

The IL-7R is present on most T cells, on progenitors of B-cells, on bone marrow macrophages and innate lymphoid cells (ILCs). It is down-regulated by its own ligand.

Also soluble IL-7 receptor has been described. [310-314] IL-7R consists of two receptor chains, the IL-7Rα (CD 127) and the common γc (CD 132). Neither of these subunits / signaling elements is unique to IL-7. Whereas γc is also a receptor for IL-4, IL-7, IL-9, IL-15, and IL-21, IL-7Rα is shared with TSLP. Since γc is ubiquitously expressed on lymphocytes, IL-7 responsiveness is mainly controlled by IL-7Rα expression regulation. IL-7 signaling abrogated the suppression capacity of Tregs[315]. IL-7 activate STAT3 preferentially in γδ cells competent to produce IL-17, expanding, activating and promoting their functional responsiveness [316].Binding of IL-7 to IL-7Ra leads to dimerization of IL-7Ra and gc. However thymic stromal lymphopoietin (TSLP) reveals a key difference from IL-7-induced signaling via mediated STAT5 phosphorylation via kinases JAK1 and JAK2[317]. JAK3 associated with the γc phosphorylates IL-7Rα after dimerization. [318] The phosphorylated IL-7Rα serves as the site for recruiting other signaling molecules to the complex to be phosphorylated and activated, including STAT5, src kinases, PI3 kinase, Pyk2 and Bcl2 proteins. Some targets of IL-7 signaling contribute to cellular survival, including Bcl2 and Pyk2. [319] Other targets contribute to cellular proliferation, including PI3 kinase, src family kinases (lck and fyn) and STAT5. [320] NFATc1 and STAT5 is a critical for thymocyte development in response to IL-7 signals [321]. IL-7 supports survival of TCRβ-expressing $CD4^-CD8^-$ double negative thymocytes[322]. The transcription factor STAT5 contributes to activation of multiple different downstream genes in B and T cells and may contribute to VDJ recombination through alteration of chromatin structure. Transcription factor miz-1 is required to regulate interleukin-7 receptor signaling at early commitment stages of B cell differentiation [323]. IL-7-mediated suppression of premature Ig light-chain rearrangement is the most definitive function [324]. IL-7 signaling phosphorylates STAT5 and ERK; induces Foxo1, Klf2, and S1pr1; and supports the differentiation of classic $CD8^+$ T cells[325]. Growth factor independent-1 (Gfi1) that is inhibitory target of dexamethasone, is a novel intermediary in glucocorticoid-induced IL-7Rα up-regulation. Gfi1 is the specific transcriptional repressor of the Il7R gene in $CD8^+$ T lymphocytes[326].

Cellular sources and targets

IL-7 is a tissue-derived cytokine. It is produced by multiple stromal tissues including epithelial cells in thymus and bone marrow. Additional sites of IL-7 production include intestinal epithelium, keratinocytes, fetal liver, adult liver, DCs, follicular DCs, B-cells and monocytes/macrophages. [327] However, it has to be mentioned that the primary sources of IL-7 are non-marrow-derived stromal and epithelial cells. Target cells of IL-7 are developing B and T lymphocytes, mature T cells, NK cells and ILCs.

Role in immune regulation and cellular networks

IL-7 stimulates the proliferation of pre-B and pro-B-cells in mice (inhibited by TGF-β) without affecting their differentiation and with no effect on mature B cells. It promotes V(D)J recombinations, and selectively supports the maturation of megakaryocytes. Furthermore, IL-7 is required for the survival of naïve T cell populations, and contributes to homeostatic cycling of naïve and memory cells. It stimulates the proliferation of thymocytes and is therefore an important differentiation factor for functionally different subpopulation of T-cells.[328] IL-7 is required for the development and maintenance of ILCs.[329] In addition, IL-7 induces the synthesis of inflammatory mediators in monocytes. [327]

Role in host defense or other immune regulatory conditions

IL-7 and its receptor are linked to the development of multiple sclerosis and other autoimmune diseases[330-333] and its expression is increased in the skin of psoriatic plaques and after *Schistosoma mansoni* infection. [334] IL-7 is capable *in vivo* to cause CD4+ T-cell dependent destruction of tumor cells and shows a potential contribution to allergen-induced eosinophilic airway inflammation in asthma. [335] T-bet suppress the expression of IL-7R. Blockade of IL-7R signaling reduced severity of $Tbx21^{-/-}$ $Rag2^{-/-}$ ulcerative colitis mice in TRUC disease [336]. IL-7 receptor blockade reverses autoimmune diabetes by promoting inhibition of effector/memory T cells[337-340]. IL-7 treatment influenced the number of virus-specific T cells, viral load and expedited viral control in mice undergoing a chronic LCMV infection[341]. IL-7 treatment holds great promise for controlling chronic viral infections via SOC3 pathways [342, 343].

Functions as demonstrated in IL-7-deleted mice, receptor-deficient mice, human mutations and the clinical use

There are several IL-7 and IL-7Rα knock out models.[344-348] Phenotypic differences between these models may be attributed to TSLP, since this cytokine also binds to IL-7Rα. However, both IL-7 and IL-7Rα KO mice showed that IL-7 is important for proper T and B cell development.[345, 347]

IL-7-deficient mice were the first example of single cytokine-deficient mice that exhibit severe lymphoid abnormalities. IL-7 deficient mice are highly lymphopenic in the peripheral blood and lymphoid organs. Bone marrow B lymphopoiesis is blocked at the transition from pro-B to pre-B cells. Splenic B cells are also reduced in number like tymic and splenic T cellularity and showed an abnormal population of immature B cells in adult animals. The remaining splenic populations of lymphocytes showed normal responsiveness to mitogenic stimuli. [345]

IL-7Rα KO mice displayed a profound reduction in thymic and peripheral lymphoid cellularity and analyses of lymphoid progenitors revealed a critical role of IL-7R during early lymphoid development. This study indicated that the phase of thymocyte expansion occurring before the onset of T cell receptor gene rearrangement is critically dependent upon, and mediated by the high affinity receptor for IL-7. [347, 346] IL-7R conditinal knockout mice displayed marked reduction in CD8 single positive Tcells, regulatory T cells, and natural killer T cells in thymus. And those mice also displayed increase in B cells, γδ T and dendritic cells in thymus. This study indicated that IL-7Rα differentially controls development and maturation of thymocyte subpopulations in late developmental stages.[349]

Transgenic over-expression of IL-7 results in T cells expansion[350], which is not only based on increased survival, as transgenic expression of Bcl-2 (which is induced by IL-7) does not compensate for IL-7.[351]

It has also to be mentioned here that transgenic expression or injection of IL-7 augments the expansion of early B cells in vivo[352-355] and pheontypes from transgenic mouse expressing IL-7 under different promoters, show range from benign increase in T and B cells to lymphoproliferative disorders particularly in the skin.[356-358]

Humans with a mutation in the common γc (as mentioned above this includes defect signaling of IL-2, -4, -7, -9, -15, -21) suffer from X-linked severe combined immunodeficiency (XSCID) 1, a disease characterized by the absence of T and NK

cells but the presence of nonfunctional B cells. Polymorphisms in IL-7R have been shown be a risk factor for a number of diseases that are autoimmune or involve excess immune and inflammatory responses including multiple sclerosis, type 1 diabetes, rheumatoid arthritis, primary biliary cirrhosis, inflammatory bowel disease, atopic dermatitis, inhalation allergy, sarcoidosis and graft-versus host disease [324, 359]

Also SCID patients with defective IL-7Rα expression have been identified. They showed a T(-)B(+)NK(-) form of SCID which underlines the non-redundant role of human IL-7Rα for T-cell but not B-cell development.[360]

Clinical use

IL-7 has a potential for adoptive immunotherapy (form of immunotherapy used in the treatment of cancer in which an individual's own white blood cells are coupled with a naturally produced growth factor to enhance their cancer-fighting capacity) since IL-7 is capable *in vivo* to cause CD4+ T-cell dependent destruction of tumor cells. Furthermore, similar to IL-2, it has potential to induce cytotoxic T-cells in lung metastases of murine sarcomas. It has additionally been shown to induce LAK (lymphokine-activated killer) cells activity obtained from patients early after bone marrow transplantation. [361] In fact, recombinant human IL-7 (also known as CYT107) was tested for potential treatment of cancer, HIV infection,[362] sepsis and lymphopenia as well as for improving recovery after allogenic stem cell transplantation. [66, 363]

IL-8

Discovery and structure

In 1987 a neutrophil-specific chemotactic factor was purified from the medium of lipopolysaccharide-stimulated monocytes,[**364**] which was later identified as a member of the CXC chemokine family and termed CXCL8 or IL-8. The gene encoding IL-8 consists of 4 exons and 3 introns and is located together with other ten members of the CXC chemokine family in a gene cluster on the long arm of chromosome 4.[**365**] The IL-8 promoter contains binding sites for the transcription factors NF kappa B (-80 to-71) and AP-1 (-123 to -12).

IL-8 is generated as a nonglycosylated precursor protein of 99 amino acids and secreted after cleavage of a 22 amino acid leader sequence. Enzymatic processing at the N-terminus results in multiple isoforms: monocytes mainly produce a 72 amino acid isoform with a molecular weight of 8.3 kDa and small amounts of the 77 amino acid, 70 amino acid, and 69 amino acid isoforms. In contrast, the 77 amino acid isoform is the major product of endothelial cells. IL-8 forms a homodimer in solution and the crystal structure reveals two anti-parallel helices situated on top of a six-stranded antiparallel beta-sheet, formed by both monomer units.[366, 367] Two disulfide bridges between cysteine 7 and 34 and between cysteine 9 and 50 are essential for the biological activity of IL-8. The conserved cysteines 7 and 9 define the family of CXC chemokines. The N-terminus of IL-8 and the majority of the other CXC chemokines bears the three amino acid residues Glu-Leu-Arg (ELR-motif), which are indispensable for receptor binding. IL-8 is a basic protein with a ph of 8.3. It was found to be resistant to plasma peptidases, heat, extreme pH, and other denaturing conditions but is rapidly inactivated upon reduction of the disulfide bonds. IL-8 does not show any homology with other interleukins, however, it shares considerable similarity with other CXC chemokines such as platelet basic protein (CXCL7), interferon gamma-inducible protein-10 (CXCL10) or platelet factor 4 (CXCL4).[368]

Receptor and signaling

IL-8 acts via two related receptors, IL-8 RA (CXCR1, CDw128a), whose 3D structure in the lipid bilayer has been recently shown[369], and IL-8 RB (CXCR2, CDw128b), both expressed in neutrophils, monocytes, lymphocytes, NK cells, and mast cells.[370, 371] Both receptors belong to the same superfamily of CXC chemokine receptors, characterized by seven transmembrane domains and signal transduction through G-protein-activated pathways, where CXCR1 predominantly couples to GRK2 and CXCR2 interacts with GRK6 [372]. CXCR1 and CXCR2 are able to form homo- and heterodimers during protein synthesis and maturation in the endoplasmatic reticulum prior to cell surface delivery. The presence of IL-8 does not influence receptor dimerization and the affinity of CXCR1 and CXCR2 dimers for IL-8 are similar to those of the corresponding homomeric interactions.[373] Upon contact of neutrophils with bacterial LPS, *Staphylococcus aureus*, or *Helicobacter pylori* CXCR1

and CXCR2 are rapidly downregulated by receptor internalization and degradation, a mechanism exploited by invading pathogens to modulate host's immune response. The internalization and recovery kinetics differs between the two receptors. CXCR1 internalize slowly but recovers rapidly, while CXCR2 internalize rapidly but recovers slowly.[372, 374-376]

Receptor-binding of IL-8 leads to activation of the coupled G-protein by the replacement of bound GDP with GTP. Subsequently the trimeric G-protein dissociates into alpha and beta-gamma subunits, both of which activate signal transduction pathways:

First, activated phosphoinositide 3 (PI3) kinase generates phosphatidyl-inositol (3,4,5) triphosphate, which leads to the activation of phospholipase D (PLD). Hydrolysis of phosphatidyl choline by PLD results in the accumulation of phosphatidic acid, actin reorganization and finally cell movement. Second, binding of IL-8 to CXCR1 or CXCR2 activates phospholipase C (PLC),[377] which cleaves phosphatidyl inositol (4,5) bisphosphate to inositol (1,4,5) trisphosphate (IP3) and diacylglycerol. IP3 increases cytosolic Ca2+, while diacylglycerol together with Ca2+ leads to the activation of protein kinase C (PKC) and the transcription factor NF kappa B. Third, CXCR1 and CXCR2 ligands were found to activate p38 MAPK.[378] Subsequently p38 is able to translocate into the nucleus and to induce the transcription factor AP-1.

Cellular sources and targets

A wide variety of different cells, such as monocytes and macrophages, neutrophils, lymphocytes, endothelial and epithelial cells, fibroblasts, keratinocytes, synovial cells, chondrocytes, hepatocytes, smooth muscle and skeletal muscle cells as well as several tumor cell types produce IL-8.[379-383] IL-8 synthesis is usually induced upon stimulation with IL-1 alpha, IL-1 beta, TNF alpha, or bacterial LPS, but also retinoic acid, zinc, nitric oxide, irradiation. Viral, Gram negative or positive bacterial infections were also found to induce its expression. Recent work has highlighted the diversity of stimuli that can lead to IL-8 expression, C5a during sepsis, prostaglandin E2, dopaminergic agonists, angiopoietin 1 (but not angiopoietin-2) in neutrophils, mechanical stress in joints in the mouse represent some recently discovered IL-8 inducers [384-388]. Compared to other cytokines IL-8 transcription is a

rapid process; IL-8 mRNA can be detected by Northern Blot within 1 hour after stimulation of the cells, a maximum of expression is reached after 6 hours and persists for further 6 hours. Pre-stored IL-8 was observed in intracellular granules, in Weibel-Palade bodies of microvascular endothelial cells.[389] Degranulation can be triggered by advanced glycation end products, in this context IL-8 triggered a series of effects leading to apoptosis and cell death.[390]

Role in immune regulation and cellular networks

The regulation of IL-8 transcription seems to depend on the stimulus, its receptor and the cell type. In human monocytes and bronchial epithelial cells TNF alpha and LPS activate the MAP kinases JNK, ERK, and p38. JNK in turn activates the transcription factor NF-kappa B, which induces IL-8 expression. ERK was found to enhance IL-8 transcription via the transcription factor AP-1, while p38 regulates the IL-8 synthesis on a posttranscriptional level by stabilizing the IL-8 transcript.[391, 392] In addition stimulation of bronchial and colonic epithelial cells with lysophosphatidic acid activated protein kinase C and protein kinase delta 2, leading to the induction of NF kappa B and IL-8 transcription.[393, 394] The major effector function of IL-8 is the recruitment of neutrophils to the site of infection or injury.[368] The neutrophil accumulation is rapid and reaches a maximum after 30 minutes, continues up to 6 hours, and remains detectable up to at least 8 hours[395]. Glycosaminoglycans (GAG) have been shown to play an important role in the creation of a chemotactic gradient, GAG were shown to increase the local concentration of IL-8 and to be responsible for its oligomerization and prolonged stability. [396] IL-8 also stimulates neutrophils to degranulate and release lysosomal enzymes and antimicrobial peptides and to express adhesion molecules such as LFA-1 and CD11b, moreover it activates them to generate respiratory burst responses by the formation of toxic oxygen-derived products, an effect that is enhanced by GAG.

Beside neutrophils, IL-8 attracts NK cells, T cells, basophils, and GM-CSF or IL-3 primed eosinophils.[397] In the presence of IL-3 IL-8 activates basophils to release leukotrienes and histamine. Thus, IL-8 plays an important role in the innate immunity, providing a first line of defense against invading pathogens.

In addition to its chemokine function IL-8 stimulates the release of hematopoietic progenitor cells from the bone marrow into the peripheral blood.[398] Activated neutrophils rapidly secrete pre-stored metalloproteinases, leading to the cleavage of extracellular matrix molecules to which hematopoietic stem cells are attached.[399]

CXC chemokines containing the ELR-motif, like IL-8, are potent promoters of angiogenesis under physiologic and pathophysiologic conditions. In contrast members of the CXC chemokine family that lack the ELR-motif and that are inducible by IFN gamma, like platelet factor 4, inhibit angiogenesis and bind to CXCR3 on the epithelium.[400] IL-8 is highly expressed by endothelial cells upon stimulation with vascular endothelial cell growth factor (VEGF), by cancer cells and infiltrating macrophages. It is supposed to mediate its angiogenic activity in an autocrine and paracrine manner via binding and activating CXCR2 on endothelial cells.[401] Enhanced survival and proliferation of endothelial cells leads to the growth of new blood and lymphatic vessels. In cancer cells IL-8 induces the production of metallo-, serine and cysteine proteinases, which degrade extracellular matrix and basement membrane, leading to reduced cellular adherence, and the migration of tumor cells into the circulation. The levels of IL-8 mRNA were found to correlate directly with intratumor microvessel counts, with the metastatic potential, and inversely with patient survival. [402-404]

Role in allergic diseases and other pathologic conditions

There is no direct importance of IL-8 described in Th2-mediated allergic diseases. However, repeated injections of IL-8 lead to neutrophil accumulation in the lung and joints, resulting in pulmonary inflammation and cartilage damage. In line with these studies in rabbits, elevated IL-8 concentrations were detected in various inflammatory sites in human diseases, such as psoriatic lesions, synovial fluids of rheumatoid arthritis patients, or in BAL of patients with acute respiratory distress syndrome, respiratory syncytical virus (RSV) infection, COPD and cystic fibrosis.[405-408] In contrast to other chemoattractants, such as C5a or leukotriene B4 that act transiently and are rapidly inactivated by oxidation or hydrolysis, IL-8 shows resistance to inactivation and slow clearance, leading to excessive accumulation of immune cells and negative effects on the outcome of the disease. For instance, in patients suffering from

rheumatoid arthritis IL-8 is released by synovial cells and chondrocytes in elevated concentrations, compared to healthy controls. Accumulated neutrophils are considered to be the major source of cartilage-degrading enzymes in this disease. During *Helicobacter pylori*-infection the expression of IL-8 is enhanced in the gastric mucosa and correlates with bacterial load, chronic inflammation and disease activity.[409] The IL-8 promoter polymorphism -251A/A is associated with a higher expression of IL-8, severe neutrophil infiltrations and an increased risk of atrophic gastritis and gastric cancer.[410] Thus, anti-IL-8 monoclonal antibodies are suggested as therapeutic intervention for distinct inflammatory diseases. It should be noted, that full human mAbs targeting IL-8 (also known as HuMax-IL-8 or ABX-IL-8) were tested in clinical trials for potential treatment of pustulosis palmoplantaris,[411] cancer,[412] chronic bronchitis and COPD.[66]

In the last few years many studies have appeared, investigating the role of IL-8 and other cytokines in periimplantic disease. Although the cytokines levels are increased in patients with periimplantic diseases, there is controversy on their effects and their usefulness as biomarkers.[413]

The IL-8 receptor has recently been identified as a binding site for the HIV-1 protein p17 on monocytes. Binding of p17 to CXCR1 triggered IL-8-like activities that have been shown to enhance HIV-1 pathogenesis.[414]

Human tumor cells exploit IL-8 to promote angiogenesis, proliferation, migration, inflammation and chemoresistance[415]. More recent data showed that IL-8 could enhance chondrosarcoma cells migration by increasing the expression of αvβ integrin[416] and that, through IL-8, tumors could retain human DCs *in vivo* without affecting their ability to stimulate T-cells[417]. The mechanism leading to the increased IL-8 production is still poorly understood, a role of the Epidermal Growth Factor (EGF)-EGFR-PI3K-Akt-Erk pathway has been recently observed in lung cancer cells[418] The importance of IL-8 in cancer is highlighted by the correlation of serum IL-8 levels with lung cancer risk, several years before diagnosis.[419] In acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) IL-8-CXCR2 pathway has a critical role. Inhibition of this pathway could be a potential therapeutical approach against the cancer-initiating cells.[420]

Functions as demonstrated in IL-8-receptor deficient mice

IL-8-receptor KO mice show a dysfunctional neutrophil response. Although neutrophils from IL-8R-deficient mice demonstrate normal rolling and arrest, their migration across the epithelial barrier is reduced, leading to neutrophil accumulation in the tissue and impaired bacterial clearance.[421, 422]

IL-9

Discovery and structure

IL-9 has first been described in mice as a potent, antigen-independent T cell growth factor.[423] Subsequently, more activities on various cell types such as mast cells, B cells, eosinophils, neutrophils, and airway epithelial cells have been demonstrated.[424] IL-9 is a monomer of 14 kDa and consists of 125 amino acids. It is a member of the four α-helix bundle cytokine family. These family members are characterized by antiparallel juxtaposed helices A, C, B, D, and two long end-to-end loops, loop AB and CD, which are connected by a short β-sheet packed against helices B and D.[104] Whereas the murine IL-9 is active on human cells, the human IL-9 has not been shown to be active on mouse cells. [425]

Receptor and signaling

The IL-9R consists of two receptor chains, the ligand specific α chain IL-9Rα and the common γc (CD132), which is also present in the receptor complexes for IL-2, IL-4, IL-7, IL-15, and IL-21. The IL-9 specific α chain is sufficient to bind IL-9 with high affinity, but it is not able to mediate alone any signal, γc is necessary for signal transduction. IL-9R activation results in phosphorylation of Janus kinase (JAK) 1 and JAK 3, which subsequent leads to the activation of signal transducer and activator or transcription (STAT)1, STAT 3, and STAT 5, IRS-PI3 kinase and MAP kinase pathways. IL-9 also seems to regulate nuclear factor-kB (NF-kB) activity through B-cell CLL/lymphoma 3 (BCL3) gene induction that encodes a protein with close homology to IkB (inhibitor of kB) proteins. [426-429] The transcription factors NFAT and NF-kB are also required for the induction of IL-9 after stimulation of antigen receptors.[430] However, there is another signaling pathway that specifically induces IL-

9 confirmed recently. Engagement of OX40 (CD134, a member of TNF receptor superfamily) on T cells increases expression of the transcription factor TRAF6, activates the NF-kB pathway and induces the production of IL-9. [431]

Cellular sources and targets

The main sources of IL-9 are Th2 cells and the recently discovered Th9 cells. [432, 433] To a lesser extend also mast cells (mainly within the airways of asthmatic patients) and eosinophils have been shown to secrete IL-9. Other Th subsets also appear to have the potential for IL-9 production, such as Th17 cells and Treg cells.[434-438] In addition, in a papain-induced airway inflammation model, innate lymphoid cells (ILCs) are approved to be the main source of IL-9 in vivo.[439] Target cells for IL-9 include B, T and mast cells. [440] Beyond those cells, IL-9 may affect other cells, such as hematopoietic cells, airway epithelial cells airway smooth muscle cells and intestinal epithelial cells. [441, 442] For the induction of IL-9, a cascade of cytokines are involved. IL-2 is required for IL-4 production, IL-2 and IL-4 are required for IL-10 production and IL-4 and IL-10 are required for the IL-9 induction. It was shown that TGF-β governs effector T-cell differentiation along a new pathway. [432, 433] TGF-β in the presence of IL-4 reprograms Th2 cell differentiation and leads to the development of a new population of Th9 cells that produce IL-9 and IL-10. [433] In other words, IL-4 blocks the generation of TGF-β–induced $FOXP3^+$ Treg cells and instead induces Th9 cells. [432, 443]. In this pathway, two transcription factors, *PU.1*, downstream of TGF-β signals, and IFN regulatory factor 4 (*IRF4*) are required for the development of IL-9 secreting cells.[444-446] IRF4 is essential for the Smad2/3-mediated *IL9* promoter activation and plays an important role in regulating allergic immune responses by inducing Th9 cells.[447] In addition, other cytokines, such as IL-25, can also enhance IL-9 production by Th9 cells and promote IL-9 production in vivo.[448, 449] The TH9 subset of helper T cells was initially shown to contribute to the induction of autoimmune and allergic diseases, but subsequent evidence has suggested that these cells also exert antitumor activities. It was recently shown that the transcription factor IRF1 is essential in IL-21-dependent anticancer functions of TH9 cells. [450]

Role in immune regulation and cellular networks

IL-9 is a multifunctional cytokine. It is a potent growth factor for T cells and mast cells, promotes proliferation of $CD8^+$ T cells and inhibits cytokine production of Th1 cells. [451, 424] IL-9 is involved in Th2 inflammatory reactions, promotes the production of IL-4 – induced IgE, induces chemokine and mucus secretion by bronchial epithelial cells, and leads to mast cell proliferation. [452, 453]

Role in host defense or other immune regulatory conditions

IL-9 is important in the protection against helminth infections. Furthermore, in Hodgkin lymphoma, IL-9 is believed to stimulate and activate the infiltrating Th2 cells and it has been identified as an autocrine growth factor for Hodgkin and Reed-Sternberg cells. [454, 455] IL-9 in the tumor bed contributes to its anticancer functions.[456] Although IL-9 is involved in what are classically thought to be Th2 responses, there are conflicting data on how it may be involved in autoimmune inflammation, such as EAE (anti-inflammatory or pro inflammatory role).[434, 436, 438, 457]

Role in allergic disease

IL-9 is important for the inflammatory responses in asthma, atopic dermatitis, contact dermatitis and allergy.[458 459] It plays a key role in the development of the asthmatic phenotype, including eosinophilic inflammation, bronchial hyperresponsiveness, elevated IgE levels, and increased mucus secretion.[460, 461] IL-9 has been shown to act on many cell types involved in asthma, including T cells, B cells, mast cells, eosinophils, neutrophils, and epithelial cells, and thus might be important in the pathophysiology of allergic asthma.[462-464]. Moreover, stimulation of OX40 in vivo results in IL-9-dependent allergic lung inflammation. [431] In addition, epithelial cell derived cytokine, TSLP, acts on both human and mouse $CD4^+$ T cells to promote Th9 differentiation and function. [465] Interestingly, humanized mAbs specific for IL-9 (MEDI-528) were tested in clinical trials for asthma treatment. [466] Furthermore, IL-9 has been suggested to play a role in food allergy.[467] For example, IL-9 might be a useful biomarker to distinguish between children with peanut allergy and children with peanut sensitization.[468]

Functions as demonstrated in IL-9-deleted mice, receptor-deficient mice, human mutations and the clinical use

Knock-out / transgenic mice

In IL-9$^{-/-}$ mice the lymphoid compartment develops normally, but these mice exhibit excessive mucus production and mast cell proliferation.[469] In a quadruple IL-4/5/9/13$^{-/-}$ model complete inhibition of allergic airway inflammation and remodelling has been shown [205]. However, systemic anaphylaxis occurred in IL-9$^{-/-}$ and IL-9R$^{-/-}$ mice, suggesting that IL-9 is not absolutely required for anaphylaxis.[470, 471] In contrast, deficiency in IL-9 or IL-9R attenuates intestinal anaphylaxis.[471]

7% of transgenic mice overexpressing IL-9 developed thymic lymphomas in a model published by Renauld in 1994.[472] In an other transgenic model, where IL-9 was selectively overexpressed in the lung, it could been shown that IL-9 is an important cytokine in asthma since these mice developed many features that resembled human asthma, including eosinophilic and lymphocytic infiltration of the lung, mucus hypersecretion, sub-epithelial fibrosis, mast cell hyperplasia and bronchial hyperresponsiveness.[460, 461] Transgenic expression of IL-9 in the intestine results in local mastocytosis and increased susceptibility to intestinal anaphylaxis.[471, 473]

Human mutations

Humans with a mutation in the common γc (as mentioned above this includes defect signaling of IL-2, -4, -7, -9, -15, -21) suffer from X-linked severe combined immunodeficiency (XSCID) 1, a disease characterized by the absence of T and NK cells but the presence of nonfunctional B cells. IL-9 polymorphisms are also linked to sex-restricted differences in lung function, allergen sensitization, IgE levels, and the severity of respiratory syncytial virus infection.[474, 475]

Clinical use

IL-9 is expressed on Reed-Sternberg cells and Hodgkin lymphoma cells and some large aplastic lymphoma cells, while non-Hodgkin lymphomas and peripheral T cell lymphomas do not express IL-9. It has also been shown as an autocrine growth modulator for Hodgkin's cell lines. In addition, diffuse large B-cell lymphoma which is the most common type of non-Hodgkin lymphoma overexpress IL-9R.[476] Furthermore, IL-9 is predominantly involved in the pathogenesis of ulcerative colitis (UC) suggesting that targeting IL-9 might become a therapeutic option for patients with UC.[477] Therefore the use of anti-IL-9 may play a role in the future in the

treatment of Hodgkin's disease and large cell anaplastic lymphomas. Because of the presence of IL-9 in allergic inflammation, blocking Abs to IL-9 are being developed as a therapy for atopic disease [478] and, as mentioned above, are now are now in clinical trials for the treatment of asthma. [466]

IL-10

Discovery and structure

IL-10 was first described in 1989 as cytokine-synthesis inhibitory factor (CSIF), a Th2-derived factor inhibiting the production of IFN-γ and other cytokines in murine Th1 cells.[479] However, in the human system IL-10 production is not a typical feature of Th2 cells as both Th1 and Th2 cells are capable of producing IL-10, whereas the main source of T cell derived IL-10 are Treg cells.

The *IL-10* gene maps to chromosome 1 both in the human (1q31-32) and murine genome.[480] Its structure is highly conserved and consists of five exons and four introns, a trait that is shared by most *IL-10* homologs. Human IL-10 has a molecular weight of 18 kDa and is secreted as a homodimer consisting of two subunits of 178 amino acids long.[481, 482] The IL-10 protein contains four conserved cysteine residues in its mature protein sequence and forms six α-helices (A-F) in its tertiary structure.[482] The first exon encodes the signal sequence and the A helix, the second exon encodes the AB loop and B helix, the third exon encodes the C and D helices, the fourth exon encodes the DE loop and E helix and the fifth exon 5 encodes the F helix, the COOH tail and an untranslated sequence that plays a role in mRNA stability.[483]

Receptor and signaling

IL-10 binds to a tetrameric receptor complex belonging to the interferon receptor family that is composed of two IL-10R1 chains and two IL-10R2 chains.[484] The IL-10R1 chain is expressed on T cells, B cells, NK cells, monocytes, mast cells and DCs whereas the IL-10R2 chain is ubiquitously expressed.[485] IL-10 can bind to the IL-10R1 chain with high affinity (K_d 50-200 pM) whereas it does not directly interact with the IL-10R2 chain.[486] Murine IL-10 binds both human and murine IL-10R1 while human IL-10 only binds to the human IL-10R1. Despite the fact that the IL-10R2

chain does not directly bind IL-10 and does not provide STAT3 docking sites, it is essential for IL-10-mediated signal transduction as was demonstrated using an *il-10r2*$^{-/-}$ mouse model. These animals developed a phenotype similar to IL-10$^{-/-}$ mice and *stat3*$^{-/-}$ mice, which is mainly characterized by the development of chronic colitis.[487]

The IL-10R1 chain is associated with Jak1 whereas the IL-10R2 chain is associated with Tyk2. The IL-10 receptor complex signals via activation of Jak1 and Tyk2 followed by phosphorylation of STAT1, STAT3 and STAT5.[488, 489] Binding of IL-10 to the extracellular domain of IL-10R1 initiates the activation of Jak1 and Tyk2, which in turn phosphorylate the tyrosine residues Y427 and Y477 or Y446 and Y496 in the murine and human IL-10R1 intracellular domains respectively.[490] These phosphorylated tyrosine residues and their flanking peptide sequences provide docking sites for STAT3 but not STAT1 and STAT5 (these STATS may be activated by IL-10 binding in a different manner). STAT3 docks to the IL-10R1 chain through its SH2 domain and is subsequently phosphorylated and released after which STAT3 either homodimerizes or forms heterodimers with STAT1 or STAT5.[490] These STAT dimers translocate to the nucleus where they bind to STAT-binding elements in the promoter regions of IL-10-responsive genes and initiate gene transcription. STAT3 was shown to be essential for all known aspects of the anti-inflammatory effects of IL-10 as was demonstrated by a mouse model with a targeted deletion of *stat3* in neutrophils and macrophages. In these animals the suppressive effects of IL-10 on the production of inflammatory cytokines were completely abolished, they were highly susceptible to endotoxic shock and developed chronic enterocolitis.[491]

IL-10 receptor-associated tyrosine kinase Tyk-2 acts as a constitutive reservoir for SHP-1 in resting T cells, and then tyrosine phosphorylates SHP-1 on IL-10 binding.[492] SHP-1 rapidly binds to CD28 and ICOS costimulatory receptors and dephosphorylates them within minutes. In consequence, the binding of phosphatidylinositol 3-kinase to either costimulatory receptor no longer occurs, and downstream signalling is inhibited. Accordingly, spleen cells from SHP-1-deficient mice showed increased proliferation with CD28 and ICOS stimulation in comparison with wild-type mice, which was not suppressed by IL-10. Generation of dominant-

negative SHP-1-overexpressing T cells or silencing of the SHP-1 gene by small inhibitory RNA both altered SHP-1 functions and abolished the T-cell suppressive effect of IL-10. The rapid inhibition of the CD28 or ICOS costimulatory pathways by SHP-1 represents a novel mechanism for direct T-cell suppression by IL-10. [492]

Cellular sources and targets

In humans, IL-10 is mainly produced by monocytes, T cells (mainly Treg cells), B cells, macrophages and DCs.[485, 493, 494] Mast cells also produce IL-10 and thereby limit the rate of leukocyte infiltration, inflammation and skin pathology in the context of contact dermatitis or chronic ultraviolet B irradiation.[495] *IL-10* gene expression is controlled by the ubiquitously expressed transcription factors Sp1 and Sp3.[496, 497] Another level of regulation of IL-10 expression results from the presence of multiple copies of mRNA destabilizing motifs present in the 3' untranslated region of the IL-10 mRNA.[497] These findings suggest that in many cells the *IL-10* gene is ubiquitously transcribed whereas the actual production and secretion of the IL-10 protein also depends on posttranscriptional signals.

IL-27 is a potent inducer of IL-10 expression in T cells, a process that is dependent on STAT1 and STAT3. This was demonstrated in *IL-27r1*$^{-/-}$ mice which were unable to generate Th1 cells producing both IFN-γ and IL-10.[498] IL-27 promotes differentiation of T regulatory type 1 (Tr1) cells through induction of c-Maf and AhR which physically interact and transactivate *il10 and il21* promoters.[499] Furthermore expression of the transcriptional repressor Blimp1 is essential for IL-10 production by Treg cells as well as CTLs.[500, 501] In addition, Egr-2 (early growth response gene 2) transcription factor is required for Blimp1 mediated IL-10 production in IL-10 stimulated T cells.[502] The transcription factor E4BP4 acts as a regulator of expression of IL-10 in Th cells. This was demonstrated through the use of E4bp4$^{-/-}$ mice in which IL-10 (as well as IL-13) expression was significantly attenuated in different CD4^{+} T cell subsets.[503]

A negative regulator of IL-10 expression in APCs is the histone deacetylase (HDAC) 11 protein that binds to the distal *IL-10* promoter region thereby inhibiting gene transcription. The mechanism for the inhibition of *IL-10* expression was explained by the formation of more compact chromatin as a result of HDAC11-

mediated deacetylation leading to impaired accessibility of this region for *IL-10*-inducing transcription factors such as STAT3 and Sp1.[504]

Besides the cellular IL-10, several viral IL-10 (vIL-10) homologues have been found in the genomes of herpes-, pox- and cytomegaloviruses, most of which show a high degree of amino acid sequence conservation compared to human IL-10. These vIL-10 homologues bind the same receptor complex (often with much lower affinity)[505] as human IL-10 and induce similar responses. Recent study identifies a novel role for vIL-10 in driving anti-inflammatory M2 monocyte, which may limit virus clearance by restricting proinflammatory and T cell responses at sites of infection.[506] Therefore, viruses expressing homologues of human IL-10 are likely more successful in immune evasion through suppression of the host anti-viral response.

Role in immune regulation and cellular networks

IL-10 is a key regulator of the inflammatory response. Its immunosuppressive effects protect the host from exaggerated inflammatory responses to microbial infections as well as autoimmune diseases. Its primary function is to limit the production of TLR agonist (mainly LPS)-induced cytokines and chemokines in macrophages and DCs. IL-10 inhibits LPS-induced CXCL8 and TNF-α transcript elongation targeting phosphorylated NF-κBp65, a Brd4-docking molecule.[507] IL-10 also directly affects macrophage/monocyte functions by downregulating surface expression of class II MHC molecules and costimulatory molecules CD80/CD86 on these cells.[508] Furthermore IL-10 inhibits the expression of many cytokines including IL-1α, IL-1β, IL-6, IL-10, IL-12, IL-18, GM-CSF, G-CSF and TNF-α, chemokines including MCP1, MCP5, MIP-1α MIP1β, RANTES, IL-8, IP-10 as well as chemokine receptors.[508, 509] IL-10 inhibits cytokine production and proliferation of $CD4^+$ T cells mainly indirectly through its effects on APCs.[508, 509]

Besides the immunosuppressive effect that IL-10 mediates through APCs, several studies have reported direct effects of IL-10 on T cell subsets. IL-10 directly affects T cell cytokine production through suppression of CD28 and inducible T cell costimulator (ICOS).[492] Furthermore Th17 as well as Th1/Th17 cells express high levels of functional IL-10 receptor complexes and IL-10 inhibits proliferation of Th17 cells.[510, 511] On the other hand, IL-10 promotes survival of $Foxp3^+$ Treg cells.[512]

Contrary to its inhibitory effects on many cell types, IL-10 enhances the expression of MHC class II molecules and stimulates the differentiation of murine B cells into antibody secreting cells. Despite this, immunoglobulin levels are normal in *il-10*$^{-/-}$ mice.[513] IL-10 enhances the survival of human B cells as well as their proliferation, differentiation and isotype switching.[514, 515] In human, IL-10–overexpressing B-cell resembles features of Treg cells through surface expression of GARP and CD25 and intracellular SOCS3 and similarly can potently inhibit the antigen-specific T-cell response.[494]

It has been suggested that IL-10 exerts its immune suppressive effects through interference with the NF-κB activation pathway through inhibition of IκB activation as well as inhibition of NF-κB DNA binding activity.[516] However, this direct inhibitory effect of IL-10 on NF-κB activation was later shown to be negligible.[517] On the other hand, an indirect inhibitory effect of IL-10 signalling on the NF-κB pathway was recently demonstrated. The transcriptional repressor ETV3 and the co-repressor strawberry notch homologue 2 were found to be specifically upregulated in mouse and human macrophages by IL-10 but not IL-6 signalling. These factors repressed NF-κB-activated transcriptional reporters, suggesting that they contribute to the downstream anti-inflammatory effects of IL-10.[518]

It appears that the primary mechanism of IL-10-induced anti-inflammatory effects is mediated by the activation of STAT3, which acts indirectly by selectively inhibiting the transcription of specific LPS-induced genes in a manner that requires the synthesis of new proteins. This was demonstrated using a mouse model in which the *Tnf-~ 3' UTR* was replaced by the more stable *Gapdh 3' UTR.* Using this system, it was shown that IL-10-induced reduction of Tnf-α (one of the genes that is selectively inhibited by IL-10) expression was the result of transcription inhibition rather than mRNA degradation or other posttranscriptional modifications.[517]

Another level of immune regulation by IL-10 is through induction or suppression of certain micro RNAs (miR) that affect mRNA stability of pro-inflammatory factors. IL-10 upregulates expression of miR-187 in human monocytes. miR-187 directly targets TNF-α mRNA stability and indirectly suppresses production of IL-6 and IL-12p40 through down-modulation of IκBζ.[519] Interestingly, IL-10 suppresses TLR4-mediated

induction of miR-155 in macrophages. This prevents miR-155-mediated stabilization of TNF and suppression of SHIP1 and SOCS1.[520]

Why IL-10 induces such a broad range of anti-inflammatory effects in a STAT3-dependent manner while other cytokines such as IL-6 that also signal through STAT3 remains largely unknown. However, a clue is provided by the fact that IL-10 induces the expression of SOCS1 and SOCS3 in monocytes.[521] SOCS3 inhibits IL-6 receptor signalling both *in vitro* and *in vivo* by binding to the gp130 subunit of this receptor whereas is does not inhibit IL-10-induced signalling.[522, 523] When the SOCS binding site on the IL-6 receptor is mutated, IL-6 receptor signalling can induce a similar anti-inflammatory response as IL-10.

Role in autoimmunity

IL-10 appears to have a protective role in several autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, diabetes mellitus. Notably, human recombinant IL-10 (Tenovil) and fusion protein consisting of targeting antibody and IL-10 (Dekavil/F8-IL-10) have been tested in clinical trials for treatment of rheumatoid arthritis.[66] In addition, epithelial derived IL-10 is critical for control of intestinal inflammation in inflammatory bowel diseases.[524] A correlation between IL-10 serum levels and the severity of SLE as well as autoantibody levels has been observed and treatment of SLE patients with monoclonal anti-IL-10 antibodies showed an improvement of the disease outcome.[525] Moreover, elevated expression of IL-10 has been associated with several cancers including melanomas and lymphomas.

Role in allergic disease

IL-10 has a protective role in allergic disease. It is constitutively expressed by APCs in the respiratory tract of healthy individuals but its expression is reduced in asthma and allergic rhinitis patients. Furthermore, T cell tolerance induced during specific immunotherapy is the result of increased IL-10 production.[526] Especially, IL-10 producing Tr1 cells play key role in allergen tolerance, and can be induced by allergen-SIT in humans.[526-529]

Tr1 cells are dominant type of T cell subset in healthy individuals. Studies clearly show that, allergen specific Tr1 cells are predominant in healthy individuals to

prevent unwanted immune response to nonpathogenic environmental antigens such as house dust mite, birch pollen, bee venom and food antigens (hazelnut, pear) which lead to allergy.[530, 531] Healthy and allergic individuals display three different allergen specific T cell subtypes as Th1, Th2 and Tr1 in different ratio.[531] The imbalance between Th2 and Tr1 cells and depending the dominant subset may conduce allergy development or recovery. Tolerance to venom allergen is an appropriate model for high dose tolerance to allergens in humans. During beekeeping season repeated exposure of non-allergic healthy beekeepers to bee venom antigens denote an estimable model to apprehend mechanisms of immune tolerance to bee venom allergens.[532] During the exposure to venom allergen, venom specific IL-10 secreting Tr1 cells are clonally differentiated from allergen specific Th1 and Th2 cells. This leads to suppression of allergen specific unwilling immune response by Th1 and Th2 cells. This immunomodulator response persists as long as venom exposure and returns to previous levels within 2-3 months after the end of beekeeping season. Interestingly, histamine receptor 2 also upregulated on specific Th2 cells suppresses allergen stimulated T cells and enhance IL-10 production related to tolerance mechanism. Non-allergic beekeepers have approximately 1000 times higher allergen specific IgG4 versus allergen specific IgE ratio compared to bee venom allergic individuals. [533] Another tolerance model with cat allergen also showed elevated levels of allergen specific IgG4 levels after exposure to high dose cat allergen.[534] This also represents a tolerance to Th2 immune response to specific allergen. Together these outcomes may be concluded as animals in the house induce tolerance and can decrease the risk of asthma. IL-10-secreting Tr1 cells not only suppress Th2 immune responses. Peripheral tolerance achieved multiple mechanisms to overcome and suppress allergic inflammation. Other roles of Tregs are suppression of DCs and by this, enhance the generation of effector or induction of DCs that support the generation of Treg cells,[535-537] suppression of Th1 and Th2 cells,[538] suppression of allergen-specific IgE and induction of IgG4 and/or IgA,[532] suppression of mast cells, basophils and eosinophils,[539] interaction with resident cells and remodelling.[540, 541]

IL-10 plays a protective role in contact hypersensitivity (CHS) as was demonstrated by enhanced T-cell recall responses in IL-$10^{-/-}$ mice and T cell, Treg or Langerhans cell-specific IL-$10^{-/-}$ mice. A recent study showed that IL-10 signalling in DCs plays an essential role to limit the magnitude and duration of CHS reactions. This was demonstrated using a DC-specific IL-$10R^{-/-}$ mouse model in which only T cell reactivation but not sensitization lead to enhanced CHS reactions.[542] One mechanism through which DCs may facilitate immunosuppression in an IL-10-dependent manner was recently published. DCs that were exposed to IL-10 could directly inhibit T cell responses. It was shown that CCL18 is selectively upregulated in IL-10-exposed DCs. CCL18 preferentially recruited regulatory T cells in *in vitro* chemotactic assays and suppressed airway reactivity and lung inflammation in a humanized mouse model of allergy.[543] IL-10-production by Treg cells was shown to be critical for development of tolerance induction in response to low doses of contact allergen (Low zone tolerance or LZT) to allergic contact dermatitis in a mouse model. This was demonstrated by the complete lack of LZT induction after depletion of $Foxp3^{+}$ Treg cells. Using adoptive transfer as well as depletion studies, IL-10 production by Treg cells was shown to be critical for their function in LZT induction. In absence of Treg cells, CD8+CD11c+ DCs in skin draining lymph nodes did not develop tolerogenic functions. This indicates a key role (which required IL-10) for FOXP3+ Treg cells in the induction of tolerogenic $CD8^{+}CD11c^{+}$ DCs during induction of LZT [544] Another study showed that Tr1 cells derived from patients with atopic dermatitis have impaired IL-10 production when treated with corticotropin-releasing hormone (CRH). CRH is a peptide that activates the hypothalamic-pituitary-adrenal axis and induces glucocorticoid synthesis. This finding suggests a disturbed mechanism for termination of inflammatory reactions in patients with atopic dermatitis.[545] However, CRH is also released outside the central nervous system where it has pro-inflammatory effects, through mast cell activation.[546] CRH secreted from mast cells can decrease the ability of Treg cells to produce IL-10, thus further increasing inflammation.[545]

Functions as demonstrated in IL-10-deficient mice, receptor-deficient mice and human mutations

Several animal models have provided insight into the mechanisms of action of IL-10. Mice overexpressing IL-10 under the control of an MHC class II promoter show a defect in αβ-T cell maturation characterized by a rapid thymic aplasia starting directly after birth.[547] Transgenic overexpression of IL-10 under control of a macrophage-specific promoter results in a suppression of systemic cytokine responses in response to LPS challenge as well as impaired clearance of *Mycobacterium bovis* infection compared to normal animals whereas no differences in T and B cell responses were observed.[548] This suggests that macrophage-derived IL-10 mainly acts in an autocrine or paracrine manner. IL-10 knockout mice show normal lymphocyte development and antibody responses, while they grow slower, are anaemic and develop chronic colitis.[513] This demonstrates that IL-10 is essential for the control of normal intestinal immune responses against enteric antigens. Interestingly, A frameshift insertion at nucleotide 3020 (3020insC) in the gene encoding Nod2 is strongly associated with Crohn's disease and impaired IL-10 production. Recently it was shown that this mutant Nod2 protein actively inhibited IL-10 transcription by blocking phosphorylation of heterogeneous nuclear ribonucleoprotein A1 (hnRNP-A1) via p38.[549]

T cell-specific IL-10-deficient mice develop a phenotype that largely resembles that of the complete IL-10-deficient model with the difference that T cell specific IL-10 knockouts are less sensitive to endotoxic shock and irritant responses of the skin. This suggests that, in these situations, IL-10 derived from other sources than T cells is more important.[550]

Many polymorphisms, including SNPs and microsatellites, have been identified in the promoter region of the human IL-10 gene that are associated with altered expression levels of IL-10.[551, 552] Altered IL-10 expression levels as a result of such genetic variations have been linked with several diseases including inflammatory bowel disease, cancer, tuberculosis, allergies and a number of autoimmune disorders.[553-555] Hematopoietic stem cell transplantation has been successfully used to treat IL-10/IL-10R-deficient patients with life-threatening early-onset enterocolitis.[556]

IL-11

Discovery and structure

Human IL-11 is a pleiotropic and redundant cytokine, which interacts with a variety of hematopoietic and non-hematopoietic cell types. It was first isolated from bone marrow derived stromal cells in 1990.[557] The human IL-11 gene consists of five exons and four introns, which are located on the long arm of chromosome 19 (19q13.3-13.4) and on the centromeric region of the chromosome 7 respectively.[558, 559] It encodes a precursor protein consisting of 199 amino acids. After cleavage of a 21 amino acids hydrophobic signal sequence, the mature protein has a molecular weight of 19 kDa, and lacks any cysteines or N-glycosylation sites. It is proline-rich and has a high basic charge (pI=11.3). Although it shows only little sequence homology with other cytokines, its three-dimensional structure is supposed to be similar to that of members of the IL-6 family, which includes IL-6, IL-11, IL-31 leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin-1 (CT-1), ciliary neurotrophic factor (CNTF), and cardiotrophin-like cytokine (CLC).[560, 561] The high helicity of IL-11 together with computer predictions of secondary structure indicate that the molecule has a 4 alpha-helical bundle structure.

Receptor and signaling

IL-11 binds to a heterodimeric receptor, consisting of the specific IL-11Rα and the signal-transducing subunit glycoprotein 130, also known as gp130 or IL6ST.[562] There are two isoforms of human IL-11Rα that differ in the cytoplasmic domain. One isoform, IL-11Rα1 also known as membrane form is a 45 kDa protein consisting of an extracellular region, a transmembrane, and a short cytoplasmic domain. It is a single-pass type I membrane protein. The other isoform, IL-11Rα2, lacks the entire cytoplasmic domain and is secreted as a 42 kDa soluble form.[562] The extracellular part of the IL-11Rα contains three domains similar to those of the IL-6 receptor: an N-terminal Ig-like domain and two fibronectin-type III-like domains, that contain the cytokine receptor-homology region defined by four conserved cysteine residues and a characteristic WSXWS sequence motif. Mutational analysis of the IL-11Rα demonstrated that the third extracellular domain is responsible for ligand binding; the

affinity of this domain for IL-11 was found to be as high as that for the whole receptor.[563] Binding of IL-11 to IL-11Rα occurs at low affinity and is not sufficient for signal transduction, as demonstrated in experiments using IL-11Rα2, which showed that the cytoplasmic domain is not required for the biological effects of IL-11. IL-11/IL-11Rα heterodimer binds with high affinity to receptor gp130 forming a heterotrimer. Gycoprotein 130 belongs to the family of class I cytokine receptors and is the common signal-transducing subunit shared by the members of IL-6 family.[560, 561] Finally, the two heterotrimer complexes associate to form a functional hexameric receptor that mediates the signaling.[564, 565]

The dimerization of gp130 initiates several signal transduction pathways in parallel, including the Janus kinase (JAK) / Signal Transducer and Activator of Transcription (STAT) pathway, the Src homology 2-domain-containing tyrosine phosphatase (SHP-2)/Ras/extracellular signal-regulated kinase (ERK) pathway, the phosphatidylinositol-3-kinase (PI3K)/Akt pathway, or the NF-κB pathway. IL-11 has also been shown to trigger the activation of mitogen-activated protein kinases (MAPK), ribosomal S6 kinases (rsk) as the $pp90^{rsk}$, and Src-family kinases such as $p60^{src}$ and $p62^{yes}$. The involvement of these pathways is cell-type specific.[566]

The signal transduction is attenuated via Protein Inhibitor of Activated STAT (PIAS) proteins, or Suppressors Of Cytokine Signaling (SOCS) family of cytoplasmic proteins.[567, 568]

Cellular sources and targets

IL-11 was originally isolated from cells derived from the hematopoietic microenvironment.[557] IL-11 is produced by a variety of stromal cells including bone marrow cells, fibroblasts, epithelial cells, endothelial cells, vascular smooth muscle cells, synoviocytes, osteoblasts, and several tumor cell lines.[569-572] Its expression is induced following the stimulation with the cytokines IL-1α, TGF-β, or TNF-α,[570, 573] IL-7F,[574] as well as IL-13 during Th2 dominated inflammatory disorders.[575] Although each cytokine is sufficient to stimulate IL-11 expression, IL-1α and TGF-β synergistically augment the production of IL-11 in various cell types, including human intestinal myofibroblasts,[576] gingival fibroblasts,[577] and vascular smooth muscle cells.[571] Moreover several tissue-specific stimuli of IL-11 synthesis have been

described. For instances parathyroid hormone, [578] hepatocyte growth factor, [579] or viral infections [580, 581] are shown to induce the production of IL-11 in osteoblasts and airway smooth muscle cells, respectively. Leukotrienes,[582] histamine and eosinophil major basic protein further enhance IL-11 expression, while IL-6, IL-4, heparin, and steroids inhibit IL-11 synthesis.[578, 583]

IL-11 acts widely in hematopoietic and non-hematopoietic cell types, including hematopoietic progenitor cells, platelets, T cells, B cells, monocytes, and hepatocytes.

Role in immune regulation and cellular networks

IL-11 acts synergistically with a wide panel of early and late acting growth factors to stimulate various stages and lineages of hematopoiesis, including megakaryocytopoiesis, thrombopoiesis, erythropoiesis and myelopoiesis. In synergy with IL-3, IL-4, IL-7, IL-12, IL-13, stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF),[584] and flt3 ligand,[585] it shortens the G_0 period of early hematopoietic progenitor cells and thereby stimulates hematopoiesis by supporting the growth of myeloid, erythroid, and megakaryocyte progenitor cells as well as plasmacytoma cells.[586, 587]

IL-11 increases peripheral platelet counts and was shown to enhance T cell-dependent secretion of Igs by B cells. Recent work demonstrates the expression of IL-11Rα and gp130 on $CD4^+$ and $CD8^+$ lymphocytes, indicating a direct effect of IL-11 on T cells. *In vivo* IL-11 acts directly on lymphocytes to enhance T_H2 and inhibit T_H1 cytokine production. *In vitro* as well IL-11 modulates the cytokine production from activated murine $CD4^+$ T cells in such a way that IL-4 and IL-10 secretion is enhanced, but the production of IFN-γ and of the T cell growth factor IL-2 is inhibited. However, no effect of IL-11 on the T cell proliferation was observed.[588]

Moreover IL-11 regulates monocyte and macrophage proliferation as well as their activation by inhibiting the synthesis of inflammatory cytokines such as TNF-α, IL-1, IL-12, IFN-γ, and nitric oxide following LPS stimulation. The decreased cytokine production is associated with inhibited nuclear translocation of NF-κB and enhanced production of several members of NF-κB -inhibitors including IκBα and IκBβ.

During the acute phase response IL-11 stimulates the production of acute phase proteins such as ferritin, haptoglobin, C-reactive protein, and fibrinogen in hepatocytes.[586] IL-11 promotes neuronal development and plays a role in adipogenesis by potently inhibiting the lipoprotein lipase activity and the differentiation of adipocytes.[589] In addition IL-11 is involved in bone remodeling as it stimulates the osteoclast development, inhibits their apoptosis and suppresses the activity of osteoblasts, which leads to decreased bone formation.[572]

IL-11 was shown to have intriguing protective effects on epithelial cells and connective tissue after cell damage induced by irradiation or chemicals.[590] It downregulates proinflammatory mediators, inhibits epithelial cell proliferation and apoptosis and induces the secretion of tissue inhibitor of metalloproteinases (TIMP-1) from chondrocytes, synoviocytes, and hepatocytes. TIMP-1 is a potent inhibitor of matrix metalloproteinases, a group of peptidases involved in the degradation of the extracellular matrix, which promotes cell proliferation while inhibiting apoptosis in a wide range of cell types.[591] Most prominent are the protective effects of IL-11 in the gastrointestinal tract, where IL-11 protects small intestinal cells after combined radiation and chemotherapy and ameliorates tissue injury in animal models of inflammatory bowel disease. Additional protective effects of IL-11 were observed in different models of inflammatory skin disease, psoriasis,[592] rheumatoid arthritis, various infection-endotoxemia syndromes, patients with Crohn's disease,[593, 594] nephrological diseases,[595] and neurological disorders[596] as multiple sclerosis.

Role in allergic diseases and other pathologic conditions

IL-11 is supposed to be a regulator of inflammation and tissue remodeling in the asthmatic airway. During asthmatic inflammation, inflammatory cytokines as IL-13 together with respiratory viruses and retinoic acid induce the expression of IL-11 in eosinophils and in a variety of structural cells as alveolar and bronchial epithelial cells in the lungs. Overexpression of IL-11 in transgenic mice showed that IL-11 causes airway hyperresponsiveness and airway remodeling, which is characterized by subepithelial fibrosis and airway obstruction, while asthma-like inflammations are inhibited.[597] IL-11 can be found in nasal secretions of children with upper respiratory tract infections, and patients suffering from moderate or severe asthma show

increased IL-11-expression in eosinophils and lung epithelial cells compared to healthy controls. In asthmatic individuals the levels, of IL-11 even correlate directly with disease severity and inversely with FEV_1.[597]

These natural protective effects of IL-11 are exploited by using recombinant IL-11 for the treatment of different diseases. Recombinantly expressed IL-11 has been approved for the treatment of thrombocytopenia induced by chemotherapy. Thrombocytopenia is frequently the major dose-limiting hematological toxicity during chemotherapeutic treatment of cancers and can be significantly reduced by the ability of IL-11 to accelerate platelet recovery and stimulate peripheral platelet counts *in vivo*.[598]

In vitro studies have identified a role for IL-11 in endometrial adhesion. IL-11 treatment of primary human endometrial epithelial cells enhances the adhesion of primary trophoblast to endometrial epithelial cells to fibronectin and collagen IV.[599] Studies have demonstrated that administration of long acting IL-11 inhibitors blocks embryo implantation resulting in infertility in mice, whereas in women the evidence is less clear.[600] In clinical studies, women with unexplained first trimester abortions (7–13 weeks of pregnancy) have plasma IL-11 significantly decreased when compared to women with normal pregnancies.[601] The anti-inflammatory and mucosal protective effects of IL-11 are of use to accelerate healing and improve T_H1-mediated inflammatory diseases. In a phase I clinical trial treatment of patients with psoriasis resulted in amelioration of the disease, as shown by reduced keratinocytes proliferation and cutaneous inflammation. Levels of pro-inflammatory cytokines such as IFN-γ, IL-8, IL-12, TNF-α, and IL-1 decreased, whereas the expression of endogenous IL-11 increased.[592] Moreover recombinant IL-11 was found to protect from acute gastrointestinal mucosal damage and to induce remission in patients with mild to moderate Crohn's disease.[593, 594] Animal models of rheumatoid arthritis as well as a phase I clinical study in patients with rheumatoid arthritis indicate a positive effect of IL-11 treatment on the outcome of the disease by inhibiting macrophage activity and modulating T cell responses.[602]

IL-11 has also been broadly documented to exhibits a wide variety of biological effects in cancer development, including gastric carcinomas,[603-605] colorectal

carcinoma,[606] prostate carcinoma,[607] renal carcinoma,[608] ovarian carcinoma,[609] breast cancer,[610] endometrial carcinoma,[611] bone cancer,[612] human primary leukemia, myeloid leukemia,[613, 614] megakaryoblastic leukemia,[615] erythroleukemic cell lines,[616] and leukemic blast colony formation.[613, 614] IL-11 could be produced HIF-1 dependently by cancer cells which is in hypoxic environment. IL-11Rα subunit on cancer cells sense self-derived IL-11 and this autocrine pathway may contribute to tumor progression.[617]

Functions as demonstrated in IL-11-deficient mice and receptor deficient mice

Although IL-11 effectively acts as a multilineage growth factor in the hematopoietic compartment, IL-11Rα-deficient mice (IL-11Rα$^{-/-}$) show no obvious hematological abnormalities.[618] The numbers of different hematopoietic cells in the bone marrow, spleen, or peripheral blood did not differ between wild-type and knockout animals, indicating that IL-11 is dispensable for hematopoiesis due to growth factor redundancy in the hematopoietic compartment. In addition, the activities of IL-11 are similar to those of IL-6 with regard to the promotion of antibody secretion by B cells, the downregulatory effects on monocytes and macrophages, and the induction of acute phase proteins. Thus, the effects of IL-11 can at least in part be accomplished by other cytokines, mainly those that signal via the common receptor subunit gp130. However, in contrast to normal hematopoiesis, IL-11Rα$^{-/-}$ mice have increased trabecular bone volume, associated with low bone resorption and formation, and decreased osteoclast numbers. Female IL-11Rα$^{-/-}$ mice are infertile due to abnormal development of the placenta. During normal pregnancy IL-11 is expressed by endometrial stromal cells and activates the expression of α_2-macroglobulin via the transcription factor STAT3. α_2-macroglobulin is a protease inhibitor essential for the development of the placenta; downregulation of α_2-macroglobulin results in degeneration of the decidua and uncontrolled trophoblast invasion.[619] This finding points out a critical action for IL-11 in non-hematopoietic organs.

IL-12

Discovery and structure

IL-12 was first described as Natural Killer Cell-Stimulating Factor in 1989. The heterodimeric cytokine consists of a 35-kDa light chain (p35 or IL-12a) and 40-kDa heavy chain (p40 or IL-12b). [620] The gene encoding p35 is located on chromosome 3 in humans and on chromosome 6 in mice. The p35 protein contains 197 amino acids and has homology to other single chain cytokines (e.g. IL-6 and G-CSF). The *IL-12p40* gene is located in the same area as *IL-3*, *IL-5* and *GM-CSF* on chromosome 5 in human and on chromosome 11 in mouse. p40 has homology to the extracellular domain of members of hematopoietic cytokine-receptor family (e.g. IL-6Rα). [621] Because of their localization on different chromosomes, protein expression of the two subunits is independently regulated and when they are co-expressed in the same cell, they form the biologically active IL-12 p70 heterodimer. [622] Both subunits are covalently linked by a disulfide bond between Cys74 of p35 and Cys 177 of p40 to form the active IL-12 p70. IL-12p40 can be produced as free monomer or homodimer ($p40_2$) in large excess over IL-12p70 heterodimer *in vitro* and *in vivo*. The p40 homodimers have been suggested to antagonize IL-12p70 signaling in mice, but not in humans. It was suggested that IL-12p40 acts as a macrophage chemoattractant. Unlike p40, p35 is not secreted in monomeric form. [623, 624]

Receptor and signaling

The heterodimeric IL-12R is composed of IL-12Rβ1 that is structurally related to the type I cytokine receptor superfamily, and IL-12Rβ2 that is homologous to the gp130 subunit. The genes for β1 and β2 chains reside on chromosomes 19p13.1 and 1p31.2, respectively. The affinity of IL-12 for either β1 or β2 alone is low, and co-expression of both β1 and β2 subunits is required for the generation of high-affinity IL-12 binding sites. [625] The receptor-like subunit, IL-12p40, interacts with the β1 subunit and IL-12p35 interacts with the β2 subunit. The β2 subunit is the signal transducing chain of the receptor. In contrast, IL-12Rβ1 has no intracellular tyrosine residues and presumably cannot signal. IL-12Rβ1 is more important for ligand binding. [626] IL-12R is expressed on T cells, NK cells, and DC. However, naïve $CD4^+$ T cells express low levels of IL-12 receptor b2 (IL-12Rb2) at the resting state, and require TCR, CD28, IL-27 or IFN-γ stimulation to increase their IL-12 responsiveness.

[627] The specific T_h1 cells transcription factor T-bet, induced by IL-27, up-regulates the IL-12Rb2, whereas IRF1, induced by IFN-γ, directly regulates the IL-12Rb1. [628] A very recent study demonstrates that many alternative splicing isoforms exist for IL-12Rb1. Un-stimulated leukocytes primarily express intracellular form of IL-12Rb1 located away from extracellular cytokine and relative abundance of the isoform, which confers IL-12/IL-23 responsiveness is only up-regulated in stimulated cells. [629] Like many cytokine receptors, IL-12R lacks intrinsic enzymatic activity and instead transduces signals through the action of the Janus kinases (JAKs). Tyk2 and Jak2 are involved in IL-12 signaling; Tyk2 associates with the β1 subunit, and Jak2 associates with IL-12Rβ2. [630, 631] Upon ligand binding, receptor-associated Jaks are activated by transphosphorylation and later STAT4 activation. The phosphorylated STATs then homo- or hetero-dimerize, translocate into the nucleus, bind specific DNA sequences, and modulate gene expression. [632]

Cellular sources and targets

IL-12 is produced by activated inflammatory cells (e.g. monocytes, macrophages, neutrophils, microglia and DC), and to a lesser extent B cells. While p35 is expressed ubiquitously and constitutively at low levels, p40 expression is limited to phagocytic cells that produce IL-12p70. [633-635]

A variety of different pathogenic organisms induce high levels of IL-12p40 and IL-12p70 production, including gram positive and gram negative bacteria, parasites, viruses, and fungi. Microbial products such as LPS, lipoteichoic acid (LTA), peptidoglycan and bacterial (CpG) DNA induce T cell-independent production of IL-12 by cells of the innate immune system via TLR signaling. [636-638] Intact gram-positive bacteria preferentially stimulate IL-12. [639] On the other hand, cholera toxin and measles virus down-regulate IL-12 production. Very recently discovered thymus-derived αβ-T cells that combine key features of T cells and DCs and are designated as T(DC) respond to Toll-like receptor-mediated stimulation also by producing IL-12. [640]

The p40 gene is regulated at the level of transcription and is highly inducible by microbial products. Numerous transcription factors, including NF-κB family members (p50, p65, and c-Rel), IRF-1, interferon consensus binding protein (ICSBP), and Ets-

family members, can bind and regulate the p40 promoter. [641-645] Krüppel-like transcription factors Klf10 and Klf11 inhibit IL-12p40 expression in mouse bone marrow-derived macrophages. [646]

IL-12 production is positively regulated by IFN-γ, which is induced by IL-12 itself. IL-12 participates in a positive feedback loop by promoting IFN-γ secretion that, in turn, potently primes monocytes and polymorphonuclear neutrophils for further IL-12 production. [643, 647] IL-12 is also produced in a T cell-dependent manner through the engagement of CD40 on antigen-presenting cells with its receptor CD40L on T cells. [648] Conversely, IL-12 production is inhibited by IL-10, IL-11, IL-13 and type I IFNs. Signaling via G-protein coupled receptors (GPCR), including the receptors for monocyte chemo-attractant protein 1 (MCP-1), prostaglandin E2, cytosolic RIG-I-like receptors, histamine and FcR crosslinking inhibit IL-12 production. However, signaling via other GPCRs, like CCR5, can up-regulate IL-12. [649, 650-654]

Dectin-1; a protein from the C-type lectin family was found to induce production of IL-12p70 from monocyte derived dendritic cells (moDCs). Dectin-1 signalling activation overcomes the transcriptional control mechanism that inhibits p35 expression in moDCs; allowing TLR signaling pathways to initiate IL-12 synthesis. Dectin-1 effect on IL-12 was connected to Syk/CARD9 and Raf-1 signalling pathways. [655]

Role in immune regulation and cellular networks

IL-12 activated cells express increased levels of transcripts for many genes involved in host defense, including IFN-γ, granzyme, TRAIL, FasL, and CCL5. Thus, the IL-12/IFN-γ pathway predominantly induces cytotoxic factors important for the direct killing of microbes or infected cells. By inducing IFN-γ production from NK cells and T cells, IL-12 indirectly activates the antimicrobial, anti-parasitic and anti-tumour activity of phagocytotic cells and promotes cytolytic activity of NK cells and lymphokine-activated killer (LAK) cells. [656-661,] IL-12 also supports the maturation of DCs by increasing the expression of the CD2, CD11a, CD45, CD56, CD69, CD71 and HLA-DR and by further inducing IL-12 production. [625, 662] IL-12 is important for the differentiation and proliferation of T cells and is a major player in the development and maintenance of T_h1 cells. Activation of the IL-12R complex stimulates IFN-γ

production and induces expression of IL-18Ra, thereby conferring IL-18's responsiveness to mature T_h1 cells. IL-18 serves as a cofactor for IL-12-induced T_h1 development and enhances IFN-γ production from effector T_h1 cells. In contrast, IL-4 inhibits IL-12Rβ2 expression. Therefore, the opposing effects of IFN-γ and IL-4 on IL-12R expression may contribute to T_h1/T_h2 differentiation. Conversely, IL-12 and IFN-γ antagonize T_h2 differentiation and the production of IL-4, IL-5, and IL-13. [627, 663]

Functions as demonstrated in transgenic mice.

Mice deficient in *Il-12p35*, *Il-12p40*, or *Il-12Rβ1* display similar phenotypes and show no obvious developmental abnormalities. Their IFN-γ secretion, T_h1 differentiation, and NK cytolytic activity are greatly impaired and decrease of IL-12 production results in higher susceptibility to intracellular pathogens. Mice lacking the Il-12p40 subunit are more immunocompromised than *Il12p35* $^{-/-}$ mice in term of their ability to generate allospecific $CD8^+$ Tcells. [664] However, the generation of T_h1 lymphocytes in *p35* null mice is totally abrogated and these mice and are highly susceptible to EAE, whereas *Il12 p40* deficient mice are resistant.[665-668] A recent study demonstrates that peripheral development of T-bet$^+$ T_{reg} cells, that potently inhibit T_h1 cell responses, is dependent on delayed induction of the IL-12Rβ2 receptor component. When these T_{reg} cells complete STAT4-dependent T_h1 cell development, they lose their ability to suppress effector T cells.[669] Also; a recent study involving pulmonary infection of mice with *Mycobacterium tuberculosis* shows that Foxp3$^+$ antigen-specific T regulatory cells that peak in number after infection are later selectively eliminated via IL-12 signaling driven T-bet expression in T-reg cells; possibly as a mechanism for the immune system to provide pathogen control in later stages of infection.[670]

IL-12 in human diseases

Patients with IL12-p40 deficiency show increased susceptibility to poorly pathogenic mycobacterial and salmonella infection. This condition seems to be more severe than IL12Rβ1 deficiency, with a mortality of 38%.[671, 672] A number of mutations in *IL12RB1* that result in the complete absence of responsiveness to IL12 and IL23 have been identified. Antigenic stimulation (eg, BCG or *M avium*) of patient peripheral blood lymphocytes resulted in markedly reduced IFN-γ production.

Activated T cell lines derived from these patients did not respond to IL-12 by the nuclear translocation of phosphorylated STAT4 protein, as detectable by electrophoretic mobility shift.[673] Atopic patients with heterozygous *IL-12Rβ2* chain mutations show decreased STAT4 phosphorylation and IFN-γ production in response to IL-12 stimulation. Recent genomewide association studies (GWAS) have identified that mutations in the *IL12B* gene encoding IL-12 p40 subunit are associated with inflammatory bowel disease and psoriasis.[674, 675]

Notably, Blocking TNF-α with infliximab in both psoriatic skin and blood-derived monocytes results in a reduction of IL-12p40 mRNA expression alongside IL-1β and CCL20; effectively dampening both Th1 and Th17 inflammatory mediators in psoriatic skin.[676] Moreover, anti-IL-12/23 Human IgG1 mAbs (Ustekinumab) is used in treatment of severe plaque psoriasis and psoriasis arthritis [677] and has been tested in clinical trials for treatment of colitis, systemic lupus erythematosus, Crohn's disease, among others.[66]

IL-12 is a powerful mediator of tumour suppression, whereas mainly the capacity of IL-12 to enhance the ability of NK cells to lyse target cells has exploited for tumour immunotherapy.[678,679] Recent study demonstrates that IL-12 initiates local anti-tumour immunity also by stimulating a subset of $NKp46^{+}$ lymphoid tissue–inducer cells.[680] In another study; cytotoxic T cells (CTL) generated via IL-12 stimulation are shown to be efficient in controlling tumours, and are capable of maintaining their high numbers and resist exhaustion compared to CTLs generated with IFN-α stimulation. This effect is a result of IL-12-stimulated cells expressing lower amount of PD-1 in comparison to IFN-α stimulation.[681] However, like other inflammation-related cytokines, IL-12 can actually function either as initiator or suppressor of tumour growth depending on tumour and cellular environment.[682]

Concordant to its function as an inducer of T_h1 type immune responses, IL-12 mainly has been shown to function as suppressor of inflammation in allergic diseases. For instance, T_h17-mediated allergic lung inflammation can be effectively suppressed by IL-12 through IL-10-dependent mechanisms.[683] Similarly, DCs from mycobacteria-infected mice inhibit established allergic airway inflammatory responses to ragweed via IL-10- and IL-12-secreting mechanisms. [684] Confirming the

suppressive role of IL-12 in allergy; IL-12 levels in serum of asthmatic children were found to be significantly lower than asthma alleviated children. This result was also confirmed with an asthma model in mice; where lower IL-12 levels in asthmatic mouse is associated with increased airway remodeling, lung inflammation and increased diseased severity, in comparison to budenosine-treated asthmatic mice. [685]

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IL-13

Discovery and structure

IL-13 was first described in 1989 as P600, a protein expressed by activated mouse Th2 cells[1] and has been cloned in 1993.[2-4] It has a molecular weight of 10kDa and is encoded in a cytokine gene cluster on chromosome 5 (5q31) that includes genes encoding for IL3, 4, 5, 9 and GM-CSF. The structure of IL-13 consists of a four-helix bundle with a characteristic up-up-down-down topology that includes a β-sheet formed between residues in the AB-loop and CD-loop. [5, 6] It shows considerable similarity to IL-4 and is highly conserved with little species-specificity. [3]

Receptor and signaling

IL-13 has two known receptors: IL-13R1α1 and IL-13R1α2.[7] It signals, together with IL-4 through the IL-4 receptor complex type II that consists of the IL-4Rα and IL-13Rα1. Interleukin 13 binds with its helical faces to the elbow shaped “cytokine binding homology region”. This driver complex and recruits its trigger complex IL-4Rα. Recently, La Porte et al defined the structural basis of type I and type II ternary signaling complexes and the subtle differences that result IL-4 and IL-13 receptor interactions leading to type II complex formation.[8] IL-13Rα1 bears an evolutionary relationship to γc, but it contains an extra N-terminal Ig-like domain (D1) not found in other receptors of the γc subfamily that is required for IL-13, but not for IL-4 signaling. For its binding specificity, the IL-13R1D1 domain has been defined as the crucial part type II complex formation that results in IL-13 signaling. IL-4-mediated signaling via this complex is not affected by mutations of this domain. IL-4 binds to IL4Rα with high affinity whereas the recruitment of either γc or IL-13Rα1 contributes little affinity. On the contrary binding of IL-13 by IL13Rα1 occurs with moderate affinity, but its affinity is significantly enhanced by the presence of its ligand, the IL-4Rα. Consequently the expression patterns of the receptors are decisive to define signaling efficiency of IL-4 and IL-13. In general, IL-4Rα is limited however e.g. in cells in which IL-13Rα1 is limiting the higher affinity for its trigger receptor may lead to more potent IL-13 signaling.[8] Another important factor is the presence of the γ-chain that allows IL-4 to signal via the type I complex. Mainly macrophages and hematopoietic cells express both the γc and IL-13R1α. Consequently γc-expression results in a 10-100 fold higher sensitivity of bone marrow derived macrophages and monocytes to IL-4 than to IL-13.[9]

After binding of IL-13 to IL13Rα1, the IL-13 type II receptor complex is formed and leads to janus kinase mediated phosphorylation of STAT6.[10] This is considered to be the major mode of action. However, recently IL-13 has been demonstrated to act also via the mitogen-activated protein kinase pathway. The activation of ERK 1/2 in mouse model with transgenic IL-13 expression in the lung was demonstrated.[11] Inhibition of the ERK 1/2 MAPK pathway decreased the expression of several chemokines MIP-1α/CCL-3, MIP-1β/CCL-4, RANTES/CCL-5, the matrix metalloproteases MMP-2, -9, 12, -14 and cathepsin B and leads to the upregulation of α1-antrypsin. MIP-2/CXCL-1 expression was exclusively ERK 1/2 dependent. Moreover, remodeling and recruitment of eosinophils was also affected by IL-13-dependent activation of ERK 1/2. IL-13-induced eotaxin/CCL-11; MIP-1/CCL-2 and C10/CCL-6 mRNA production, IL-13 receptor regulation,15-lipoxygenase regulation (in vitro experiments) and mucus cell metaplasia (in vivo) in an ERK 1/2 independent manner.[11] In addition to ERK1/2, JNK-dependent effects have been suggested to play a role on AHR by impacting Ca++-influx in airway smooth muscle cells.[12]

The second receptor, IL-13Rα2, is assumed to act as a decoy receptor. It binds IL-13 with a higher affinity than IL-13Rα1 and is considered to serve as potent inhibitor of IL-13 induced actions.[13, 14] Indeed, TNF-α/IL-17 synergy inhibits IL-13 bioactivity via IL-13Rα2 induction.[15] In a double-knockout asthma model (IL10 $^{-/-}$ IL13Rα2 $^{-/-}$) an additive inhibitory effect of IL-13Rα2 on IL-13-induced airway hyperreactivity, mucous production, inflammation and fibrosis with IL-10 was observed.[16] Furthermore, a role of IL-13Rα2 in IL-13-induced fibrosis by TGF-ß1 in the presence of TNF-α has been demonstrated in mouse models for oxazolone- or TNBS-induced colitis and bleomycin-induced lung fibrosis. After an initial step of upregulation of IL-13Rα2 by IL-13 (via the IL-13Rα1), TNF-α mediates fibrosis, which is induced via IL-13Rα2 in an STAT-6 independent fashion via AP-1.[17, 18] There is some evidence that the N-linked glycosylation of IL-13Rα2[19] plays a decisive role for IL-13Rα2-mediated inhibition.

Cellular sources and targets

IL-13 is produced by T cells, mast cells, basophils, eosinophils and NKT cells, Th2 cells.[20, 21] IL-13 production by Th2 cells is dependent on the transcription factor GATA-3.[21] During chronic infections IL-13 is expressed by Th1 cells and the plasticity of the cytokine is regulate by transcription factor E4BP4.[22] Major target cells are B

cells, mast cells, epithelial cells, eosinophils, smooth muscle cells, fibroblasts, and macrophages.[23, 24]

Role in immune regulation and cellular networks

IL-13 is antagonized via the Th1 type cytokines INF-γ, IL-12, IL-18, TNF-α and the regulatory cytokine IL-10. IL-13 can induce class switching to IgG4 and IgE in combination with CD40 stimulation.[25] The expression of CD23, MHC II is up-regulated on B cells in the presence of IL-13. In addition, the induction of the adhesion molecules CD11b, CD11c, CD18, CD29, CD23, and MHC II on monocytes takes place. Moreover IL-13 activates eosinophils and mast cells, recruits eosinophils and prolongs their survival.[26]

IL-13Rα1 is expressed on human $CD4^{+}$Th17 cell, and IL-13 attenuates IL-17A production at polarization and restimulation. Although IL-13 is an attractive therapeutic target for decreasing symptoms associated with asthma, suggest that therapies inhibiting IL-13 production could have adverse side effects by increasing IL-17A production.[27, 28]

Let-7 family of microRNAs inhibit IL-13 expression and represent a major regulatory mechanism for modulating IL-13 secretion in IL-13-producing cell types.[29]

Role in allergic disease

OVA-transgenic Th2-type T cells from IL-13-deficient mice fail to induce AHR in B and T cell deficient mice in the presence of airway eosinophilic infiltrates, IL-4 and IL-5.[30] Thus, IL-13 itself is sufficient to induce AHR. IL-13 dependent AHR and mucous secretion was induced independently of IL-5 or ECP. However, the presence of IL-5 and ECP seems to be crucial for maintenance of IL-13 production of Th2 cells. Chiba et al reported an IL-13-induced upregulation of a monomeric GTP-binding protein called RhoA, which is supposed to be involved in increasing the sensitivity of myofilaments to Ca++.[31] Interestingly, both, an IL4Rα and even a STAT6 independent pathway through which IL-13 induces AHR and mucous secretion have been suggested.[32, 33]

The role of IL-13 on asthma is supported by epidemiological data. A combination of polymorphisms of the IL4/IL13 pathway increased the risk to develop asthma 16.8-fold.[34] Polymorphisms restricted to IL-13 itself lead to a higher frequency of asthma exacerbations in childhood and elevated total IgE and blood eosinophilia.[35] In addition, the IL13 -1112C/T and +2044A/G polymorphisms are risk factors for

asthma. IL-13 also contributes to allergic rhinitis late phase responses, whereas its impact on acute response appears to be limited in vivo.[36]

In addition, IL-13 plays an important role in tissue remodeling and fibrosis.[37-39] In a *S. mansoni* infection model IL4R$^{-/-}$ and STAT6$^{-/-}$ mice had a significantly reduced granuloma size and reduced fibrosis, whereas ablation of IL-4 had no effect. Thus, suggesting a key role of IL-13 in this process. Moreover, IL-13 is a potent inducer of collagen production in fibroblasts. Furthermore, it is able to induce Arginase 1 in macrophages that are termed alternatively activated. This Arginase uses L-arginine as a substrate to make L-ornithine and is converted to Proline and polyamines. Proline is known to be necessary for the development of fibrosis. Increased polyamine production in the presence of IL-13 leads to rat aortic smooth muscle cell proliferation that can be inhibited via dexamethasone treatment.[40]

Role in host defense or other immune regulatory conditions

IL-13 plays a unique role in parasite defense. IL-13-deficient mice are unable to expel *Nippostrongylus brasiliensis*. Importantly, this defect is more pronounced in IL-13$^{-/-}$ mice than in IL4 deficient mice, with comparable IL-5 levels as wild type mice.[41, 42]

Anti-proliferative effects (human breast cancer cells, renal cell carcinoma, B-All), as well as promotion of proliferation by inhibition of Th1 type tumor rejection via the STAT6 pathway, were reported for IL-13. Thus, blocking or antagonizing IL-13 or targeting of IL-13Rα1-expresssing cells may serve as a promising anti-cancer immunotherapy.[43, 44] In addition, targeting of IL-13Rα2 could be a useful treatment for inhibiting squamous cell carcinoma.[45] However, a detailed understanding of IL-13 in case of malignancies is needed.

IL-13-induced IRAK-M suppress airway epithelial TLR2 signaling, partly through inhibiting activation of nuclear factor kB.[46]

Recently, signaling pathway from chloride channel calcium-activated 1(CLCA1) to MAPK13 was define, that is responsible for IL-13-driven mucus production human airway epithelial cells. The same pathway is also highly activated in the lungs of humans with excess mucus production due to COPD. Development of inhibitors guided by structural analysis of MAPS13-inhibitor cocrystals and scaffold offers the opportunity to better define the regulation of a major disease end point and to respond to the unmet need for an antimucus therapeutic for inflammatory airway disease.[47]

Functions as demonstrated in IL-13-deficient mice, receptor-deficient mice and transgenic models.

IL-13-deficient mice produce reduced levels of IL-4, -5, -10 and IgE. They are unable to expel *Nippostrongylus brasiliensis*. Moreover IL-$13^{-/-}$ mice fail to mount a profound goblet cell hyperplasia although IL-4- and IL-5-producing cells are present. Mast cell cytokine production is unaffected in knockout mice upon stimulation with PMA and Ionomycin.[41, 42] Interestingly, IgE levels do not change in IL-13-deficient mice.

Recently, IL-13Rα1-deficient mice have been generated.[48, 49] Mice were healthy and showed no fundamental changes in the lymphocyte compartment. IL-13Rα$1^{-/-}$ mice do not develop airway hyper-reactivity and mucous hyper-secretion, whereas soluble IL-13Rα2 and IL-13 were upregulated.[48] Surprisingly, the percentage of $CD4^+$ Th2 cells were reported to be significantly higher upon S. mansonii infection in IL13Rα$1^{-/-}$ mice.[49] In addition, significantly less hepatic fibrosis and a modestly increased frequency of eosinophils in granuloma related to a higher IL-5 production were reported.

In mouse model of IL-13-induced AD, IL-13 is a potent mediator in generating pathologic fibrosis in AD, and the TSLP and TSLPR signaling pathway is critical in the pathogenesis of the detrimental tissue remodeling and skin fibrosis in AD.[50] Treatment of $Id_3^{-/-}$ mice, which represent a model for T cell mediated primary Sjogren's syndrome, with anti IL-13 antibodies over a two-month period resulted in a reduction of both serum IL-13 levels and the number of mast cells in the salivary gland tissue.[51]

TGF-β has been linked to IL-13-related fibrosis. TGFß1 and MMP-9 were increased in IL-13Rα$1^{-/-}$ mice when challenged with schistosoma antigen.[49] Thus, IL-4R complex II seems to be involved in the activation of fibroblasts and epithelial cells. Moreover, IL-13Rα1 knockout mice had lower[49] or non-detectable[48] serum IgE levels without any changes of other Ig titers.

Specific over-expression of IL-13 in the lung leads to typical features of asthma including pulmonary eosinophilia, airway epithelial hyperplasia, mucous cell metaplasia, sub-epithelial fibrosis, Charcot-Leyden like crystals, airway obstruction, non-specific airway hyper-responsiveness to cholinergic stimulation.[52]

Development of peanut-induced intestinal allergy in mice is mediated through a mast cell-dependent, IgE-$F_{c\varepsilon}$RI-IL-13 pathway. Targeting IL-13 may be a potential treatment for IgE-mediated peanut allergic responses in the intestine.[53]

IL-4 and IL-13 together account for most allergen–induced pulmonary genes in the mouse lung. The identification of genes selectively induced by individual cytokines, especially IL-13, may provide novel therapeutic targets for the treatment of asthma.[54-56]

In monkey model of asthma, the dual IL-4/IL-13 antagonist, pitrakinra, significantly reduces allergen-induced AHR with only limited inhibition of allergen-induced airway eosinophilia, indicating the therapeutic potential in the treatment of atopic asthma.[57]

Clinical use

CAT-354 is a potent and selective IL-13-neutralizing IgG4 mAb*. In vitro* CAT-354 functionally inhibit IL-13 induced eotaxin production, an analogue of smooth muscle airways hyperresponsiveness, CD23 upregulation and IgE production. CAT-354 inhibited airways hyperresponsiveness and bronchoalveolar lavage eosinophilia in humanized mouse and cynomolgus monkey antigen challenge models.[58]

Humanized neutralizing mAb blocks IL-13 activity in patients with mild atopic asthma (IMA-638 and IMA-026, Pfizer, New York, NY). IMA-638 specifically prevents recruitment of the IL-4Rα subunit to complex with IL-13 Rα1 after initial binding of IL-13 to the IL-13Rα1 subunit. IMA-026 inhibits the initial interaction between IL-13 and the IL-13Rα1 and IL-13Rα2 subunits. The effect of antibodies might have significant clinical implications in human asthma and eosinophilic esophagitis.[59-62] Studies of both tralokinumab and lebrikizumab suggest that IL-13 inhibition might be most effective in patients who have evidence of residual IL-13 activity with persistent Th2 inflammation.[63, 64] However, anti-IL-13 mAb (GSK679586) did not demonstrate clinically meaningful improvements in patients with severe asthma.[65] Therefore, further studies are needed to determine whether therapies targeting IL-13 can provide clinical benefit in patients with severe refractory asthma.

IL-14

Alternative names: high molecular weight B cell growth factor (HMW-BCGF, BCGF-H)

Discovery and structure

Several years ago, IL-14 was originally discovered as a high molecular weight B cell growth factor with a molecular size of 60 kDa [66] which differs from the human low molecular weight B cell growth factor (LMW-BCGF). Human IL-14 is a member of B cell growth factors including IL-2, IL-4, IFN-α, IFN-β, IFN-γ, TNF-α and LMW-BCGF. There is evidence that IL-14 is eventually a precursor for the low molecular weight B cell growth factor, which has a molecular weight of 12 to 14 kDa.[67] The human IL-14 gene maps on chromosome 1p34-6, the murine IL-14 gene is located on chromosome 4. Two transcripts are produced from opposite strands of the IL-14 gene termed IL-14a and IL-14b.[68]

IL-14 as originally cloned from a Burkitt lymphoma cell line and cloning of IL-14 cDNA revealed a 53 kDa protein composed of 498 amino acids including a signal peptide of 15 amino acids and three potential N-linked glycosylation sites. The sequence is rich in cysteines.[69] Concerning the sequence, no homology to other interleukins and cytokines has been observed and its 3D structure has not been yet solved.

Receptor and signaling

IL-14 binds to a 90 kDa receptor, identified by using a monoclonal antibody (BA5). This monoclonal antibody recognizes a binding site for IL-14 on solubilized membranes of activated B cells. A high correlation between the expression of the receptor and capacity of the cells to react on stimulation was seen. The expression of IL-14R is very low on resting normal tonsillary or peripheral blood B lymphocytes (50-350 IL-14R/cell), hence these cells do not respond efficiently to IL-14, whereas activated normal tonsillary or peripheral blood B lymphocytes express much more IL-14R (1-5x10^4 IL-14R/cell) and proliferate in the presence of IL-14 .[70] However, it is still unknown in which stage of human B cell ontogeny the B cell lineage cells express the receptor and are able to respond to IL-14 stimuli.

Cellular sources and targets

IL-14 has been identified in normal T cells, T cell clones, B lineage and T lineage lymphoma cell lines. [67, 71-73]

Role in immune regulation and cellular network

It was found that IL-14 inhibits the Ig secretion of activated B cells, but the mechanism is still poorly understood.[74] Furthermore, IL-14 stimulates B cell precursor acute lymphoblastic leukemia cells, hairy cell leukemia cells, prolymphocytic leukemia cells and chronic lymphocytic leukemia cells.[66, 71, 75] The complement

component, Factor B, related antigenically to IL-14, is also a mitogenic factor for B lymphocytes and competes with IL-14 for binding to the B cell membrane.[76] A recent study showed production of IL-14 by aggressive intermediate lymphomas of B cell type non-Hodgkin's lymphoma (NHL-B) in humans. These cells express IL-14mRNA, secrete IL-14 and proliferate in response to IL-14. Since exogenous IL-14 causes proliferation of NHL-B cells *in vitro* as well, it is suggested that IL-14 acts in an autocrine and a paracrine manner.[75] Biological relevance of IL-14 in transplantations is recently investigated. IL-14 is shown to participate in alloantigen responses, which is suppressed by clinically used immunosuppressive therapies, *in vitro*, much like IL-2, but not suppressed in renal transplant recipients during follow-up, *in vivo* and also increased mRNA content of IL-14 was observed during rejection, infection or allograft injury. This is claimed to be important in promotion of alloantibody production following acute graft injury. [77]

Functions as demonstrated in IL-14 transgenic mice

Data from a recent study with IL-14a transgenic mice stress a role for IL-14a in the development of autoimmunity and lymphoma genesis. Two distinct transcripts are produced from opposite strands of the IL-14 gene designated IL-14a and IL-14b. Increased expression of IL-14a in transgenic mice results in a phenotype that is very similar to this from systemic lupus erythematosus and Sjögren's syndrome. The changes in the transgenic mice include hypergammaglobulinemia where IgG, IgA and IgM autoantibodies are detectable. Immunoglobulins were also found in the kidney and increased number of lymphocytes was observed in the salivary glands of these mice. The peritoneal cavities of the transgenic mice are more infiltrated with B1 cells. Mice vaccinated with T-dependent and T-independent antigens show a stronger immune response as wild type mice. B cell malignancies ($CD5^+$B cell lymphoma) similar to these observed in patients with systemic lupus erythematosus and Sjögren's syndrome appear in aged IL-14a transgenic mice. [68, 78] Furthermore, in peripheral blood of patients with primary and secondary Sjögren's syndrome high levels of IL-14a are expressed. [78]

IL-15

Discovery and structure

IL-15 was discovered by its ability to mimic IL-2-mediated T cell proliferation. [79, 80] Many of the biological actions attributed to IL-2 can also be induced by IL-15.

However, there are important *in vivo* differences in the actions of these two cytokines. IL-15 is a monomer of 14-15 kDa and consists of 114 amino acids. It is a member of the four α-helix bundle cytokine family. These family members are characterized by antiparallel juxtaposed helices A, C, B, D, and two long end-to-end loops, loop AB and CD, which are connected by a short β-sheet packed against helices B and D. [81]

Receptor and signaling

The IL-15R consists of three subunits, IL-15Rα chain, IL-2Rβ chain (CD122), and the common γc (CD132). [82, 80] Only the IL-15Rα subunit is unique to IL-15. IL-2Rβ is also a receptor for IL-2, and the common γc is shared by IL-2, IL-4, IL-7, IL-9, and IL-21. The IL-2Rα consists of two sushi domains, whereas the IL-15Rα contains only one. These domains are structurally different from other cytokine receptors. Both IL-2Rα and IL-15Rα use their sushi domains for ligand binding. The biological activities of IL-15 are mediated through JAK-STAT signal transduction pathways and are remarkably similar to those of IL-2. [83] IL-15 and IL-2 use receptors with the same signaling subunits but distinct immunological functions. New structure data show that the signal complexes (IL-15—IL-15Rα—IL-2Rβ—γc and IL-2—IL-2Rα—IL-2Rβ—γc) they form are topologically nearly identical, which suggests that other factors are responsible for the distinct signaling properties of these complexes.[84] Thus, IL-15 and IL-2 induce similar signals, and the cytokine specificity of IL-15Rα versus IL-2Rα determines cellular responsiveness.[85]

Cellular sources and targets

IL-15 is produced by nonimmune cells (keratinocytes, skeletal muscle cells, fibroblasts, various epithelial cells, bone marrow stromal cells, nerve cells) and immune cells (monocytes, macrophages, DCs and activated $CD4^+$ T cells) in response to viral infections, LPS, and other signals that trigger innate immunity. [86] Target cells include innate immune cells (NK, NKT, monocytes, macrophages, DCs, neutrophils, eosinophils, mast cells) and adaptive immune cells (T cells and B cells). [86, 87] In NK cells, the mammalian target of rapamycin (mTOR) is essential for IL-15 singnaling.[88]

Role in immune regulation and cellular networks

Although IL-15 shares some function with IL-2, such as T cell activation, stimulation of NK cell proliferation and induction of NK cytolytic activity, differences in their biological function have been clearly identified. [89] IL-15 is important for the $CD8^+$ memory, NK, and NKT cells homeostasis and is necessary for the

development/differentiation γδ T cells. [90-92] Furthermore, IL-15 suppresses IL-2-induced AICD of T cells. [93] Unlike IL-2, IL-15 is not required for the maintenance of Treg cells that can attenuate anti-tumor immune responses.[94] In addition to the effect on T and NK cells, IL-15 also has several effects on other components of the immune system.[95] It allows induction of antibody responses partially independent of CD4 help. [96] Dendritic cells cultured with IL-15 demonstrate maturation with increased CD83, CD86, CD40 and MHC class II expression, are also resistant to apoptosis, and show enhanced IFN-γ secretion.[97] In addition, IL-15 protects neutrophils and eosinophils from apoptosis.[98]

Role in host defense or other immune regulatory conditions (autoimmunity)

IL-15 plays a role in the defense against microorganisms and tumors.[99] There is increasing recognition of a link between inflammation and the development of cancer.[100] Since IL-15 is produced in response to viral infection, its stimulation of NK proliferation occurs in the first few days after infection. IL-15 is believed to be equivalent of IL-2 in the early innate immune response. Because IL-15 stimulates the proliferation and maintenance of NK cells, B and T cells, it is probable that IL-15 could play a role in some hematological malignancies. [101-103] However, in non-hematological malignancies, IL-15 may play a role in immunosurveilllance and protection from tumor formation.[104]

Increased levels of IL-15, disordered expression, or abnormal IL-15 signaling have been reported in various autoimmune and inflammatory diseases, such as rheumatoid arthritis, Behçet's disease, inflammatory bowel diseases, inflammatory synovitis, psoriasis, diabetes mellitus, asthma bronchiale, autoimmune vasculitis, systemic lupus erythematosus, pemphigus vulgaris, sarcoidosis, multiple sclerosis, as well as celiac disease.[83, 105] In addition, IL-15 can play a major role in the airway inflammation in COPD directly by amplifying the type 1 immune responses and decreasing apoptosis or indirectly, via modulating molecules associated with cytotoxic activity of NK and $CD8^+$ T cells.[106]

Role in allergic disease

IL-15 enhances the differentiation into Th2 cells. Furthermore it has been recently shown that endogenous IL-15 plays an important role in the suppression of allergic rhinitis at effector phase.[107] It has been confirmed that IL-15 can increase the number of IgG antibody secreting cells, but decrease the number of IgE antibody secreting cells by ex vivo investigations in humans.[108] These findings support the idea that IL-

15 can serve as a therapeutic agent for treatment of allergic disorders and that IL-15 can influence in vivo the generation of Ag specific IgG, for instance, during vaccination.[108]

Functions as demonstrated in IL-15-deleted mice, receptor-deficient mice, human mutations and the clinical use

Knock-out / transgenic mice

IL-15 and IL-15R$\alpha^{-/-}$ mice show a reduced number of NK cells, NKT cells, $CD8^+$ T cells and almost a total lack of memory phenotype $CD8^+$ T cells, showing that IL-15 is important in the development and homeostasis for NK cells, naive and memory $CD8^+$ T cells.[91, 92] In vesicular stomatitis virus and lymphocytic choriomeningitis virus infection models IL-15 has been shown to be critical in the generation and expansion of virus specific effector $CD8^+$ T-cell clones.[109, 110]

Transgenic expression of IL-15 increases $CD8^+$ T-cell numbers, IL-2-induced AICD was inhibited,[93] and spontaneous development of $CD8^+$ T cell leukemia is observed in IL-15 transgenic mice.[101] Moreover, overexpression of a modified stable form of IL-15 mRNA causes $CD8^+$ T-cell lymphomas.[111] The overexpression of IL-15 in a mouse model of asthma inhibited the allergic inflammation. It also increased antigen-driven memory $CD8^+$ T cells following a microbe exposure.[112, 113] Transgenic mice that over-express human IL-15 from an enterocyte-specific promoter recapitulate pathologic features of celiac disease.[114]

Furthermore, using IL-15-transgenic mice showed the importance of IL-15 in the elimination of colon-carcinoma cells. Whereas wildtype mice were found to die with pulmonary metastases by 40 days after intravenous infusion of the carcinoma cells, IL-15-transgenic mice with large quantities of IL-15 did not develop such metastases and survived. [115]

Human mutations

Humans with a mutation in the common γc (as mentioned above this includes defect signaling of IL-2, -4, -7, -9, -15, -21) suffer from X-linked severe combined immunodeficiency (XSCID) 1, a disease characterized by the absence of T and NK cells but the presence of nonfunctional B cells.

Clinical use

In several studies it has been shown that aberrant expression of IL-15 is associated with the pathogenesis of various autoimmune diseases, therefore the use of IL-15 antibody may play a role in future for the treatment of these diseases.[116, 117]

Recently, IL-15 has emerged as a candidate immunomodulator for the treatment of cancer because boosting IL-15 activity can enhance innate and specific immunity and fight tumors.[95] The direct administration of IL-15 has shown anti-tumor effects in several preclinical mouse tumor models.[118, 119] IL-15 has been shown to be effective when administrated as a vaccine adjuvant in preclinical models of cancer and infectious diseases. [97, 120, 121] There have been several clinical trials initiated using IL-15 . The trials with cancer and HIV infections targeting are either ongoing or recently completed and have yet to be published.[95, 122]

IL-16

Discovery and structure

IL-16 was discovered in 1982 as a T cell-specific chemoattractant secreted from peripheral blood mononuclear cells (PBMCs) and therefore named lymphocyte chemoattractant factor (LCF).[123] The gene for IL-16 is localized on chromosome 15q26.1-3 and Northern Blot analysis identified two transcript of IL-16 mRNA deriving from alternative splicing. There are three main forms of IL-16, including a pro-form that acts as a transcriptional repressor (pro-IL-16),[124] the mature secreted form (IL-16),[125] and a neuronal form (NIL-16).[126]

The IL-16 promoter lacks a TATA box (TATA-less), but contains two CAAT box-like motifs and three binding sites for GA-binding protein (GABP) transcription factor. After translation the 631 amino acids precursor-protein pro-IL-16 (80 kDa) is cleaved by caspase 3 at a serine residue (Ser^{511}),[127] resulting in an N-terminal and C-terminal domain.[124] The 60 kDa N-terminal domain comprises two PDZ domains that mediate protein-protein interactions by binding to other PDZ domains or to the C-terminus of a certain target proteins in a sequence specific fashion. A dual phosphorylation-regulated nuclear translocation sequence drives the protein to the nucleus where it is able to regulate the cell cycle.

IL-16 is a 121 amino acids long basic protein (pI 9.1). The shorter C-terminal fragment has a molecular weight of 14-17 kDa, and it consists of six beta-sheets and a PDZ domain. The peptides aggregate into homotetramers (56 kDa), to form biologically active IL-16 molecules that mediate cytokine functions.[125] IL-16 is an atypical interleukin as it lacks the classical structural motifs present in either interleukins or chemokines.

NIL-16, detected only in neurons of the cerebellum and the hippocampus, is a cytosolic protein that consists of 1322 amino acids (180 kDa). Its N-terminal portion contains four PDZ domains and interacts selectively with a variety of neuronal ion channels. In contrast, the C terminus could be proteolysed by caspase 3, which resulted in the release of secreted mature IL-16.[126]

Cellular sources and targets

IL-16 is mainly produced by lymphatic tissues including T cells, eosinophils, mast cells, monocytes, and dendritic cells (DCs), but also by non-immune cells as fibroblasts, epithelial cells, or synoviocytes under pathological conditions. IL-16 mRNA and pro-IL-16 are constitutively expressed in immune cells, whereas non-immune cells such as epithelial cells have to be induced to transcribe IL-16 mRNA. The generation of mature IL-16 is regulated by the activity of caspase 3. Only $CD8^+$ T cells constitutively express active caspase 3 and cleaved IL-16 homotetramers are stored in cytoplasmic lipid bodies. Upon stimulation of the $CD8^+$ T cells with antigen, histamine, serotonin, or GM-CSF, a preformed protein is rapidly released within 1-4 hours. In contrast $CD4^+$ T cells, eosinophils, mast cells, and DCs depend on stimulation with antigen, IL-4, GM-CSF, IL-1β or TGF-β to activate caspase 3 and generate bioactive IL-16, taking up to 24 hours until IL-16 is released.[128, 129] Like IL-1, IL-16 does not display a signal peptide mediating secretion and ongoing work is investigating the secretory pathway. The targets of IL-16 include all CD4-expressing cell types, such as $CD4^+$ T cells,[130] monocytes,[131] eosinophils,[132] and DCs.[133]

Receptor and signalling

The glycoprotein CD4 is the first cell surface molecule to be described as a functional receptor for IL-16. The binding on CD4 has been localized to the D4 domain.[134] *In vitro* assays demonstrated that IL-16 was shown to mediate its biological activity via CD4.[125] First, recombinant IL-16 was seen to bind to recombinant soluble CD4 and could be purified by affinity chromatography using immobilized CD4. Second, monomeric Fab of anti-CD4 antibody (anti-OKT4 monoclonal antibody) specifically inhibits IL-16-induced functions. The binding site for IL-16 was found to be distant from the MHC class II and human immunodeficiency virus type 1 (HIV-1) gp120 binding regions. Third, the chemoattractant activity of IL-16 for $CD4^+$ monocytes directly correlates with the amount of cell-surface expressed CD4. Moreover transfection of human CD4 into IL-16 nonresponsive mouse T cell

hybridoma cells leads to the activation of signaling cascades and migration upon IL-16 stimulation.

CD4 is constitutively expressed on $CD4^+$ T cells, on $CD8^+$ T cells after anti-CD3 and anti-CD28 stimulation, as well as on monocytes, macrophages, DCs, eosinophils, and mast cells. Binding of tetrameric IL-16 leads to cross-linking of CD4 and the activation of src-related kinase p56lck, which is associated with the intracellular domain of CD4.[135] The kinase activity of p65lck is not required for CD4-mediated motile response, however it is supposed to recruit further signaling molecules via its SH2 and SH3 domains. The activation of protein kinase C (PKC)[136] and its translocation from the cytosol to the cell membrane, together with the activation of phosphatidylinositol 3–kinase (PI3K), increased intracellular Ca^{2+}. The inositol 1,4,5-triphopsphate (IP_3) provide then the link to the cytoskeleton for motile responses.

CD4 knockout mice experiments indicate that PBMCs[137] and Langerhans cells[138] are as responsive to IL-16 as the corresponding cells from wild-type mice suggesting that at least one alternate receptor for this cytokine must exist. The chemokine receptor CCR5 is constitutively linked with CD4 in plasma cell membranes, and soluble CCR5 and CD4 associate *in vitro*.[139] Studies using T cells from CCR5-deficient mice demonstrate that the presence of CCR5 significantly increases binding of IL-16 to the cell surface and migration of T cells.[140] Signaling of IL-16 via CD4 leads to reciprocal desensitization of CCR5 and loss of macrophage-inflammatory protein (MIP)-1β /CCR5-induced chemotaxis, [141] suggesting that the functions of the chemokine receptor CCR5 and CD4 are intimately connected. However, the precise physiological role of CCR5 in IL-16-induced signaling remains unknown.

In mast cells lacking CD4, the IL-16-mediated effects were shown to depend on the tetraspannin CD9, as CD9-specific antisense oligonucleotides or anti-CD9 monoclonal antibodies block the binding of IL-16 to the cell, Ca^{2+} mobilization, and their chemotactic response.[142]

Role in immune regulation and cellular networks

IL-16 serves as a chemoattractant for $CD4^+$ T cells mainly, but also for $CD8^+$ T cells, monocytes, mast cells, and eosinophils.[123] Among the $CD4^+$ T cells, IL-16 preferentially induces migration of T_H1 cell[140] and $FOXP3^+$ Treg cells.[143] Moreover it facilitates *de novo* production of $FOXP3^+$ Treg cells *in vitro*.

IL-16-induced chemotaxis is accompanied by the expression of HLA-DR on monocytes, by increased adhesion of eosinophils to the extracellular matrix, and by the expression of the IL-2Rα subunit (CD25), leading to proliferation in the presence of IL-2. Although IL-16 does not induce the synthesis of IL-2, the pro-inflammatory cytokines TNF-α, IL-1β, and IL-15 are released from T cells upon IL-16 stimulation. At the same time, the synthesis of the T_H2 specific cytokines IL-4 and IL-5 is inhibited without affecting the release of IFN-γ or IL-10.[144] Thus, IL-16 contributes to T_H1-mediated responses and dampens T_H2-mediated inflammation.

In addition, it was shown that binding of IL-16 to CD4 inhibits T cell proliferation induced by antigen, anti-CD3 antibodies, or mixed lymphocyte reactions.[145] By this means, IL-16 renders T cells refractory to antigen-specific activation, but favors the recruitment of nonclonotypic T cells and antigen-independent inflammation. It remains to be elucidated whether this transient inhibition of responsiveness via the CD3/T cell receptor (TCR) complex is due to a negative signal delivered by CD4 or if IL-16 binding sterically inhibits the association of CD4 and the CD3/TCR complex.

Pro-IL-16, the precursor of secreted IL-16, is a T cell growth suppressor. It was found to have a nuclear function independent of its role as a cytokine precursor. In resting T cells pro-IL-16 translocates into the nucleus and recruits histone deacetylase 3 to block gene transcription, resulting in G_0/G_1 cell cycle arrest. Upon activation of the cells the levels of pro-IL-16 decline and the transcription repressor complex dissociates, leading to cell cycle progression and proliferation.[146, 147]

The neuronal variant NIL-16 may play two separate roles, serving as scaffolding protein that anchors ion channels in the membrane and, after processing by caspase 3, as a signaling molecule with autocrine effects.[126]

Role in allergic diseases and other pathologic conditions

IL-16 is associated with exacerbations of various immune-mediated, autoimmune, and infectious inflammatory disorders.[148] For instance patients with allergic asthma show increased secretion of IL-16 from mast cells, epithelial cells, or T cells upon antigen-challenge.[149] Although the levels of IL-16 in the airways were found to correlate with the infiltration of $CD4^+$ T cells, several studies indicate that IL-16 does not play a negative role in asthma, but rather downregulates the allergic response by altering the ratio of T_H1/T_H2 cells. In a murine model of allergic asthma, the administration of exogenous IL-16 during allergen-challenge decreases histological and physiological markers of allergic airway inflammation. Airway hyper-reactivity

was inhibited, accompanied by reduced numbers of eosinophils in BAL. Lymph node cells from IL-16 treated mice produced near baseline levels of IL-4 and IL-5 upon *ex vivo* antigen-stimulation.[144] In human asthmatics, IL-16 is secreted by airway epithelial cells and subepithelial T cells and can be detected in the BAL following allergen or histamine bronchoprovocation. In line with the murine model of allergic asthma, PBMCs from ragweed-allergic individuals release less IL-5 in the presence of IL-16, whereas the level of IFN-γ increased after antigen-stimulation.[150, 151] Moreover IL-16 reduces the expression of the C epsilon transcript and the secretion of IgE in stimulated PBMCs from atopic individuals.[152] Thus IL-16 is supposed to be a natural modulator of allergic inflammation in the lungs, providing opportunities for further investigations and for the potential use of IL-16 or IL-16 derived compounds in the treatment of allergic asthma.

Patients with atopic dermatitis, Crohn's disease, systemic lupus erythematosus, or rheumatoid arthritis have elevated levels of IL-16 in skin, colonic biopsies, sera, or synovial fluids, leading to influx of immune cells into the skin, the colonic mucosa, or the synovial membranes and articular structures of multiple joints.[153-156] The observed levels of IL-16 were found to directly correlate with the numbers of infiltrating $CD4^+$ cells.

Moreover, the TT genotype of a described single nucleotide polymorphism in the IL-16 promoter region (-295 T-to-C) is frequently observed in patients with Asthma[157] and Crohn's disease, and it is supposed to be responsible for increased IL-16 levels in these patients relative to healthy controls.[158] Since IL-16 is supposed to exacerbate the mucosal inflammation in Crohn's disease by promoting the infiltration of $CD4^+$ T cells, treatment of mice with anti-IL-16 monoclonal antibody substantially attenuates colonic injury and inflammation induced in a mouse model of colitis.[154]

Recently distinct single-nucleotide polymorphisms of the IL-16 gene have been reported to be associated with the susceptibility to a range of cancers, including nasopharyngeal carcinoma,[159] colorectal, gastric, and prostate cancers.[160, 161] Several other studies have focused on a close association between IL-16 and cancer, including ovarian carcinoma, breast, lung, gastrointestinal, uterine renal/bladder cancer,[162] hematologic malignancies,[163] such as multiple myeloma[164] or Sézary syndrome.[165] Breast cancer cell derived IL-16 can promote infiltration of monocytes or macrophages into tumor tissue, which is associated poor prognosis.[166] Thus,

inhibition of IL-16 production or activity in the tumor site could be a novel therapeutic strategy.

Interestingly, IL-16 is also detectable in the central nervous system and markedly increased in multiple sclerosis lesions compared to the healthy tissue.[167, 168] During experimental autoimmune encephalomyelitis in mice, which resembles the immunopathology of multiple sclerosis, the levels of IL-16 in the central nervous system correlate with the extent of $CD4^+$ T cell infiltrations and the disease severity.[169] Treatment of paralysed mice with neutralizing anti-IL-16 monoclonal antibody ameliorated the relapsing disease, diminished the $CD4^+$ T cell infiltrations, and reduced axons demyelination.

IL-16 has been identified as a suppressor of human immunodeficiency virus (HIV-1) and simian immunodeficiency virus (SIV) infection. During HIV infections IL-16 was shown to suppress viral replication.[170] Although HIV-1 envelope glycoprotein gp120 and IL-16 share the CD4 receptor, no steric inhibition of viral binding was observed. In contrast binding of CD4 by IL-16 induces a repressor of HIV promoter activity, resulting in inhibition of Tat and PMA induced HIV transcription.

Functions as demonstrated in IL-16- deficient mice and receptor deficient mice

Studies with IL-$16^{-/-}$ mice have demonstrated that pro-IL-16 expression is dynamically regulated during $CD4^+$ T activation, although is not sufficient to alter the proliferation of naive murine $CD4^+$ T cells. Mice deficient in pro-IL-16 have normal proportions of $CD4^+$ and $CD8^+$ T cells, although T cells from spleens of mature knockout mice is ~70% of the total for wild-type mice.[171]

Cells from CD4 deficient mice are as responsive to IL-16 as cells from wild-type animals, indicating that CD4 is not necessarily required for IL-16 function and another molecule may substitute CD4 in transmitting IL-16-induced signaling.[137] CCR5 is supposed to substitute CD4 in transmitting IL-16-induced signaling since studies using T cells from CCR5 deficient mice show reduced binding of IL-16 to the cell surface and diminished T-cell migration.

IL-17A

Discovery and structure

The cDNA encoding IL-17A, initially named CTLA-8 (cytotoxic T lymphocyte-asssociated-8), was first identified by screening a cDNA library from murine cytotoxic

T lymphocyte (CTL) hybridomas.[172] It exhibited 57% identity to a predicted open-reading frame, HSVS13, in the T-lymphotropic herpesvirus *Herpesvirus samiri*.[173] The gene has been cloned and used to search for a receptor binding to CTLA-8. Thereafter, viral and mammalian homologues were renamed IL-17, and the receptor was termed IL-17R. Subsequently, five homologous cytokines have been identified and IL-17, as the founding member of this new cytokine family, has been designated IL-17A. Structurally, the IL-17 family represents a distinct cytokine family with no sequence similarity to any other known cytokines or proteins. The C-termini of all IL-17 family members are conserved and contain four cysteines that account for a characteristic structure, called cysteine-knot.[174] IL-17A is a glycoprotein consisting of 155 amino acids and acts as a disulfide-linked homodimer with a molecular weight of 35 kDa.[173] Heterodimers of IL-17A and IL-17F also exist.[175] Human IL-17A shares significant structural homology as well as glycosylation sites with both mouse and rat IL-17A.[176]

Receptor and signaling

Similar to the cytokines, IL-17 receptors also form a unique family[173], suggesting that IL-17 cytokines and receptors represent a distinct signalling system. In addition to the first identified IL-17R, also named IL-17AR, four additional members have been found based on their sequence homology and have been termed IL-17RB, IL-17RC, IL-17RD and IL-17RE. Although they share only limited sequence similarity, they are all predicted to be type I transmembrane proteins with long intracellular tails. Interestingly, alternative splicing of the receptors IL-17RB and IL-17RC introduces stop codons leading to secreted soluble proteins.[177, 178] IL-17RA consists of a 293 amino acid long extracellular domain, a 21 amino acid long transmembrane domain and a 525 amino acid long cytoplasmic tail.[173] It binds to IL-17A and to IL-17F although with a tenfold lower affinity to the latter.[174] As described for all other known cytokine receptors, IL-17RA is apparently expressed as a preformed multimeric complex before ligand binding.[179] Binding of IL-17A or IL-17F to this complex leads to a conformational change followed by the dissociation of the intracellular domains. Another member of the receptor family, IL-17RC, also contributes to effective binding of IL-17A.[180] Moreover, IL-17RC$^{-/-}$ mice displayed milder disease in the MOG-EAE model and were more susceptible to fungal infections, similar as IL-17RA$^{-/-}$ mice.[181, 182] The signalling cascade downstream the receptors involves mitogen-activated protein kinases (MAPK)[183], as well as NF-κB and PI-3 kinase-Akt pathways[184]. NF-κB

activator 1 (Act1) binds to the cytoplasmic tail of IL-17RA and thereby acts as a critical adaptor for IL-17RA signaling.[185, 186]

Cellular sources and targets

IL-17 cytokine family members appear to come from very distinct cellular sources. IL-17A was originally found to be expressed by activated memory $CD4^+$ T cells.[173] Analysis of various T cells clones revealed that IL-17-producing T cells cannot be classified into Th1 or Th2 subsets, but rather represent a distinct cell population.[187] Some years later, further evidence for a distinct IL-17 secreting effector cell lineage has been provided and this new subset has been named Th17.[188, 189] However, expression of IL-17A has also been detected in $CD8^+$ T cell, $\gamma\delta$ T cells, NK cells, neutrophils, iNK-T cells, LTi and innate lymphoid cells.[190-194]

mRNA encoding the IL-17RA can be found in various tissues like lungs, spleen, kidney and liver.[173] On cellular level, it is detected in fibroblasts, epithelial cells, vascular endothelial cells, B and T lymphocytes, myelomonocytic cells and marrow stromal cells.[176, 195] Expression of the IL-17RC, which is apparently also involved in IL-17A binding, is found in human prostate, cartilage, kidney, liver heart and muscle.[178]

Role in immune regulation and cellular networks

Given the broad expression pattern of its receptor, it is not surprising that IL-17A acts on a large variety of cells. IL-17A was initially found to potently induce IL-6 and IL-8 (CXCL8) in fibroblasts.[173, 196] Subsequently, the induction of further CXC-chemokines like CXCL1 (Gro-α), CXCL6, CXCL10 and CINC by IL-17A in different cells has been reported.[197-200] Tissue fibroblasts and bronchial epithelial cells release IL-6 and IL-11 upon stimulation by IL-17A[201], while certain monocytes respond by secreting TNF-α and IL-1β.[202] Furthermore, IL-17A has been shown to induce colony-stimulating factors like GM-CSF and G-CSF, the monocyte chemotactic protein (MCP)-1 as well as metalloproteases.[200, 203-205] In accordance with induction of these factors, IL-17A has a high potential in the recruitment and activation of neutrophils.[206]

IL-17A's role in neutrophil recruitment is crucial for host protection against various extracellular pathogens, as shown in several *in vivo* infection studies. IL-17A signalling plays an important role in the defence of certain bacteria like *Klebsiella pneumoniae*[207], *Toxoplasma gondii*[208], and *Porphyromonas gingivalis*[209], but also in infections by *Candida albicans.*[210] Furthermore, it plays an important role in neutrophil attraction and abscess formation upon *Bacteroides fragilis* infection.[211]

Role in allergic disease and other pathologic conditions

Increased levels of IL-17A have been found in patients with asthma.[201, 212, 213] This increase may explain the high numbers of neutrophilic granulocytes in allergic airways.[198, 214, 215] IL-17A has also been described to induce expression of two mucin genes MUC5AC and MUC5B, contributing to mucus hypersecretion.[216] Besides, IL-17A might have a role in airway remodelling, a feature commonly observed in severe asthma, as it was shown to induce the profibrotic cytokines IL-6 and IL-11.[217]IL-17A direct action on fibroblasts leads to proliferation and release of proinflammatory factors.[218] Moreover, IL-17A (not IL-17F), produced by αβ T cells, directly enhances the contractile response of airway smooth muscle cells and drives hyperresponsiveness.[219] Therefore, evidence suggests an involvement of IL-17A in chronic inflammation and irreversible changes in asthmatic airways.

Also in the lung, IL-17A is involved in the pathogenesis of chronic obstructive pulmonary disease (COPD) being implicated during exacerbations and in end-stage disease state.[220-222] Additionally, IL-17A production is commonly observed in skin inflammation. Nickel-specific IL-17A secreting T cells have been described in human keratinocytes,[223] and neutralization of IL-17A ameliorated contact hypersensitivity in a mouse model.[224] Furthermore, emerging evidence suggest that IL-17A is involved in the pathogenesis of atopic dermatitis, where IL-17A is expressed preferentially in acute lesions,[225] which are frequently colonized by *Staphylococcus aureus* producing alpha-toxin.[226]

Besides important roles in host defence, IL-17A is involved in several inflammatory disorders. Psoriasis, a chronic inflammatory disease of the skin, was initially suggested to be a Th1 dominated disease, due to the high expression of IFN-γ, IL-2, IL-18 and the p40 subunit of IL-12. However, also levels of IL-17A and other Th17 cytokines are increased in serum and skin of patients with psoriasis.[227] Consistently, IL-23, which induces IL-17A and shares the p40 subunit with IL-12, seems to play a role in the pathogenesis of psoriasis,[228, 229] suggesting a contribution of Th17 cells to the disease. IL-17A induces anti-microbial peptides and matrix metalloproteases that are commonly found in psoriatic skin[230, 231] and in addition, phase I trial of the anti-mAb ixekizumab has shown IL-17A as a key cytokine involved in activation of pathogenic inflammation in patients with psoriasis. [232] In fact, human mAbs neutralizing IL-17A (Secukinumab/AIN457) is used to treat severe plaque

psoriasis[233-235] and has been tested in clinical trials for treatment of psoriatic arthritis, [236, 237] rheumatoid arthritis[238, 239], nail psoriasis, [240] and anklyosing spondylitis.[241, 242]

Clearer is the situation in rheumatoid arthritis (RA), an autoimmune disease characterized by chronic inflammation of synovial tissue in several joints, accompanied by destruction of bone and cartilage. Similar to psoriasis, RA and collagen-induced arthritis (CIA), a mouse model for RA, thought to be Th1-dominated, as mice deficient in the IL-12 subunit p40 were resistant to CIA. It then became clear that IL-23, which also consists of the p40 subunit, is responsible for the disease, rather than IL-12. Increased levels of IL-17A have been found in sera, synovial fluid and in the T cell rich area of the synovium in RA patients,[243, 244] and these levels are predictive of a more severe joint damage progression.[245] Furthermore, IL-17RA is required for full progression of destructive synovitis.[246] Therefore, besides the enhancement of inflammation commonly observed in arthritis, IL-17A also mediates bone and cartilage destruction.

Although elevated levels of IL-17A mRNA have been found in blood and cerebrospinal fluid of patients with multiple sclerosis (MS)[247], very few studies have investigated the role of IL-17A in this disease. Evidence for a function of IL-17A in MS comes from studies using the mouse model experimental autoimmune encephalomyelinitis (EAE). Although previously it was considered to be a Th1-disease, it became apparent that IL-17A-producing cells are sufficient to induce EAE upon adoptive transfer into susceptible mice.[248] In the human disease MS, recent data suggest that IL-17A disrupt the blood-brain barrier, thereby promoting inflammation of the central nervous system.[249] In addition to Th17 cells, IL-17A secreting CD8+ T cells support the initiation of CNS inflammation.[250] Apparently, more work is needed to characterize all effects of IL-17A in this disease.

An involvement of IL-17A becomes apparent in inflammatory bowel disease (IBD), specifically in Crohn's disease and ulcerative colitis, as biopsies from inflamed colonic tissue of IBD patients showed increase levels of IL-17A.[251] As IL-17A stimulates production of matrix metalloproteases and the release of proinflammatory cytokines in colonic subepithelial myofibroblasts, [252] it strongly contributes to the chronic inflammation characteristic for this disease. In addition, IL-17A inhibits the proliferation of intestinal epithelial cells,[253] suggesting that it might interfere with the repair mechanism important for the maintenance of the tissue integrity.

IL-17A has been associated with graft-versus-host-disease. It was shown that the cytokine increases proinflammatory cytokines and recruitment or priming of Th1 cells in lymphoid organs following bone marrow transplantation.[254]

Functions as demonstrated in IL-17A-deficient mice, receptor-deficient mice and transgenic models

Initial studies investigating IL-17A$^{-/-}$ mice suggest an important role for IL-17A in allergen-specific T cell-mediated immune responses, as airway hypersensitivity responses as well as T cell dependent antibody production were significantly reduced in these mice.[255] More recent studies showed that, in line with IL-17A's role in host defence, IL-17RA-deficient mice have a markedly reduced survival after pulmonary *Klebsiella pneumoniae* infection, accompanied by a reduced number of neutrophils in the lung.[207] These mice were also more susceptible to *Toxoplasma gondii*[208], *Candida albicans*[210], *Porphyromonas gingivalis*[209] infections.

IL-17A$^{-/-}$ mice develop significantly less arthritis[256] and IL-17RA is required for full progression of destructive synovitis[246], indicating a function of IL-17A in RA. Similarly, IL-17A plays a role in EAE, as adoptive transfer of Th1 lines into IL-17A-deficient mice lead to reduced EAE clinical outcomes.[257] In addition, IL-17RC$^{-/-}$ mice similar as IL-17RA$^{-/-}$ mice display milder disease in the MOG-EAE model and are more susceptible to fungal infections.[181, 182]

Another study suggests a role for IL-17A signalling in haematopoiesis after radiation, as haemopoietic toxicity is significantly more pronounced in IL-17RA knockout mice when challenged with gamma irradiation.[258] However, it should be kept in mind that IL-17RA binds also to IL-17F. Effects observed in IL-17RA-deficient mice can therefore be due to defective signalling of IL-17A or IL-17F or even both.

IL-17B

Discovery and structure

IL-17B has been identified based on its sequence homology to IL-17A.[259,260] With 29% homology, it is less related to IL-17A than IL-17F, but more than the other family members. Human IL-17B shares 88% homology with mouse IL-17B and it is localized to the human chromosome 5q32-34. IL-17B is a glycoprotein of 180 amino acids in length, giving rise to a molecular weight of 41 kDa. Like the other IL-17 family members, it bears four cysteines in its C-terminus that account for a characteristic

structure called cysteine-knot.[174] This cysteine-knot is a common structural motif found in many growth factors such as bone morphogenetic proteins (BMP), transforming-growth factor (TGF)-β or nerve growth factor (NGF). However, the knot in these proteins is formed by six cysteines compared to four cysteines found in IL-17 family members. Interestingly, while the subunits of IL-17A, IL-17C, IL-17D, IL-17E and IL-17F are covalently linked by a disulfide bond in the dimeric structure, IL-17B dimers are non-covalently linked.

Receptor and signalling

The receptor for IL-17B, IL-17RB (also named IL-17RH1, evi27 or IL-25R), has been identified by sequence homology to the IL-17RA.[259] IL-17RB is 426 amino acids in length and, surprisingly, lacks the long cytoplasmic tail observed in its homologue IL-17RA. Receptor binding revealed that IL-17B binds with relatively high affinity to IL-17RB, while no binding to IL-17RA was observed.[259,260]

Interestingly, alternative splicing of IL-17RB introduces stop codons, leading to the production of secreted soluble proteins that might act as decoy receptors.[178,177] It has not been demonstrated yet whether this happens *in vivo.* Later, IL-17RB has been found to bind also IL-17E (also termed IL-25), another IL-17 family member.[261] The affinity of IL-17RB for this cytokine was even higher than that observed for IL-17B. Although the intracellular parts of IL-17RA and IL-17RB differ dramatically in size, they share some elements, suggesting that these receptors engage similar signalling pathways. This is supported by the finding that signalling by IL-17E through IL-17RB induces activation of NF-κB, a transcription factor also involved in IL-17RA signalling. Further studies need to be done to elucidate the exact mechanism of the signalling downstream IL-17RB.

Cellular sources and targets

In contrast to its homologue IL-17A, IL-17B does not seem to be expressed in immune cells. Instead, IL-17B was detected in spinal cord, testis, small intestines, pancreas, stomach, prostate, ovary and colon mucosal lining.[259,260] Another study confirmed the high expression in spinal cord.[262] In an analysis of human spinal cord, dorsal root ganglia, cerebral cortex, cerebellum, and hippocampus, IL-17B protein was shown to be primarily localized to the neuronal cell bodies and axons.

Other reports describe the expression of IL-17B in chondrocytes and mouse limb buds, suggesting a role for IL-17B in chondrogenesis and osteogenesis.[176,263] Similarly, the receptor IL-17RB is expressed in kidney, liver, pancreas, testis, colon,

and small intestines, but not in lymphocytes.[261,259] The expression pattern of IL-17B and its receptor together with the fact that IL-17B stimulates the release of TNF-α and IL-1β from a cell line[260], suggest IL-17B to be involved in inflammatory responses like its family member IL-17A.

Role in immune regulation and cellular networks

Compared to IL-17A and IL-17F, relatively little is known about the physiological function of IL-17B. One study describes IL-17B to be expressed in calf articular cartilage but not in adult cow cartilage, suggesting a role in cartilage development.[263] Consistently, IL-17B mRNA was maximally expressed in the limb buds of 14.5 days post coitus (dpc) mouse embryos and declined to low level at 19.5 dpc. IL-17B expression was high in cells of the bone collar in the primary ossification center, while chondrocytes in the resting and proliferative zones expressed moderate levels of IL-17B. In accordance with these findings, another report identifies IL-17B expression during fracture healing, where IL-17B was localized in prehypertrophic chondrocytes of both the growth plate and the fracture callus.[264] Therefore, IL-17B appears to be involved in embryonic chondrogenesis as well as in tissue regeneration.

One study addressing the mechanism of Bacillus Calmette-Guerin (BCG) treatment found that, among many other cytokines, IL-17B was induced upon intravesical BCG application.[265] While acute BCG instillation upregulated IL-17A, IL-17B, and IL-17RA, chronic BCG also induced IL-17RB. In another report, intraperitoneal injection of IL-17B into normal mice was found to cause marked neutrophil migration in a dose-dependent manner.[259] These findings suggest a role for IL-17B in host defence, especially in tissues where IL-17A and IL-17F are not expressed.

Role in allergic disease and other pathologic conditions

So far, no role for IL-17B in asthma or allergy has been described. One study found an association of IL-17RB gene polymorphism with asthma.[266] However, given IL-17B's expression pattern, it is more likely that these effects are due to signaling by IL-17E, a Th2 cytokine also using IL-17RB as a receptor.

In pancreatic cancer, IL-17RB overexpression correlates with metastasis and a lower patient survival rate. IL-17B induces chemokine secretion, which can increase the tumour's malignancy. Anti-ILRB treatment was effective in a mouse model.[267]

Given the clear involvement of IL-17A in RA together with the finding that IL-17B and IL-17RB are expressed in cartilage, it can be suspected that IL-17B is implicated

in RA as well. A few studies addressed the expression of IL-17B and its receptor in RA patients. One of them found that synovial fluid mononuclear cells (SFMC) expressed IL-17RB.[243] However, the expression has not been compared with levels in SFCM from healthy individuals. Another study detects IL-17B expression in 17 of 19 nodules of patients with RA, while IL-17A gene expression was present in only 1 of 19 nodules.[268] Stronger evidence for a role of IL-17B in RA comes from a report using collagen-induced arthritis (CIA), a mouse model of RA.[269] In this study, elevated levels of IL-17B could be observed in the arthritic paws of CIA mice. *In vitro*, IL-17B induced TNF-α production in mouse peritoneal exudate cells, while adoptive transfer of IL-17B transduced $CD4^+$ T cells evidently exacerbated arthritis. Furthermore, IL-17B bone marrow chimeric mice exhibited elevated serum TNF-α concentration and a high arthritis score upon CIA induction, while neutralization of IL-17B significantly suppressed the progression of arthritis and bone destruction in CIA mice.

As IL-17B is expressed in prostate and ovary, its role in cancer affecting these tissues has been studied. In one study, an association between the expression ratio of homeobox 13 (HOXB13) to IL-17RB and increased relapse and death has been found in patients with tamoxifen treated breast cancer.[270] Taken together, while evidence strongly suggests a role of IL-17B in RA, its involvement in cancer and other diseases is less clear. Further studies need to be done to elucidate the functions of IL-17B, and to analyse, which of these functions overlap with IL-17A and which of them are distinct.

IL-17C

Discovery and structure

IL-17C has been identified based on a sequence similarity search of an expressed sequence tag (EST) database and a full-length cDNA was isolated from a human fetal kidney library.[260] IL-17C shares 23% homology with the founding family member IL-17A and 83% homology with its murine homologue. Consisting of 197 amino acids, it is the second longest family member and has a molecular weight of 40 kDa. Like the other IL-17 family members, its structure is characterized by four cysteines in the C-terminus that account for the so-called cysteine-knot.[174] This cysteine-knot is a common structural motif found in many growth factors such as bone morphogenetic proteins (BMP), transforming-growth factor (TGF)-β or nerve growth factor (NGF).

However, the knot in these proteins is formed by six cysteines compared to four cysteines found in IL-17 family members. IL-17C is likely to act as a homodimer with the two monomers covalently linked by a disulfide bond. It has been mapped to chromosome 16q24 in human and 8E1 in mice.[260]

Receptor and signalling

IL-17C, like IL-17B, is not binding to the IL-17RA, as shown in an immunoprecipitation experiment.[260] Recently, IL-17RE was shown as a specific to IL-17C. The signalling occurs via IL-17RA-IL-17RE receptor complex and the downstream adaptor Akt1.[271, 272]

Cellular sources and targets

In contrast to IL-17B, which is expressed in many tissues like spinal cord, testis, small intestines, pancreas, stomach, prostate, ovary, colon mucosal lining, IL-17C has not been detected in these tissues.[260] Furthermore, under these conditions, IL-17C is not detected in $CD4^+$ T cells, which are a major source of IL-17A and IL-17F. However, it has been found as a rare EST in an adult prostate and fetal kidney libraries. Several reports describe expression of IL-17C under certain pathological conditions. For example, one study finds IL-17C to be expressed in arthritic paws of collagen-induced arthritis (CIA) mice.[269] More specifically, IL-17C was expressed in $CD4^+$ T cells, $CD11b^+$ MHC class II^+ macrophages, and CD11c+ MHC class II^+ dendritic cells. Consistently, expression of IL-17C has been found in synovial fluid mononuclear cells (SFMC) of rheumatoid arthritis (RA) patients, but also in peripheral blood mononuclear cells (PBMC).[243] Furthermore, IL-17C expression was found in lung tissue of mice infected with *Mycoplasma pneumoniae*.[273] IL-17C wa shown to induce expression of nuclear IkappaB family member, IκBξ, in Th17 cells, what potentiates their response.[271]

IL-17C was found to bind to the surface of the monocytic cell line THP-1 and to induce IL-1β and TNF-α production in these cells, suggesting that it acts on cells of this cell line.[260] Interestingly, while IL-17A is known to induce IL-6 production in fibroblasts, no influence of IL-17C has been observed on these cells. In a second study, IL-17C was shown to induce IL-6, IL-8, leukemia inhibitory factor (LIF) and matrix metalloproteinase (MMP)-3 secretion in human subepithelial myofibroblasts (SEMF), although the effects of IL-17A and IL-17F were more pronounced.[252] Recently, colon epithelial cells, tracheal epithelial cells and keratinocytes were described as main cellular sources and targets for IL-17C.[272, 274]

Like IL-17A, IL-17C is increased in IBD. The cytokine is released by enteroendocrine and goblet cells.[275]

Role in immune regulation and cellular networks

To date, relatively little is known about the function of IL-17C. As IL-17C was shown to act on cells in a similar ways as its better known family members, namely to induce proinflammatory cytokines like IL-1β and TNF-α and IL-6, it can be supposed that IL-17C has similar functions as IL-17A. In particular, IL-17C might take over functions of IL-17A in tissues where IL-17A is not expressed, or it might act on cells that do not express the IL-17RA. Interesting is the fact that IL-17C seems not to depend on IL-23 for its induction but instead rather induces IL-23.[269, 273] Therefore, one could imagine a mechanism, in which IL-17C upregulates IL-17A through the induction of IL-23, thereby representing a potent inducer of a proinflammatory cascade. Further investigations are needed to elucidate these complex but interesting and important events.

A report showing an upregulation of IL-17C in mice infected with *Mycoplasma pneumonia*, suggests a role for IL-17C in host defense.[273] IL-17C was increased not only in bronchoalveolar lavage (BAL), but also in lung tissue of infected mice compared to the control. Interestingly, IL-23, a strong regulator of IL-17A and IL-17F, did not have any influence on IL-17C expression, suggesting a distinct upstream regulatory pathway. Moreover, the mucosal and cutaneous epithelial cells produce IL-17C in response to cytokines: IL-1β and TNF-α, and after TLR2 and TLR5 stimulation.[274, 276] Recently, IL-17C was shown to act in synergy with IL-22 to induce the expression of antibacterial peptides in colon epithelial cells, what confirmed IL-17C role in early host defense.[272] In addition, Il-17C influence on intestinal barrier function includes tight junction protein occluding expression regulation.[277]

Role in allergic disease and other pathologic conditions

IL-17A and IL-17F seem to contribute to allergic disease by attracting neutrophils to the inflamed airways. One study addressed the question, whether a similar role could be attributed to IL-17C. Indeed, adenoviral administration of IL-17C induced neutrophilia in bronchoalveolar lavage of treated mice.[278] As IL-17C expression was found in lung tissue of mice infected with *Mycoplasma pneumoniae*[273], it might contribute to the attraction of neutrophils in asthma as well. It remains to be

elucidated, whether IL-17C is also found in human lungs and if yes, under which conditions.

Although only few studies addressed the role of IL-17C in disease, there is some evidence for an involvement of this cytokine in rheumatoid arthritis (RA), given IL-17C's potential to induce proinflammatory cytokines and metalloproteases. One study reported the expression of IL-17C in synovial fluid mononuclear cells of rheumatoid arthritis patients, but also in peripheral blood mononuclear cells (PBMC).[243] Interestingly, while IL-15 decreased the levels of IL-17C in normal PBMC, IL-17C was clearly upregulated by IL-15 in SFMC and PBMC of RA patients. Similarly, a study investigating nodules of RA patients found IL-17C expression in 18 of 19 nodules, while IL-17A was present in only one nodule.[268] As tissue destruction in the nodules was observed also in the absence of IL-17A, and as IL-17C is known to induce matrix metalloproteinase (MMP)-3 secretion in certain cells, it might be that IL-17C accounts for the destruction of the nodule tissue. However, further experiments need to be performed to confirm the hypothesis.

The role of IL-17C has also been addressed using collagen-induced arthritis (CIA), a mouse model of RA. IL-17C expression was found to be elevated in the arthritic paws of CIA mice, specifically in $CD4^+$ T cells, $CD11b^+$ MHC class II^+ macrophages, and $CD11c^+$ MHC class II^+ dendritic cells.[269] In this study, IL-17C induced IL-1β in the fibroblast cell line *3T3* and IL-1β and IL-23 expression in peritoneal exudate cells (PEC). While these results are a hint for an involvement of IL-17C in RA, stronger evidence comes from an experiment, in which IL-17C-transduced $CD4^+$ T cells were adoptively transferred before onset of arthritis. In the recipients, an exacerbation of arthritis was observed, strongly suggesting a role for IL-17C. Moreover, bone marrow chimeric mice of IL-17C exhibited elevated serum TNF-α concentration and a high arthritis score upon CIA induction. Additionally, higher levels of IL-23 and IL-6 could be found in the spleen of these mice. In summary, these reports suggest a role of IL-17C in RA, as it is observed for the better-known family member IL-17A.

Interestingly, IL-17C was shown to be necessary to pathogenesis of EAE, as increased numbers of CD4+ lymphocytes producing this cytokine were detected in CNS of mice with EAE.[271] Moreover, IL-17C seems to contribute to proinflammatory cytokines and chemokines release in psoriasis-like murine model. In the contrary, loss of IL-17C led to DSS colitis severity increase.[274] As IL-17C can exhibit different type of response depending on the site of action, further investigation of its role is

needed. Taken together, although relatively few reports investigated the role of IL-17C in disease, there is a strong potential for this cytokine in several disorders.

Functions as demonstrated in IL-17C-deleted mice, receptor-deficient mice and transgenic models

A recent study analyzed mice deficient in IL-17RE and revealed IL-17C specific function in the intestine.[272] Lower expression of genes encoding antibacterial molecules, greater bacterial burden and early mortality during infection represent effects due to lacking IL-17C action.

IL-17C function in CNS was studied in IL-17C$^{-/-}$ mice.[271] This cytokine seems to be important in EAE pathogenesis and CNS inflammation as IL-17C$^{-/-}$ mice exhibited decreased EAE symptoms and Th17 cell-related mediators.

IL-17D

Discovery and structure

IL-17D was identified and cloned based on its homology to the other IL-17 family members.[279] With 202 amino acids in length and a molecular weight of 52 kDa, it is the largest IL-17 family member. IL-17D shares 25% homology with the founding family member IL-17A and with 27% identity, it is most homologous to IL-17B. 78% homology is found between human and mouse IL-17D. As commonly observed for IL-17 family members, IL-17D has four cysteine residues that may participate in interchain disulfide linkages. It probably exists as a homodimer with the two monomers covalently linked by a disulfide bridge. Unlike other members of the IL-17 family, IL-17D shows an extended C-terminal domain, which may mediate a unique receptor interaction. IL-17D was mapped to chromosome 13p11, a region that has been linked to translocations found in Hodgkin's lymphoma.

IL-17D is the most evolutionary conserved member as four divergent fish species share significant sequence identity and synteny with mouse and human IL-17D genes. In Lamprey (*Lethenteron japonicum*) for example, a single IL-17 gene (*LampIL-17*) has been found.[280] This gene was most homologous to IL-17D of other species. Similarly, the IL-17 protein from pacific oyster, *Crassostrea gigas* (*CgIL-17*) was compared with other sequences and it was found to be most similar to the IL-17D member of other species.[281] IL-17D genes have been identified also in rainbow trout, sea urchin, zebrafish, pufferfish as wells as in chicken and opossum.[282, 283] As IL-17 family members can be regulated by TGF-β and IL-1β, which are components

of the innate immune system, the IL-17 family might have been evolved to bridge innate and adaptive immunity.

Receptor and signalling

The receptor of IL-17RD/SEF also known as SEF; HH18; IL-17RD; IL17RLM has been identified. This gene encodes a membrane protein belonging to the interleukin-17 receptor (IL-17R) protein family.

Cellular sources and targets

IL-17D is highly expressed in skeletal muscle, brain, adipose tissue, heart, lung, and pancreas.[279] Lower levels of expression were found in bone marrow, fetal liver, kidney, lymph node, placenta, spleen, thymus, tonsil, resting $CD4^+$ T cells, and resting $CD19^+$ B cells. Interestingly, while IL-17A and IL-17F are expressed in T cells upon activation, IL-17D in contrast is poorly expressed in activated $CD4^+$ T cells and activated $CD19^+$ B cells. Both resting and activated $CD8^+$ T cells as well as resting and activated $CD14^+$ monocytes show low levels of IL-17D. The expression of IL-17D has also been analyzed in zebrafish (*Danio rerio*) and was observed in intestines and gills in both normal and LPS stimulated tissues.[282] Expression in non-induced conditions has not been observed for other members of the IL-17 family, indicating that IL-17D may have a unique role under normal conditions. In chicken, however, IL-17D expression was increased following *Eimeria maxima* infection in $CD4^+$, $CD8^+$ and $TCR1^+$ intestinal intraepithelial lymphocytes, while decreased expression was seen in $TCR2^+$ cells[283], suggesting some differences between species.

Similar to IL-17C, no receptor for IL-17D has been identified so far. Even though, some cellular targets have been identified. Among them are endothelial cells and myeloid progenitor cells like granulocyte/macrophage, erythroid and granulocyte/erythroid/monocyte/megakaryocyte progenitors.[279, 284] Like other family members, IL-17D acts on epithelial cells and chicken fibroblasts.[279, 283] Furthermore, IL-17D was shown to modulate human umbilical vein endothelial (HUVEC) cells and subepithelial myofibroblasts.[252, 279] Taken together, although differences between species may exist, IL-17D seems to be expressed mainly by immune cells and to act on many different tissue cells, similar to IL-17A and IL-17F. The conditions, under which IL-17D is expressed, however, appear to be different.

Role in immune regulation and cellular networks

Interestingly, IL-17D has been shown to suppress myeloid progenitor cell proliferation.[279] At a dose of 200 ng/ml, IL-17D inhibited granulocyte/macrophage,

erythroid and granulocyte/erythroid/monocyte/ megakaryocyte progenitor colony formation by an average of 39%, 32%, and 38%, respectively. However, IL-17D did not influence the proliferation of resting normal peripheral blood mononuclear cells (PBMC) or $CD5^+$ T cells. Like other family members, IL-17D acts on epithelial cells and stimulates them to produce IL-6 and IL-8. The same effect was also observed in chicken fibroblasts.[283] Furthermore, in HUVEC cells, which normally do not produce GM-CSF, significant secretion of GM-CSF was observed upon stimulation with IL-17D. IL-17D was also shown to induce IL-6, IL-8, leukemia inhibitory factor (LIF) and matrix metalloproteinase (MMP)-3 secretion in subepithelial myofibroblasts, although the effects was only modest compared to IL-17A and IL-17F.[252] Taken together, IL-17D seems to act on tissue cells in similar ways as IL-17A and IL-17F, although under different conditions, suggesting non-overlapping roles for these cytokines.

The fact that IL-17D is evolutionary highly conserved, strongly suggests an important role for this cytokine in the defence of pathogens. Indeed, the bacterial component LPS upregulates the lamprey homologue of IL-17D (*LampIL-17*) in the skin, mainly in basal layer epithelial cells.[280] Similar observations have been made in pacific oyster *Crassostrea gigas*.[281] Hemocytes from oysters injected with bacteria showed a very large and rapid increase in the IL-17D homologue *CgIL-17*. The rapid induction upon encountering pathogens suggests it to be a very early response gene that may be responsible for the stimulation of other immune genes in oyster. In chicken, levels of the IL-17D transcript were significantly increased in jejunum, bursa, lung and spleen after infection with *Eimeria maxima*, the parasite causing avian coccidiosis.[283] The greatest increase was noted in $CD4^+$ intestinal intraepithelial lymphocytes (IEL). These reports support an important role for IL-17D in the defence of bacteria and parasites. It remains to be determined, whether IL-17D plays a similar important role in host defence in human, or whether its function can be covered by other IL-17 family members that do not exist in lower species.

Role in allergic disease and other pathologic conditions

Until present, no role for IL-17D in asthma or allergy has been described. As IL-17D has been shown to induce proinflammtory and granulocyte-attracting factors, it can be supposed to play a role similar to the one observed for its family members. However, only few reports addressed the function of IL-17D in disease. One of them identified IL-17D in 16 of 19 nodules of patients with rheumatoid arthritis (RA).[268] Interestingly, IL-17A, which has an important role in RA, was present in only one

nodule out of 19, suggesting that IL-17D might take over its job in tissues where IL-17A is not expressed. In contrast, IL-17D was not detected in synovial fluid or in peripheral blood mononuclear cells of RA patients.[243] Another study finds IL-17D to be increased in inflammatory cardiomyopathy (DCMi), a cardiac phenotype characterized by dilation and dysfunction of the ventricles.[285] As IL-17D stimulates production of IL-6, IL-8, and granulocyte/macrophage colony-stimulating factor (GM-CSF) in human endothelial cells, its upregulation may enhance the activation of the endothelium and contribute to the inflammation. This hypothesis, however, awaits confirmation. In a third study, IL-17D has been detected in nasal granulomas of patients with Wegener's granulomatosis, a disease characterized by an inflammation of blood vessels that lead to damages in important organs of the body.[286] The role of IL-17D in this disease is still unknown, although a contribution to the observed inflammation can be hypothesized from the functions observed in other studies. Finally, IL-17D expression is decreased in metastatic human tumours. This cytokine indirectly recruits NK cells for tumour rejection, being a possible approach for tumour immune therapy.[284] Therefore, the proinflammatory nature together with the broad expression pattern make lL-17D likely to be involved in many inflammatory disorders, acting in organs were IL-17A is not expressed. However, more work is needed to investigate this interesting and relevant issue.

IL-17F

Discovery and structure

IL-17F has been identified based on its sequence homology to IL-17A, as, so far, last member of the IL-17 cytokine family.[287, 288] IL-17A and IL-17F show the highest degree of homology, being 50% identical on protein level. While the other family members are located to different chromosomes, IL-17A and IL-17F are syntenic on mouse chromosome 6, suggesting a common regulatory mechanism. Two isoformes of IL-17F have been identified, a longer and a shorter form (ML-1).[287, 288] The crystal structure of IL-17F has been solved.[174] It reveals that IL-17 family members adopt a monomer fold typical of cysteine knot growth factors such as TGF-β, nerve growth factor or bone morphogenetic proteins. In contrast to these factors, where the cysteine knot is formed by six cysteines, the knot in IL-17 family members consists of four cysteines. The structural features of IL-17F suggest it to form homodimers with each monomer forming a flat interface that is covalently linked by a disulfide

bridge.[174] Given high sequence homology, it is not surprising, that also heterodimers consisting of an IL-17A monomer and an IL-17F monomer exist.[175, 289, 290]

Receptor and signalling

Like IL-17A, IL-17F binds to the receptor IL-17RA, although with more than tenfold lower affinity.[174] IL-17RA consists of a 293 amino acid long extracellular domain, a 21 amino acid transmembrane domain and a 525 amino acid long cytoplasmic tail.[173] As described for all other known cytokine receptors, IL-17RA is apparently expressed as a preformed, multimeric complex before ligand binding.[179] Binding of IL-17A or IL-17F to this complex leads to a conformational change followed by the dissociation of the intracellular domains. Both IL-17A and IL-17F have been shown to bind with high affinity to IL-17RC, another family member of the IL-17 receptors.[291] Apparently, both IL-17RA and IL-17RC are required for efficient IL-17F signalling, at least under certain conditions.[292] The signalling cascade downstream involves mitogen-activated protein kinases (MAPK)[183], as well as NF-κB and PI-3 kinase-Akt pathways.[184] NF-κB activator 1 (Act1) binds to the cytoplasmic tail of IL-17RA and thereby acts as a critical adaptor for IL-17RA signaling.[185, 186] Furthermore, TRAF6-mediated ubiquitination of the receptor is critical for IL-17F signaling.[293]

Cellular sources and targets

In accordance with the close localization of IL-17A and IL-17F on chromosome 6, there are no reports showing a discordant expression to date. Like IL-17A, both isoforms of IL-17F have been found in activated memory T cells, later defined as Th17 cells.[188] The shorter isoform has also been detected in blood basophiles and mast cells, while the longer isoform was expressed by monocytes.[287, 288]

The receptor for IL-17F, IL-17RA can be found in various tissues like lungs, spleen, kidney and liver.[173] On cellular level, it is detected in fibroblasts, epithelial cells, vascular endothelial cells, B and T lymphocytes, myelomonocytic cells and marrow stromal cells.[176, 195] Expression of the IL-17RC, also important for IL-17F signalling, is found in human prostate, cartilage, kidney, liver, heart and muscle.[178]

Role in immune regulation and cellular networks

Like IL-17A, also IL-17F acts on a large variety of cells and induces a similar panel of proinflammatory cytokines. IL-17F was shown to induce IL-6 and IL-8 in epithelial and endothelial cells and fibroblasts[174], but also C-X-C chemokines like CXCL1 (Gro-α) and epithelial cell-derived neutrophil-activating protein (ENA)-78[294]. Endothelial cells stimulated with IL-17F respond with increased expression of IL-2, TGF-β and

monocyte chemoattractant protein (MPC)-1.[287] Other studies report induction of MIP-1beta/CCL4, IL-1β, G-CSF, GM-CSF and IFN-γ-inducible protein 10 (IP-10).[295-298] The potency of IL-17A/IL-17F heterodimers in the induction of IL-6 and CXCL1 in one study demonstrating an intermediate activity for the heteromer as compared to the homodimers.[289] Therefore, similar to IL-17A, IL-17F has a highly proinflammtory and chemoattractant potential.

The protective role of IL-17F against infection has not as extensively studied as it has been done for IL-17A. However, given the high potential in the recruitment and activation of neutrophils, it can be assumed that IL-17F contributes to host defence in a similar way. This idea is supported by the observation that not only IL-17A, but also IL-17F is induced upon infection by gram-negative bacteria like *Klebsiella pneumoniae*.[299]

Given the fact that IL-17F induces a similar panel of genes, signals via the same receptor, and is induced under similar conditions as IL-17A, it can be assumed to be involved in psoriasis and rheumatoid arthritis as well. Although the role of IL-17F in disease is not extensively studied, a recent report investigated the potency of IL-17F in the induction of the neutrophil attractant chemokine IL-8 and found that IL-17F was a stronger inducer of IL-8 compared to IL-17A.[300] IL-17F induced IL-8 in both human epidermal keratinocytes (NHEK) and in mouse skin, where also neutrophilia was observed. Furthermore, the study identified elevated levels of IL-17F in injured skin of psoriasis patients, supporting a role of IL-17F in this disease. IL-17F's potency to attract neutrophils has also been shown by another report. Using an adenoviral gene transfer method, IL-17F was introduced to the mouse airways, resulting in bronchoalveolar lavage neutrophilia and inflammatory gene expression in the lung.[278] Elevated levels of IL-17F mRNA have been detected in inflamed colonic lesions of patients with Crohn's disease.[301] Although the exact role of IL-17F in the disease is still unknown, it can be assumed to be similar to that of IL-17A, namely to contribute to the characteristic chronic inflammation and to interfere with tissue integrity. Surprisingly, a recent study shows that IL-17A, but not IL-17F, was required for the initiation of EAE, providing evidence that IL-17A and IL-17F might act differently in some situations.[302] While these studies suggest an involvement for IL-17F in inflammation in diseases like psoriasis and Crohn's disease, the role of IL-17F in other inflammatory disorders like rheumatoid arthritis and multiple sclerosis awaits further elucidation.

Role in allergic disease and other pathologic conditions

Several reports support a role for IL-17F in allergic asthma and severe asthma.[303] The shorter isoform of IL-17F (ML-1) was observed in allergen-specific T cells, mast cells and basophils and it was increased following allergen challenge in asthmatic subjects, suggesting a function in allergic inflammatory responses.[288] Further evidence comes from studies using mouse models. IL-17F was induced in bronchial epithelial cells and infiltrating inflammatory cells upon challenge with OVA.[304] Pulmonary gene transfer of an IL-17F expression construct induced pulmonary neutrophilia and amplified antigen-induced allergic response.[305] Interestingly, another study found that mice deficient in IL-17F, but not IL-17A, had defective airway neutrophilia in response to allergen challenge.[302] In contrast to IL-17A-deficient mice, IL-17F-deficient mice displayed enhanced Th2 cytokine production and eosinophil function, suggesting a diverse effect of IL-17A and IL-17F.

Therefore, IL-17F seems to contribute to allergic disease by attracting neutrophils, a phenomenon, also observed for IL-17A as well as IL-17A/IL-17F heterodimers.[175] Besides, IL-17F has an influence on goblet cell hyperplasia and pulmonary mucus hypersecretion, as it enhances mucin gene expression. Moreover, induction of IL-17F by IL-33 was shown in patients with asthma, indicating an importance of IL-33/IL-17F axis in this disease.[306] The observation that TGF-β is induced by IL-17F in human endothelial cells might be a hint of an involvement in airway remodelling, commonly observed in severe asthma.

Functions as demonstrated in IL-17F-deleted mice, receptor-deficient mice and transgenic models

A recent study analysed mice deficient in IL-17F and revealed several differences between IL-17A and IL-17F.[302] In contrast to IL-17A, IL-17F was not required for the initiation of EAE. In addition, IL-17F deficiency resulted in reduced colitis, while IL-17A knockout mice developed more severe disease. Mice deficient in IL-17F, however, had defective airway neutrophilia in response to allergen challenge, but displayed enhanced type 2 cytokine production and eosinophil function. It therefore seems that IL-17F functions differently from IL-17A, at least in certain conditions.

It should be kept in mind that also IL-17F signals via IL-17RA and that effects observed in IL-17RA-deficient mice could be ascribed to functions of either IL-17A or IL-17F or both. Therefore, the increased susceptibility of IL-17RA knockout mice to *Klebsiella pneumoniae*, *Toxoplasma gondii*, *Candida albicans* and *Porphyromonas*

gingivalis infection might be, at least partially, an effect of a impaired IL-17F signaling.[207-210]

As IL-17F is located to a genomic region linked to asthma and asthma-related phenotypes, it has been tested for associations between single-nucleotide polymorphisms (SNP) and asthma.[307] A total of 50 SNP and two insertions/deletions were detected in IL-17F. Interestingly, an IL-17F sequence variant where one histidine is substituted with arginine (His161Arg) is associated with protection against asthma.[308] This variant of IL-17F lacks the ability to activate the signalling pathway and thereby antagonizes wild-type IL-17F activity. Consistent observations have been made in a study investigating the His161Arg variant in chronic fatigue syndrome (CFS), where a lower frequency of this protective IL-17F variant in chronic fatigue syndrome patients was detected.[309] Association of this variant with IBD is controversially discussed. One study describes His161Arg variant as a risk factor for ulcerative colitis[310], whereas another report found no association of the polymorphism with this disease[301]. While most reports concentrated on the His161Arg SNP, analysis of the variants Ala126Gly, Gly155Ala, and Ala161Gly revealed that certain combinations of these SNP might influence the susceptibility of Behcet's disease.[311]

IL-18

Discovery and structure

IL-18, a member of IL-1-super-family, was first described 1989 as an interferon gamma-inducing factor and later the gene was cloned and termed IL-18. [312] The human IL-18 gene is localized on chromosome 11q22.2-q22.3. [313] IL-18 shares structural features with other IL-1 family cytokines. IL-18 also lacks a signal peptide, and it is synthesized as a 24-kDa biologically inactive precursor, named pro-IL-18 that requires like IL-1β caspase-1 cleavage to become a biologically active molecule. Upon activation of caspase-1 and forming of an immune complex called inflammasome; where pro-IL-18 as well as pro-IL-1β is processed to an active mature form, which can be released from the cell. [314, 315, 316]

Receptor and signaling

The IL-18 receptor complex (IL-18R) consists of a heterodimer containing two chains, which are members of the IL-1R family. [317] IL-18Rα alone binds IL-18 with a low affinity, but IL-18Rβ alone cannot bind IL-18. High affinity binding is reached by

forming a heterodimer of IL-18Rα and IL-18Rβ. [313] Experiments with IL-18Rα and IL-18Rβ gene-deficient mice have shown that both chains are important for IL-18-signaling. [318, 319] Ligand binding IL-18α-chain is abundantly expressed on the surface of T cells, NK cells, macrophages, epithelial cells, chondrocytes and on a variety of other cells. On binding of IL-18 to IL-18Rα, IL-18Rβ is recruited in to a signaling complex and induces signaling pathways shared with other IL-1 receptor family members. After approximation of cytoplasmic TIR domains the adaptor molecule MyD88 is recruited, which leads to activation of the IRAKs followed by interaction with TRAF6, which activate IKK. This results in activation of IκB and consecutively of NF-κB[320, 321] subsequently inducing production of both Th1 and Th2 cytokines by Th1 cells. [322] There is a second signaling pathway known which involves activation of MAPK p38 and PI3K in neutrophils.[323]

The IL-18 binding protein is a soluble protein that binds to IL-18 with a high affinitity (K_d 0.4nM) and exerts a neutralizing activity against IL-18. [324, 313, 325] Recent publications suggest that the IL-18R may have a soluble form. Soluble IL-18Rα exhibits antagonistic function *in vitro*, containing a dimeric IL-18 protein and a soluble form of IL-18Rβ. [326] IL-37, a recently described cytokine requires the receptors IL-18Rα and IL-1R8 (SIGIRR) to carry out its signal transduction. [327]

A recent publication showed that treatment of melanocytes with IL-18 increased expression of c-Kit, the transcription factor MITF and its downstream targets TRP-1 and TRP-2 as well as enhanced migration. In addition IL-18 protected from H_2O_2 induced damage by increased level of PTEN phosphorylation. [328]

Cell sources and targets

A wide range of cells including macrophages, Kupffer cells, keratinocytes, osteoblasts, astrocytes and dendritic cells express IL-18. [329] In addition to these well described IL-18-producing cells, a new study shows renal tubular epithelial cells are also a primary source of IL-18 during obstructive injury. [330] IL-18 alone induces only small amounts of IFN-γ in naïve T cells, whereas the combination with IL-12 induces high amounts of IFN-γ.[331] The combination of IL-12 and IL-18 provides a TCR-independent activation mechanism for CD161+ CD8+ mucosa associated invariant T cell (MAIT) subset. [332] IL-12 and IL-18 combination also elicits programmed proliferation and high IFN-γ production from memory CD8+ T cells. [333] In addition IL-18 can promote either Th1 or Th2 cell responses in early stages of differentiation dependent on the ambient cytokine milieu. [334, 335] Moreover, IL-18 induces IL-13

production in T cells and NK cells together with IL-2. [336] IL-18 alone is a strong inducer of IL-13 from basophils. [337] IL-18 can also promote the expression of Fas ligand in NK cells and consequently enhance NK cell cytotoxicity. [338] The biological activity of IL-18 can be neutralized by IL-18 binding protein (IL-18BP), which binds to mature IL-18 with a high affinity. IL-18BP does not bind pro-IL-18 and other members of the IL-1 family. [339]

Role in immune regulation and cellular targets

In contrast to all other members of the IL-1 family the extra cellular domain of IL-18BP comprises only one Ig-like domain and its amino acid sequence is only distantly related to the ligand-binding chain IL-18Rα. [340] IFN-γ induces the gene expression of IL-18BP in several intestinal epithelial cell lines and human keratinocyte cell lines. The gene induction of IL-18BP by IFN-γ was also observed in cultures of colonic biopsy specimens. [341] These findings are consistent with previous work showing reduced expression of IL-18BP in IFN regulatory-1-deficient mice. [342] In summary; by inducing IL-18 BP, IFN-γ appears to trigger a negative feedback loop that limits IFN-γ-dependent and IFN-γ-independent actions of IL-18.

Role in host defense and autoimmune diseases

IL-18 plays in an important role in host defence. As well as for IL-1β a great number of publications reported about the role of IL-18 during infections. Almost invariably, both cytokines were found to have a protective function. [343, 344] IL-18 enhances both innate and acquired immunity. As described above, IL-18 can enhance the function of NK cells and development of T_h1 cells. Both cell types are important for the protection and defence against microbes. Moreover, IL-18 enhances the production and secretion of IFN-γ, which play a key role in the bacterial defence. The critical function of IL-18 in host immunity to intracellular microbial infections was demonstrated on IL-18 deficient mice infected with *Leishmania major*. These mice showed a reduced resistance to *Leishmania major* infection, whereas the administration of IL-18 and IL-12 inhibited the expansion of *Leishmania major*. [345] In this context, it was shown that IL-18 is contributes to the NK cell response in visceral leishmaniasis. [346] IL-18 seems also to be important for the protective immunity against *M. tuberculosis* because IL-18 lack in mice contributes to high susceptibility to *M. tuberculosis*. [347]

Furthermore IL-18 was shown to provide protection from *Streptococcus pneumoniae* and Group B Streptococci infection through induction of INF-γ. [348, 349]

Several groups demonstrated that different inflammasomes and caspase-1 activation induce pyroptosis and secretion of IL-1β and IL-18 during an infection with *Listeria monocytogenes*. [350, 351, 352, 353] IL-18 deficient mice were more susceptible to *L. major infection* and showed uncontrolled disease progression, which was accompanied by depressed Th1 cell response. [345] In contrast to IL-1β, although protective in some studies, IL-18 seems to play a more important role in protection during Listeria infections. [354] The same protective role has been found in studies where IL-18-/- have been infected with *Legionella pneumophila* [355], *Shigella flexneri* [356], and *Burkholderia pseudomallei.* [357]

In addition IL-18 is important for the viral clearance because of its potent activation of CD8 positive T cells. [358] In this context, it was shown that IL-18 deficient mice are also more susceptible to viral infections with a profound impairment in the ability of NK cells to mediate cytotoxic activity. [359] Many poxviruses encode functional vIL-18BPs. [360, 361] Additionally, some poxviruses, e.g., vaccinia virus, also contain an IL-1βR homolog (vIL-103R or vIL-1βR), which can bind and sequester IL-1β. [362] The H1N1 strain is producing a NS1 IAV protein containing a RNA-binding domain, which suppresses the activation of IL-1β and IL-18. [363] All together indicating an important role for IL-18 in bacterial and viral infections.

IL-18 plays also important roles in several autoimmune disorders, in which IL-18 expression is often increased and correlates with disease severity in humans as well as in experimental mice models. For example, in IL-18 deficient mice collagen-induced arthritis was less severe compared to wild type mice.[364] Blocking of IL-18 by administration of recombinant IL-18BP in mice with collagen-induced arthritis resulted in a clear reduction of the disease severity compared to placebo treated mice. [365] Furthermore, neutralizing IL-18 *in vitro* also inhibited TNF-α, IL-6 and IFN-γ secretion by macrophages.

In humans, the importance of IL-18 in rheumatoid arthritis was also proven by several studies. In 1999, it was first shown by Gracie et al. that in the joints of patients with rheumatoid arthritis (RA) significantly higher amounts of IL-18 mRNA and protein were found than in those of patients with osteoarthritis. [366] These results were later confirmed by other groups and interestingly also elevated levels of IL-18 in the serum of RA patients are present. Serum and synovial fluid IL-18 levels as well as synovial tissue IL-18 expression were correlated with disease activity in patients with RA and juvenile idiopathic arthritis.[367] Moreover, polymorphisms in the promoter

region of the IL-18 gene have been found and were associated with RA. IL-18 promoter region polymorphisms were also recently associated with increased overall cancer risk, especially with nasopharyngeal carcinoma, gastrointestinal cancer [367] and coronary artery disease. [368] In addition, it was shown that the mechanism of the impaired NK cell function in systemic-onset juvenile idiopathic arthritis involves a defect in IL-18Rβ phosphorylation. [369] IL-18 could be an interesting target in the treatment of rheumatoid arthritis and one opportunity for antibody-based biological therapies in RA. Furthermore, a recent study suggests soluble IL-18R as a biomarker for rheumatoid arthritis. [326]

In addition to RA, IL-18 is important in Crohn's disease. In experimental mouse models of colitis the inflammatory pathology correlates with increased levels of tissue and serum levels of IL-18, whereas anti-IL-18 treatment resulted in a dose-dependent reduction of the severity of colitis. [370] In addition it was not possible to induce significant colitis in the IL-18-deficient mice whereas in IL-18 transgenic mice IL-18 overproduction exacerbates the development of colitis. [371] Mice deficient in caspase-1, that cleaves IL-1β and IL-18, showed a near complete resistant to induction of experimental colitis, reflected by significantly reduced clinical scores and almost absent histological signs of colitis. In parallel a reduced spontaneous release of the pro-inflammatory cytokines IL-18, IL-1β, and IFN-γ from total colon cultures of those mice was observed. [372] Similar inhibition of colitis by reduction of IL-18 expression was shown by treatment with inhibitors of caspase-1. [373]

In chronic Crohn's disease lesions a local increase of IL-18 expression has been demonstrated compared with uninvolved areas or normal controls. [374] In addition chronic lesions also displayed intense transcription of IL-18-induced cytokines, IFN-γ, IL-1β, TNF-α, and IL-8 and a marked increase in IL-18R-positive immune cells was observed. [375]

IL-18 also plays important roles in many other diseases like diabetes and psoriasis. In murine model of insulin dependent diabetes IL-18 is up regulated and can promote diabetes development in mice. [376] In humans also a pathogenic role for IL-18 in development is described and recently, an association between serum levels of IL-18 and glycemic control was demonstrated. [377] High levels of IL-18 have also been detected in keratinocytes of patients with psoriasis and in the serum. The expression of IL-18 was correlating with the disease severity. [378, 379] Although keratinocytes under non-pathologic conditions produce pro-IL-18, they are not able to

convert it to mature IL-18 due to the lack of caspase-1. [380] However, in keratinocytes caspase-1 can be induced by immunologic and inflammatory stimuli that result in secreting of biologically active IL-18. [381] Moreover, mice deficient in Keratin 1 show prenatal increased IL-18 and S100A8/A9, accompanied by a barrier defect and perinatal lethality. Depletion of IL-18 partially rescued these animals, indicating a functional link between IL-18, Keratin 1 and inflammatory skin diseases. [382]

In Alzheimer's disease (AD) the expression of IL-18R complex on blood cells is perturbed and even more markedly in its preclinical state of Mild Cognitive Impairment, confirming that an increased peripheral activity of IL-18 may be involved in the early phase of AD pathophysiology. [383]

Role in allergic diseases

IL-18 induces the production of IFN-γ in Th1 cells, B cells, and NK cells, thereby stimulating Th1-mediated immune responses and inhibiting IgE synthesis. [384] Therefore it is reasonable to assume an important role for IL-18 in response to allergens. IL-18 polymorphisms have been implicated in allergic rhinitis [385] and in atopic eczema. [386] In addition, IL-18 serum levels correlated inversely with peak expiratory flow suggesting that IL-18 might reflect the disease activity in asthma exacerbations [387] as poorly controlled asthma is associated with higher serum IL-18 levels. [388, 389] In a Japanese population; a genetic variation of IL-18 was found with an increased transcriptional activity associated with severity of asthma. [390] As well as polymorphism in the IL-18R gene (on 2q21) have been identified to be in relation with increased susceptibility in childhood asthma. [391, 392] Mice with IL-18 overexpression specific to the lungs was shown to have increased production of Type I interferons, IFN-γ and IL-13; alongside an increase in IL-13 producing CD4+ T cell population and airway hyperresponsiveness in an ovalbumin induced asthma model. [393] Similarly, airway hyperresponsiveness and airway remodelling were inhibited in IL-18-deficient mice in comparison to wild-type mice. [394]

IL-10 subfamily cytokines

Within the IL-10 cytokine family IL-19, IL-20, IL-22, IL-24, and IL-26 are forming a subgroup termed as IL-20 subfamily. IL-20 subfamily cytokines primarily acts on various epithelial cells and participate in the prevention of the tissue damage caused by infections and inflammation. They protect the tissues from extracellular bacterial or fungal invasion by enhancing the innate antimicrobial responses. Moreover, these

cytokines promote tissue remodeling and wound-healing, and thus help to maintain tissue integrity and restore homeostasis. *Il19, Il20*, and *Il24 genes* are closely linked to *Il10* on human chromosome 1q32 and all of them have similar genomic structures composed of five exons and four introns. All these cytokines can be induced from myeloid cells through TLR activation. [395]

IL-19

Discovery and structure

IL-19 was first isolated from an EBV-transformed B-cell library in 2000 and was described as a novel IL-10 homologue consisting of 177 amino acid residues showing 21% identity with IL-10 and the *IL-19* gene has a similar intron-exon structure. [396]

Human *IL-19* is located on chromosome 1q31-32 and contains six introns and seven exons whereas only five of these exons (exons three to seven) encode for the IL-19 protein. [397] Two different mRNA species have been identified with different 5'-sequences. The shorter form of the IL-19 mRNA encodes a protein with a classical signal peptide targeted for secretion whereas in the longer form a 38 amino acid sequence is added to the N-terminus of the protein which may affect its secretion. [396]

Its predicted molecular weight is ~21 kDa but due to N-linked glycosylation, secreted IL-19 has an apparent molecular weight of ~35-40 kDa. Despite the relative low amino acid similarity between IL-19 and IL-10, their three-dimensional structure is highly similar. Unlike IL-10, IL-19 contains six conserved cysteine residues and is therefore secreted as a functional monomer (as is described for IL-20). Crystallographic studies demonstrated that the IL-19 protein contains seven amphipathic helices that form a unique helical bundle. [398]

Cellular sources and targets

IL-19 mRNA is expressed in monocytes within 4 hours after stimulation with LPS and GM-CSF. Pre-priming of monocytes with IL-4 and IL-13 enhance LPS-induced IL-19 expression whereas pre-priming of monocytes with IFN-γ inhibits LPS-induced IL-19 expression. [396] Low levels of IL-19 mRNA expression were also observed in B cells. [399] Recently, the expression of IL-19 was shown to be induced in airway epithelial cells in response to IL-17A, IL-4 and IL-13 treatment and elevated IL-19 levels were observed in airway epithelia from asthmatic patients. [400, 401]

Immunohistochemistry staining of a tissue microarray revealed that IL-19 is expressed in a large number of tissues whereas macrophages, epithelial, endothelial cells were the major cell types positive for IL-19. [402]

Receptor and signaling

IL-19 binds to and signals through a heterodimeric receptor complex formed by IL-20R1 and IL-20R2. [403] Skin tissue also positively stains for IL-20R1 and IL-20R2. [404] IL-19 forms a stable complex with both receptor chains. [403] IL-19 binding to its receptor leads to the activation of STAT1 and STAT3. [405] From its crystal structure it became apparent that the residues that interact with the receptor are on helix B, loop BC, helix C, helix G and the C-terminal beta strand. [398]

Role in immune regulation and cellular networks

Murine IL-19 induces the production of IL-6 and TNF-α in monocytes and induced apoptosis and ROS production in these cells, providing evidence for a role in inflammatory responses. [397] Furthermore, IL-19 was shown to induce the expression of IL-4, IL-5, IL-10, and IL-13 by activated T cells, indicating a role for IL-19 in the induction of Th2 responses. [406] IL-19 has been primarily associated with psoriasis and allergic disorders.

Role in psoriasis

TNF-α and IL-6 are the major effector cytokines in the pathogenesis of psoriasis and their expression in monocytes is induced by IL-19. A study aimed at elucidating the role of IL-19 in psoriasis revealed that serum levels in psoriasis patients were decreased while epidermal expression of IL-19 was increased compared to healthy individuals. [407] Another study shows an increase of IL-19 expression and consequent upregulation of keratinocyte growth factor in wounded mouse skin, suggesting a role in wound healing and psoriasis. [408] IL-19 is produced by keratinocytes as a result of IL-17A stimulation and the main target of IL-19 in skin is also keratinocytes, as characterized by high expression of IL-20R1 and IL-20R2. The main effect of IL-19 on keratinocytes was shown to be an increase of the antibacterial proteins of the S100 family, namely S100A7 (psoriasin), S100A8 and S100A9. [409] Several studies have demonstrated an association between SNPs in the IL-19 and IL-20 genes and increased risk of developing psoriasis as will be discussed later in the section covering IL-20. In skin lesions of good-responder psoriasis patients, therapeutic TNF-α- inhibitor (etanercept) acutely suppresses gene expression of the IL-20 subfamily of cytokines (including IL-19, IL-20, IL-24) even prior to substantial clinical

improvement. Considering, that *in vitro* TNF-α (as well as IL-17A) is able to stimulate the expression of the IL-20 subfamily cytokines in keratinocytes, the decreased epidermal hyperplasia (therapeutic response) might result specifically from acute suppression of the IL-20 subfamily by antagonism of TNF-α. [410]

Role in allergic diseases

Elevated serum levels of IL-19 have been reported in asthmatic patients as well as in a mouse model for asthma. Furthermore, IL-19 was shown to induce the expression of Th2 cytokines from activated T cells. [406] Later it was found that IL-19 expression is higher in airway epithelia from asthmatic patients than epithelia from chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF) patients as well as healthy individuals. [401] It was further shown that IL-19 expression was enhanced by IL-4, IL-13 and IL-17A in normal human bronchial epithelial cell lines in a STAT6-dependent way. [401] IL-19 expression; along with other pro-inflammatory factors, was upregulated by IL-4 in human keratinocytes, suggesting a role for IL-19 in atopic dermatitis. [411] Long–term exposure of naïve T cells to IL-19, IL-20 and IL-22 downregulates IFN-γ expression but upregulates IL-4 and IL-13 expression. This indicates that these cytokines may function to polarize naïve T cells to Th2 cells. [412]

IL-19 mRNA is up-regulated in the polyp tissue of chronic rhinosinusitis patients with nasal polyps (CRSwNP) and – at lower extent – in nasal biopsies of chronic rhinosinusitis patients without nasal polyps in comparison with nasal biopsies of healthy controls. IL-19 is also increased at protein level in patients with CRSwNP (vs. healthy controls). Recombinant IL-19 increased proliferation in a nasal epithelial cell line (RPMI 2650) *in vitro*. [413]

Anti-inflammatory activity and vascular protective effects

It has been shown using IL-20R2 knockout mice that IL-20R2 signaling through IL-19, IL-20, and IL-24 directly inhibits CD8 and CD4 T cell responses *in vitro* and *in vivo*. IFN-γ and IL-2 secretion is significantly elevated after stimulation of IL-20R2-deficient CD8 and CD4 T cells with Con A or anti-CD3/CD28, *in vitro*. Significantly more Ag-specific, IFN-γ+ CD8 and CD4 T cells develop in response to locally applied DNA vaccines in IL-20R2-deficient mice. In a T cell-dependent model of contact hypersensitivity, IL-20R2 knockout mice are more sensitive to the contact allergen compared to their wild type counterparts. [414] Vascular smooth muscle cell migration is an important cellular event in multiple vascular diseases, including atherosclerosis, restenosis, and transplant vasculopathy. IL-19 injected mice fed with an atherogenic

diet show Th2 cell polarization, decreased expression of IFN-γ, IL-1β and IL-12β. IL-19 treated atherosclerotic mice also have less macrophage infiltration into vascular plaques; suggesting an inhibitory role for IL-19 on the vascular inflammation seen in atherosclerosis. [415] IL-19 has inhibitory effects on PDGF-driven activation of various cytoskeletal regulatory proteins (heat shock protein-27, myosin light chain and cofilin) that play an important role in smooth muscle cell motility. IL-19 also decreases PDGF activation of the Rac1 and RhoA GTPases. Rac1 seems to be crucial in its inhibitory effects on smooth muscle cell motility. [416] IL-19 induces Heme oxygenase-1 (HO-1) mRNA and protein expression mainly via activation of STAT3, and thus significantly reduced ROS concentrations in cultured human VSMC. [417] In primary human VSMC culture IL-19 significantly reduces stability of mRNA transcripts of proliferative and inflammatory genes by the means of the reduction of serine phosphorylation of HuR, and activation of PKCα, a known regulator of HuR translocation. [418]

Role in arthritis

IL-19 is highly expressed in the synovial tissue and synovial fibroblasts isolated from rat joints with collagen induced arthritis. Neutralizing anti-IL-19 antibody (1BB1) significantly ameliorated the severity of arthritis, prevented bone destruction and inhibited the pro-inflammatory cytokine production. [419]

Role in cancer

IL-19 plays pivotal role in the pathogenesis of breast cancer. IL-19 expression shows positive correlation with advanced tumour stage, metastasis and increased tumour cell proliferation. [420] *In vitro*, IL-19 induces IL-1β, IL-6, TGF-β, matrix metalloproteinase 2 (MMP2), MMP9, CXCR4, and fibronectin expression in 4T1 breast cancer cell line and promotes proliferation and migration, which can be inhibited by neutralizing anti-IL-19 antibody. *In vivo*, mice injected with IL-19-overexpressing 67NR cancer cell clones show larger tumors and more metastasis in the lung. Moreover, the high IL-19 expression in invasive ductal carcinoma is associated with advanced tumor stage, high metastasis formation, and worse disease-specific survival and metastasis-free survival. [421]

IL-19 is also expressed in esophageal squamous cell carcinoma; and its increased expression correlates with tumour progression and metastasis. IL-19 induces colony formation, increased proliferation and migration in CE81T esophageal cancer cells, and results in increased TGF-β, Cyclin B1, MMP-1 and CXCR expression. IL-19

antagonism has the potential to be a strong therapeutic target for esophageal cancer. [422]

Functions as demonstrated in IL-19-deficient or transgenic mice

So far, transgenic overexpression of IL-19 has not been reported. However, unpublished observations mentioned in a study describing the receptor complexes for IL-19, IL-20 and IL-24 indicated no overt skin phenotype in transgenic mice overexpressing IL-19. [405] *IL-19*$^{-/-}$ mice have a normal phenotype and show no developmental abnormalities. However, they are more susceptible to experimental acute colitis induced by DSS. This correlates with increased macrophage infiltration of the colonic mucosa whereas B cell recruitment was impaired. Furthermore, higher levels of pro-inflammatory cytokines were expressed by *IL-19*$^{-/-}$ mice-derived macrophages upon LPS stimulation. These data indicate a protective role for IL-19 in this particular model. [423]

Bronchoalveolar lavage CD11c^{+} cells from IL-19$^{-/-}$ mice express significantly less Major Histocompatibility Complex class II (MHCII) in response to intranasal Aspergillus antigen exposure. Airway inflammation and histological changes in the lungs were also ameliorated in IL-19$^{-/-}$ mice after intranasal administration of Aspergillus antigen. [424]

IL-20

Discovery and structure

IL-20 was discovered in 2001 through EST database screening for sequences encoding amphipathic helices together with a signal sequence. [425] The human *IL-20* gene maps to chromosome 1q32 (together with IL-10, IL-19 and IL-24) and the encoded protein shows 28% amino acid sequence identity to IL-10 but shows the highest homology (40%) with IL-19. Both mouse and human IL-20 consist of 176 amino acids. [425] Mature IL-20 contains 6 conserved cysteine residues that prevent the formation of an intercalating dimer such as formed by IL-10. As a result, this protein exists as a functional monomer. [425]

Cellular sources and targets

Like IL-19, IL-20 is expressed mainly by LPS-stimulated monocytes as well as epithelial and endothelial cells. [404, 426] Furthermore, IL-20 (together with IL-28 and IL-29) is highly expressed by DCs in response to LPS stimulation. [427] Furthermore, IL-20 specifically enhances colony formation by CD34+ multipotential progenitors

suggesting a role for this cytokine in haematopoiesis. [428] IL-20 might contribute to the activation or formation of lymphatic vessels as well through activation of lymphatic endothelial cells. [429] IL-20 induces proliferation and migration of human umbilical vein endothelial cells, as well as vascular tube formation *in vitro*. *In vivo*, IL-20 also enhanced tumor angiogenesis. [430] IL-22, IL-17A and TNF-α are able to induce IL-20 mRNA and protein in human keratinocytes *in vitro*, and cutaneous IL-20 was also elevated in mice following IL-22 treatment *in vivo*. [431] IL-20 expression at the mRNA level was observed in NHEK and HaCaT cell lines. [425] IL-31 also induces IL-20 and IL-24 expression in HaCaT keratinocytes. [432] IL-20 induces the expression of psoriasin and β-defensin-2 in keratinocytes, indicating a function in clearance of bacterial infection. [427] Keratinocyte specific deletion of suppressor of cytokine signaling 3 (SOCS3) caused severe skin inflammation and epidermal hyperplasia accompanied by up-regulation of IL-6, as well as increased IL-19, IL-20 and IL-24 production with constitutive STAT3 activation, high expression level of IgE and anti-microbial peptides (S100A8, S100A9, and β-defensin) in mice. [433] IL-20 plays a role in epidermal function as was clearly demonstrated by the abnormal skin phenotype of IL-20 transgenic mice. [425]

Receptor and signaling

Two receptor complexes for IL-20 have been identified: IL-20R1/IL-20R2 (shared with IL-19 and IL-24) and IL-22R1/IL-20R2 (shared with IL-24). [403, 405, 425] This receptor complex most commonly activated by IL-20 appears to be IL-20R1/IL-20R2. However, IL-22R1 expression is found in some tissues were IL-20R2 is absent, suggesting a predominant role for IL-22R1/IL-20R2 there.[405] Furthermore, high levels of IL-20R1, IL-20R2 and IL-22R1 were found on epithelial cells and stromal cells in skin, lung, pancreas and breast tissues suggesting that their ligands act mainly on tissue resident cells. [404] IL-20R2 signaling through IL-19, IL-20, and IL-24 directly regulates CD8 and CD4 T cell responses *in vitro* and *in vivo*. It has been proved using common IL-20R beta-chain (IL-20R2) knockout mice. IFN-γ and IL-2 secretion is significantly elevated after stimulation of IL-20R2-deficient CD8 and CD4 T cells with Con A or anti-CD3/CD28, *in vitro*. Significantly more Ag-specific, IFN-γ+ CD8 and CD4 T cells develop in response to locally applied DNA vaccines in IL-20R2-deficient mice. In a T cell-dependent model of contact hypersensitivity, IL-20R2 knockout mice are more sensitive to the contact allergen compared to their wild type counterparts.[414]

Binding of IL-20 to its receptor complexes leads to activation of STAT1 at supraphysiological concentrations (EC_{50} 800PM) and STAT3 at much lower concentrations (EC_{50} 1-5PM) suggesting that STAT3 activation is the most relevant signal transducer.[405] IL-20 induces the proliferation of endothelial cells (HUVEC and HMEC), an effect that was abolished when IL-10 was simultaneously applied. Furthermore, IL-20 treatment of HUVEC cells induced the phosphorylation of ERK1/2, p38 kinase and JNK suggesting a potential role for these molecules in IL-20-mediated signal transduction.[430]

Role in asthma

A recent study has identified a role for IL-20 in airway remodeling in asthma patients. IL-20, alongside its receptors IL-20R1 and IL-20R2 are upregulated in the airway epithelium of asthma patients. Overexpression of IL-20 and its receptors in mice with an ovalbumin-induced asthma model results in increased fibronectin and smooth muscle expression in asthmatic mice, suggesting that IL-20 might play a role in airway remodeling. [434]

Role in obesity

Circulating IL-20 level is significantly higher in obese than control premenopausal women, while IL-10 levels were significantly lower. IL-20 levels are positively associated with body weight and visceral fat (waist-hip ratio), and are reduced by weight loss.[435]

Role in psoriasis

Several observations have suggested that IL-20 plays a role in the pathogenesis of psoriasis. Important information was obtained from the transgenic overexpression of IL-20 in mice which leads to skin abnormalities including hyperkeratosis, thickened epidermis and a compact stratum corneum as well as growth retardation and death within the first days after birth.[425] These skin abnormalities as well as the direct activation of STAT3 by IL-20 observed in a keratinocyte cell line provided the first indications that this cytokine is involved in epidermal function and possibly psoriasis.[425] Furthermore, all receptor chains involved in IL-20 binding are expressed in human skin and their expression is increased in psoriatic skin.[405, 436] A recent study described IL-20 to be mainly produced by keratinocytes and taken up by skin-resident mononuclear cells; suggesting that IL-20 produced by keratinocytes can have a role in driving pathological inflammation in psoriasis.[437] Another finding supporting the role of IL-20 (and IL-19) in the pathogenesis of psoriasis is that their

mRNA is expressed in psoriatic lesions whereas no expression was detected in uninvolved psoriatic skin.[436] Genes with increased expression pattern in psoriatic lesions overlap with genes generally induced by IL-1, IL17A and IL-20 family of cytokines. [438] IL-20 concentration is also higher in the peripheral blood of psoriasis patients compared to healthy controls.[431] In a human skin xenograft transplantation model in which human psoriatic plaques or nonlesional skin biopsies were transplanted onto immuno-deficient mice, blocking of IL-20 signaling led to psoriasis resolution. On the other hand, mice engrafted with non-activated PBMC that received continuous IL-20 infusion developed psoriasis in nonlesional skin xenografts.[439] The increased mRNA level of IL-20 in psoriatic skin lesions is significantly reduced within 4 days by monoclonal anti-TNFα antibody (adalimumab) treatment, even before clinical and histological improvement is detectable. IL-20 is regulated by p38 MAPK, and the early effects of anti-TNFα include the reduction of p38 MAPK phosphorylation. This pathway is an important mechanism of action of anti-TNFα therapy in psoriasis.[440] Another observation, that therapeutic anti-TNF-α (etanercept) suppresses gene expression of the IL-20 subfamily cytokines (IL-19, IL-20, IL-24) in psoriasis patients is also underlining the crucial role of these cytokines in the pathogenesis (see above in chapter IL-19). [410] IL-20 expression in lesional skin of psoriasis patients decreased significantly 6 weeks after alefacept (a lymphocyte function-associated antigen (LFA)-3 Ig fusion protein) treatment and correlated positively with the Psoriasis Area and Severity Index. However, the resistance of the synovial IL-20 expression to the alefacept treatment is explaining the therapeutic failure in psoriatic arthritis.[441]

Role in ulcerative colitis

The expression of IL-20 and its receptor complex IL-20R1 and IL20R2 were found to show an increase in patients with ulcerative colitis; suggesting a similar role of IL-20 in driving the pathological mechanisms of ulcerative colitis to psoriasis and asthma.[442]

Role on host defence

Skin proliferative and and protective properties of IL-20 does not lend itself to skin immune response to bacterial infections. A recent study has shown that signalling through the IL-20R type 1 impairs response against cutaneous infections of *Staphylococcus aureus*. IL-20 and IL-19 severely inhibit IL-17A response in skin after *S.aureus* infection, and IL-1β expression is also diminished. Blockage of IL-20R

receptor pathway; or inhibition of the secretion of IL-20 family of cytokines holds therapeutic potential for the treatment of recurrent infections of methicillin resistant S. *aureus*. [443]

Role in rheumatoid arthritis

IL-20 is increased in plasma of rheumatoid arthritis patients.[444] IL-20 and all three of its receptor subunits are expressed in synovial membranes and synovial fibroblasts derived from the synovial tissue of rheumatoid arthritis patients and in rats with collagen-induced arthritis. IL-20 is expressed at significantly higher levels in synovial fluid of the patients than that in control individuals.[445] Treatment with anti-IL-20 antibody (7E) significantly reduces the severity of collagen-induced arthritis (a rat model of the rheumatoid arthritis) by decreasing the inflammation, preventing cartilage damage and bone loss. The combined treatment with 7E and TNF-α inhibitor (etanercept) is more effective than etanercept alone.[446]

Role in osteoporosis

IL-20 has a pivotal role in osteoclast differentiation. The serum IL-20 level is higher in patients with osteopenia and osteoporosis and in ovariectomized mice. IL-20 mediates osteoclastogenesis by up-regulating the receptor activator of NF-κB (RANK) expression in osteoclast precursor cells and RANK ligand (RANKL) in osteoblasts. Anti-IL-20 monoclonal antibody (7E) treatment completely inhibits osteoclast differentiation induced by macrophage colony-stimulating factor and RANKL *in vitro*, and protects mice from ovariectomy-induced bone loss *in vivo*. IL-20R1-deficient mice have significantly higher bone mineral density compared with wild-type controls. IL-20R1 deficiency also abolishes IL-20-induced osteoclastogenesis and increase bone mineral density in ovariectomized mice. Consequently, the possible therapeutic application of anti-IL-20 monoclonal antibody (7E) for treating osteoporosis has been proposed.[447]

Role in hypoxia

In vitro, IL-20 expression increased in hypoxic HaCaT, HEK293 cells, chondrocytes, monocytes, and glioblastoma cells (GBM8901). There are two putative hypoxia responsive elements in the human il20 gene promoter. *In vivo*, experimental ischemic stroke up-regulates IL-20 in the sera and brain tissue of rats. IL-20 immunostaining is positive in glia-like cells in peri-infarcted lesions, and anti-IL-20 neutralizing antibody ameliorates ischemia-induced brain infarction.[448] On the other

hand, IL-20 strongly induced endothelial cell vessel tube formation and is beneficial for the re-establishment of vessel networks in an ischemic hind-limb rat model.[449]

Role in atherosclerosis

The endothelial cells lining the intimal microvessels, vasa vasorum in the macrophage-rich areas of the human atherosclerotic lesions are expressing IL-20 and its receptor complex IL-20R1/IL-20R2 (immunohistochemical staining is positive). However, the IL-20 and IL-20R1/IL-20R2 expression is rare in nonatherosclerotic arteries. Furthermore, *in vivo* administration of IL-20 expression vector promoted atherosclerosis in apolipoprotein E-deficient mice.[450]

Role in cancer

Expression of IL-20 and its receptor subunits are higher in clinical oral tumor tissue than in nontumorous oral tissue. *In vitro*, IL-20 promotes colony formation of OC-3 and OEC-M1 oral cancer cell lines. Anti-IL-20 monoclonal antibody (7E) reduces tumor growth and inflammation in an ex vivo mouse model of tumor growth.[451] IL-20 plays pivotal roles in the tumor progression of breast cancer. Clinical breast cancer tumor tissue expresses higher levels of IL-20 and its receptors than the nontumorous breast tissue. IL-20 is also highly expressed in breast cancer bone-metastasis tissue. Tumor IL-20 expression is associated with advanced tumor stage, greater tumor metastasis, and worse survival. *In vitro*, IL-20 upregulates matrix metalloproteinase-9, matrix metalloproteinase-12, cathepsin K, and cathepsin G, and enhances proliferation and migration of breast cancer cells, which can be inhibited by anti-IL-20 antibody (7E). Anti-IL-20 antibody also reduces tumor growth, suppresses bone colonization, diminishes tumor-mediated osteolysis, and lessens bone density decrement in mice injected with breast cancer cells.[452] Both IL-20 and IL-20R1 is up-regulated in muscle invasive bladder cancer tissue. IL-20 significantly increases the expression of matrix metalloproteinase (MMP)-9. ERK1 and ERK2 inhibitor U0126 significantly inhibits IL-20-induced tumor cell migration and invasion *in vitro*.[453]

Functions as demonstrated in IL-20-deficient or transgenic mice and human mutations

As mentioned earlier, transgenic mice overexpressing IL-20 have shown that IL-20 plays an important role in skin biology and may be involved in the pathogenesis of psoriasis.[425] Several SNPs in the IL-19 and IL-20 genes have been linked with increased risk of developing psoriasis. The IL-19 and IL-20 haplotype CACCGGAA was shown to be a significant susceptibility factor for psoriasis, whereas a protective

effect has been described for the IL-20 and IL-24 haplotypes CAAAC, TGGGT and CGAGT.[454, 455] Significant association has been revealed between a single nucleotide polymorphism in the promoter of IL-20 and the systemic juvenile idiopathic arthritis.[456] A genome-wide association meta-analysis has linked the IL-10 locus, including IL-10, IL-19, and IL-20, with type I diabetes.[457]

IL-21

Discovery and structure

IL-21 was identified and cloned in a screen searching for a ligand to the already identified IL-21 receptor.[458] IL-21 consists of 131 amino acids, forming a four-helix-bundle cytokine domain. It shares significant homology to IL-2, IL-4 and IL-15 and belongs to the same cytokine family, namely the family of γ-chain (γ_c) cytokines. IL-21 has been mapped to chromosome 4q26-q27, adjacent to IL-2. As the IL-15 gene lies in the same cluster, these three highly related genes may have arisen by gene duplication. Human IL-21 has a predicted molecular weight of 15 kDa and shows 57% identity to murine IL-21.

The three-dimensional structure of IL-21 has been solved by NMR spectroscopy.[459] As predicted, the structure is dominated by a central four-helical bundle, arranged in an up-up-down-down topology, as observed for other cytokines. Interestingly, one segment of the IL-21 molecule apparently exists in two distinct and interchangeable states.[459]

Receptor and signaling

The IL-21R was discovered as an orphan receptor and first named novel interleukin receptor (NILR).[458, 460] Based on its sequence homology to the IL-2 receptor β chain, it was related to the γ_c cytokine family. Cytokines of this family bind to a complex formed by a common γ_c and an individual receptor component. Therefore, the functional receptor of IL-21 consists of γ_c and the IL-21R.[461, 462] IL-21 signals via Jak-STAT pathway and involves Jak1 and Jak3.[461, 462] These signals can activate Stat1 and Stat3, and to a lesser extend Stat5a and Stat5b.[463, 464] Experiments using Stat3 knockout mice suggest Stat3 to be the most important STAT protein in IL-21 signaling.[464] The cytoplasmic domain of IL-21R contains six tyrosine residues. One of them, Tyr510, can be phosphorylated and serves as a docking site for both Stat1 and Stat3. Beside the Jak/STAT pathway, also PI-3 kinase and MAP kinase pathways seem to be involved.

Cellular sources and targets

IL-21 is produced by T cells and NK T cells.[458, 465] More recently, lL-21 was attributed to the Th17 subset[466, 467], the Th9 subset,[468] as well as the Tfh subset of $CD4^+$ T cells.[469] Similarly, also its receptor IL-21R was detected on $CD4^+$ T cells and NKT cells, but also on $CD8^+$ T cells, B cells, DCs, macrophages and keratinocytes.[458, 460, 470-473] High expression of the IL-21R was observed on B cells, even in the resting state.[470] During B cell development it is expressed at low levels at the pre-B cell stage and the first transitional stage (T1) while it is increasing at the second transitional stage (T2).[474] Mature follicular B cells express high levels of IL-21R, which can be further increased by signals through the B cell receptor or through CD40.[475] In contrast to follicular B cells, marginal zone B cells have low levels of IL-21R, while this receptor is absent on plasma cells.[470] Another study showed that IL-21R was expressed on plasma cells from lymph nodes, spleen and tonsils but not on terminally mature bone marrow plasma cells.[476] Moreover, for plasma cells residing in secondary lymphoid organs, IL-21 derived from T follicular helper lymphocytes served as survival factor.

B10 cells represent a rare subset of B cells, which is able to produce IL-10 and regulate inflammation and autoimmune diseases in mice and humans. Using a mouse model of multiple sclerosis (MS) Tedder and colleagues [477] showed that maturation of B10 cells into IL-10-secreting effector cells and autoimmune disease inhibition requires IL-21 and CD40-dependent cooperation with T cells. When transferred into mice with established autoimmune disease, generated ex vivo with IL-21 and CD40L, B10 effector cells remarkably reduced disease symptoms. Autologous B10 cells ex vivo expansion with IL-21 and reinfusion, may serve as a novel treatment strategy for autoimmune diseases.

IL-21 is required for human B-cell differentiation in vivo and in addition, long-lived humoral immunity is dependent on IL-21 mediated signalling, which was shown in IL-2RG/JAK3-deficient patients receiving hematopoietic cell transplantation.[478]

Within the T cell lineage, IL-21R is induced during transition from double negative to double positive lymphocytes. While both mature $CD4^+$ and $CD8^+$ T cells express low levels of IL-21R, the expression is increased upon T cell receptor stimulation or IL-21 signals.[461, 470] Given the broad range of IL-21R expression, IL-21 signalling seems to play an important role in the communication of many immune cells.

IL-21 can act as a T cell growth factor. Recent studies showed that IL-21 can counteract Treg suppression by acting on conventional T cells and it is associated with inhibition of IL-2 production.[479] Also, while IL-21 is able to substitute for IL-2 in boosting conventional T-cell responses it is unable to substitute for IL-2 in supporting Tregs. Other group demonstrated antitolerogenic properties of IL-21 by showing that IL-21 interferes with different checkpoints of FoxP3 Treg cells in late phase of immune response. [480] Both data suggest that blockade of IL-21 signaling pathway could be considered in transplantation as precondition for tolerogening protocols.

Role in immune regulation and cellular networks

IL-21 has been shown to reduce IgE class-switch *in vitro*.[481] However, regulation of IgE by IL-21 seems to be context dependent, as IL-21 was shown to decrease IgE when combined with PHA and IL-4, but in contrast induced IgE in combination with anti-CD40 and IL-4.[482] The exact mechanism of this regulation remains to be determined.

Another finding where IL-21 leads to a context dependent outcome is apoptosis. IL-21 was found to enhance proliferation of human B cells stimulated via CD40, but to inhibit it upon anti-IgM or IL-4 stimulation.[458] Whether IL-21 induce proliferation or apoptosis therefore depends on the way of the B cell activation: Proliferation dominates in B cells that are activated via B cell receptor stimulation together with costimulatory signals, while apoptosis is observed in B cells upon TLR activation, for example stimulation with LPS or CpG.[470, 483, 484] Therefore, IL-21 plays an important role in the regulation of B cell expansion: it prevents expansion of B cells receiving non-specific TLR signals, but promotes proliferation of specifically activated B cells, thereby supporting important versus deleterious antibody response. In addition, IL-21 together with CD40L is implicated in plasma cell differentiation through induction of B lymphocyte-induced maturation protein-1 (Blimp-1), a master transcription factor for terminal differentiation to plasma cells.[485] Interestingly, IL-21 also sensitizes B cells towards the stimulatory effects of IL-2, this way further driving B cell differentiation.[486] Taken together, IL-21 is important for B cell function, affecting antibody isotype balance, proliferation, apoptosis as well as differentiation to plasma cells.

IL-21 was also found in $CD4^+$ cells. While all effector Th cell subsets, Th1, Th2 and Th17 cells, can express IL-21, Th17 cells produce far the highest levels.[466, 467] Induction of IL-21 by IL-6 in Th17 cells leads to a further autocrine upregulation of IL-21.[487] IL-21 plays a crucial role in the development of Th17 cells, as it induces the IL-

23R, which is not expressed in naïve T cells.[467, 487] IL-23 signalling is important for the expansion and stabilization of Th17 cells and for their effector function.[488]

Interestingly, IL-21 alone has little or no effect on proliferation of naïve or memory $CD8^+$ cells, but strongly synergizes with IL-7 or IL-15 in the expansion of these cells.[489] Synergy of IL-21 and IL-15 was also observed for the induction of granzyme B, an enzyme mediating cytolytic function of $CD8^+$ cells. Furthermore, IL-21 seems to be important in maintaining costimulatory functions of the surface proteins CD28 and CD62L[490] and to enhance production of perforin[491].

An influence of IL-21 was observed on NK cells.[492] The actions of IL-21, however, are dependent on the maturation stage. IL-21 enhanced *in vitro* generation of NK cells from bone marrow precursors and proliferation of committed immature NK cells in response to suboptimal IL-2 or IL-15 doses.[493] Similar to its effect on NK cells, IL-21 can increase the proliferation of NKT cell when combined with either IL-2 or IL-15.[465] Furthermore, IL-21 upregulates production of IL-4, IL-13 and granzyme B by NKT cells, thereby enhancing their effector function. It was also shown that primary IgG response, affinity maturation, germinal-center formation - all main features of B cell differentiation - were uniquely dependent on IL-21 derived from iNKT cells. [494] Nevertheless, help from iNKT cells did not enhance humoral memory responses.

In contrast to the stimulatory effect of IL-21 on most of the immune cells, DCs are rather inhibited by IL-21. For example, when bone marrow precursor cells are cultured in the presence of GM-CSF and IL-15, they develop into mature DC. In the presence of IL-21, however, the DC maintain an immature phenotype, characterized by low MHCII expression.[471] Others have shown, that IL-21 is even inducing apoptosis in conventional DCs by counteracting the effects GM-CSF. [495] Moreover, IL-21 primed DCs have an inhibitory effect on T cell response, even when the priming is only for 2 h.

Role in host defense or other immune regulatory conditions

The fact that IL-21 increases effector functions of both $CD8^+$ T cells and NK cell suggests that it might have a positive effect on tumor regression. Several studies addressed this question in animal models. IL-21 was found to inhibit growth of melanomas, fibrosarcomas[496], and pancreatic carcinomas[497]. In both studies, the effect was predominantly mediated by NK cells rather than by $CD8^+$ cells, while a third study showed a fully $CD8^+$ T cell dependent prevention of tumor initiation in mammary carcinoma.[498] NK cell-mediated tumor killing upon IL-21 treatment,

however, seems to depend on the expression of NKG2D ligands on the surface of the targets cells[499], limiting a future IL-21 anticancer therapy to certain types of tumors. In the case of $CD8^+$ T cell mediated tumor killing, it has been shown by several studies that IL-21 is more potent than IL-2 or IL-15, but synergized efficiently with these cytokines in tumor regression.[489, 500] These reports suggest that IL-21 mediated activation of NK cells and cytotoxic T cells can be exploited in combination with other chemotherapies. In fact, recombinant human IL-21 (Denenicokin/BMS-982470) has now entered the clinical trials, and phase I result are promising.[501] At the end of the study, one patient reached complete remission, while 9 of 29 patients achieved a stable disease. Other preclinical data indicate enhanced anti-tumour activity in metastatic colorectal cancer when combining rIL-21 with cetuximab[502]. In addition, in pathogenesis of Sézary syndrome (SS), cutaneous T-cell lymphoma, positive autocrine feedback loop of IL-21 production and following STAT3 activation were shown to play a pivotal role in disease[503]. Furthermore, in contrast to IL-2 and IFN-α therapies, low toxicity is observed for IL-21, making it to a valuable tool in cancer therapies. However, in contrary to these evidences showing an ameliorating effect of IL-21 in various cancers, signalling by activated T cells via CD40 and IL-21 was seen to lead to an increased proliferation of chronic lymphocytic leukemia cells.[504]

Several reports addressed the involvement of IL-21 in autoimmune disease, but because IL-21's pleiotropic functions, the exact role is still not fully clear in most of the diseases. High levels of serum IL-21 were detected in patients with systematic lupus erythematous, and these levels correlated with disease severity[505], consistent with observation reported by a study using mouse models of systematic lupus erythematous[484]. Although neutralization of IL-21 could delay the progression of the disease, it should be kept in mind that IL-21 might also have a beneficial effect in this disease by inhibiting activation of self-reactive B cells. In Lyn-deficient mice, a mouse model for SLE, it was shown that IL-21 promotes production of anti-DNA IgG antibodies but is not responsible for kindey damage in those mice.[506]

In EAE, IL-21 seems to contribute to the inflammation, as mice that received IL-21 before induction of EAE suffered from a more severe disease accompanied by higher numbers of inflammatory T cells in the central nervous system.[507] This effect is probably due to the induction of Th17 cells, a population that plays a major role in EAE. Consistently, IL-21 or IL-21R knockout mice have tenfold reduced number of IL-

17-producing cells and markedly reduced EAE progression.[466, 467] A similar role of IL-21 might be found in RA, a disease likewise dominated by Th17 cells. Higher levels of IL-21R are found in patients with RA suggesting a role for IL-21 in the disease.[508, 509] Role of IL-21 in pathogenesis of rheumatoid arthritis is supported by increased serum IL-21 levels in RA patients which correlate with 28-joint count disease activity score (DAS28), anticyclic citrullinated peptide Ab levels (anti-CCP Ab) and frequencies of T follicular helper-like cell suggesting that neutralization of IL-21 could be a novel strategy for RA therapy. However, like in systematic lupus erythematosus, the mechanisms by which IL-21 contributes to the disease are not fully clear and IL-21 might have both adverse as well as beneficial effects. It should be noted, however, that IL-21-specific mAbs (known also as NNC0114-0006) were tested in clinical trials for treatment of RA, Crohn‘s diesease and Systemic Lupus Erythematosus . [510]

From mouse models of BALB/c mice infected with respiratory syncytial virus (RSV) it is known that endogenous IL-21 exhibit potent and specific role on mucosal defences, viral clearance by regulation of T and B cells response.[511] In patients with chronic hepatits B, serum IL-21 levels may serve as a biomarker for HBeAg seroconversion and may help in individualization of antiviral therapy in HBeAg-positive patients.[512] Recently, it was also found that IL-21 is suppressing HIV-1 replication in CD4+ T cells by inducing microRNA-29 in an HIV-infection model.[513]

Studies considering potential roles of Th17 cells and IL-21 in pathogenesis of chronic graft-versus host disease suggest, that IL-21 and Th17 cells may contribute to the development of cGVHD[514], and anti-IL-21 mAb treatment may be considered for prevention of this disease in clinic[515]. In Behçet disease, a chronic systemic inflammatory disease of unknown etiology, IL-21 by promoting Th17 cells and suppressing Tregs plays critical role in development of inflammatory lesions.[516]

Role in allergic disease

IL-21’s role in allergy and asthma has not been extensively studied. However, *in vivo* injection of IL-21 has been shown to prevent antigen-specific IgE but not IgG2a production.[481] IL-21 did not affect Th2 cell differentiation or IL-4 production from $CD4^+$ T cells, but inhibited IL-4-induced germ line Cε transcription in B cells. In mouse model of IgE-mediated cutaneous immediate hypersensitivity reaction, IL-21 exhibit regulatory effect suppressing production of allergen-specific IgE and mast cell degranulation[517]. However, recently it was found that CD4+ T cell-derived IL-21

together with IL-25 is indirectly leading to airway eosinophilia via stimulation of Th2 cells.[518]

On the other hand, in psoriasis, IL-21 induces IFN-γ-dependent pathogenic response in vivo, inducing epidermal hyperplasia and by that sustains skin-damaging inflammation.[519]

Functions as demonstrated in IL-21-deleted mice and receptor-deficient mice

Although IL-21R is induced during B cell development, it is apparently not essential for B cell development, as suggested by experiments using IL-21R knockout mice. No defects in B cell numbers have been observed in these mice, neither in bone marrow nor in the periphery.[492] However, IL-21R knockout mice have reduced serum IgG1 levels while IgE is increased, an unexpected result as IgG1 and IgE are usually regulated in coordination. Similar to the B cell development, IL-21 signaling is not required for $CD4^+$ T cell and NK cell development, as IL-21R KO mice exhibit normal $CD4^+$ T cells and NK cells.[492] Likewise, development of $CD8^+$ cells is not affected in IL-21R KO mice. However, expansion and cytotoxicity of $CD8^+$ T cells are impaired in these animals, [489, 520] consistent with IL-21's antitumor activity. Both IL-21 or IL-21R knockout mice have tenfold reduced number of IL-17-producing cells and, as a consequence, a markedly reduced EAE progression[466, 467], underlining the importance of IL-21 and IL-17A in inflammatory conditions. Also, IL-21R knockout mice were shown to have less efficient Th2 responses.[518] Taken together, IL-21 seems not to be crucial for the development of immune cells, but to play a role at later stages and under certain immune regulatory conditions.

IL-22

Discovery and structure

IL-22 was originally identified in mice as a gene induced by IL-9 in T cells, and it was termed IL-TIF, for IL-10-related T cell-derived inducible factor.[521] The human gene encoding IL-22 is located on 12q15, close to IL-26 and IFN-γ.[522] The secreted IL-22 is 146 amino acids in length, approximately 70 kDa in weight and shares 80.8% identity with mouse IL-22.[523] As a member of the IL-10 family, it has 22.8% identity to IL-10 and shares the anti-parallel alpha-helical structure with its family members.[524] Four cysteine residues, three of which are conserved between IL-10 and IL-22, form intramolecular disulfide bridges. IL-22 is heavily glycosylated, which does not seem to be important for its tertiary structure, but for receptor binding.[524, 525]

Receptor and signaling

The IL-22R complex is built of IL-22R1 and IL-10R2, the second chain of the IL-10 receptor.[521, 523, 526] IL-22R1 has a long intracellular tail containing four putative STAT recruiting sites.[526] Evidence suggests that IL-22 undergoes conformational change during the interaction with its receptor chains.[525, 527] Recently, the crystal structure of the IL-22/IL-22R1 complex has been solved and residues important for binding have been identified.[528, 529]

IL-22 signaling occurs mainly via the Jak/STAT pathway. Which of the Stat and Jak molecules are involved and whether also MAP kinases are activated seem to depend on the cell type analyzed, although Stat3 appears to be generally involved.

Interestingly, also a soluble form of IL-22R exists, the IL-22 binding protein (IL-22BP).[530-532] Whereas its soluble receptors are generated by proteolytic cleavage or alternative splicing, IL-22BP is encoded by an independent gene. IL-22BP is mainly expressed by resting dendritic cells and to a lesser extent by activated dendritic cells, resting and activated T and B cells and activated mast cells.[404] It binds to IL-22, but not to other members of this cytokine family. *In vitro*, IL-22BP can inhibit function of IL-22 and is therefore frequently used in *in vitro* experiments as a naturally occurring antagonist. However, the situation *in vivo* might be different and it remains to be elucidated whether IL-22BP inhibits IL-22 signalling also under physiological conditions or whether IL-22BP instead positively regulates its function by prolonging its half-life.

Cellular sources and targets

IL-22 has been found in activated T cells and, at lower levels, in activated NK cells, NKT cells and lymphoid tissue inducer cells.[399, 533] Among T cells, IL-22 is mainly expressed by memory $CD4^+$ T cells and to a minor extent by CD8+ memory T cells.[534, 535] Th17 and Th22 cells were demonstrated to be the most important IL-22 producers.[536] Th22 cells are characterized by expression of CCR4, CCR6, CCR10, but not CXCR3 chemokine receptors, high expression of aryl hydrocarbon receptor (AhR) and develop primarily during interaction of T cells with TNF-α and IL-6 producing plasmacytoid DCs [537, 538], skin langerhans cells (LCs), CD1c (+) CD14 (-) dendritic cells [539] or mast cells.[540] IL-22 production can be augmented further by Notch signaling, which promotes endogenous stimulators for AhR.[541]

Notch signaling promoted production of endogenous stimulators for AhR, which further augmented IL-22 secretion. Our studies identify a Notch-AhR axis that

regulates IL-22 expression and fine-tunes immune system control of inflammatory responses.

In addition to αβ T cells, murine γδ T cells expressing CCR6, RORγt, AhR and IL-23R produce IL-22 together with IL-17A and IL-21[542, 543] showing that IL-22 production could be independent of T cell receptor engagement. Similarly, a distinct subset of IL-22-producing NK cells located in mucosa-associated lymphoid tissues of mice and humans was identified, referred to as NK-22 cells.[544] IL-22-expression was also found in neutrophils[545] and most recently, also mast cells were reported to produce large amounts of [546]

Moreover IL-22 expression has been described for mouse and human innate lymphoid cells (ILCs). These cells lack a specific antigen receptor but can still produce cytokines, which match T helper cell subsets. RORγt$^+$ ILCs secrete IL-22 but not IL-17, and are part of mucosal immune system mostly in small and large intestine.[547] In contrast, no expression of IL-22 has been found in monocytes and B cells.

Up to date only one negative regulator of IL-22 production is know.[548] TGF-β induced c-Maf transcription factor was shown to bind to Il22 promoter and suppress IL-22 production by T cells, which indicates differential regulation of IL-22 and IL-17 production by TGF-β.

The IL-10R2 chain is ubiquitously expressed, as expected from its role as common part of several cytokine receptors. Thus, the IL-22R1 is likely to determine which cells are targets for IL-22. Interestingly, IL-22R1 could not be detected on primary immune cells like monocytes, skin-derived mast cells, macrophages, DCs, T cells, B cells, and NK cells.[549] In contrast, some organs like kidney, small intestine, liver, colon and lung, and particularly pancreas and skin showed expression of IL-22R1. Consistently, IL-22R1 has been found in several epithelial cell lines corresponding to these tissues, as well as in primary keratinocytes. Interestingly, both components of the receptor, IL-10R2 and IL-22R1, are upregulated by IFN-γ.

Role in immune regulation and cellular networks

Investigations addressing the functions of IL-22 rapidly revealed that, despite the structural relation, IL-22 is not functionally related to IL-10. Initial studies observed an up-regulated production of acute phase reactants and IL-10 in several cells lines[550], suggesting a functional role for IL-22 in inflammation. *In vitro* treatment with recombinant IL-22 or overexpression of IL-22 promoted cell growth and survival in a

hepatocellular cell line.[551] These reports analyzing immortalized cell lines give hints for a role of IL-22 in the acute phase of infections as well as in proliferation of certain cells. Further investigations using primary cells are required in this area.

Role in host defense or other immune regulatory conditions

Consistent with the high expression of the IL-22 receptor on keratinocytes, IL-22 increases the antimicrobial defense of these cells by enhancing the expression of β-Defensin 2 and β-Defensin 3, psoriasin, calgranulin A, calgranulin B.[231, 549] IL-22 also contributes to skin immunity by synergizing with IL-17A and IL-17F in the induction of antimicrobial peptides in keratinocytes.[230] A role of IL-22 in the defense of several bacteria has been found. IL-22 is important for the defense of *Citrobacter rodentium*[552], a bacterium that induces IL-22-secreting NK (NK-22) cells in the lamina propria[544] and IL-22 secreting ILCs.[553]. Furthermore, IL-22 is increased upon infection with *Mycobacterium tuberculosis*, *Klebsiella pneumoniae* and *Borellia burgdorferi* suggesting a role for IL-22 in the defense of these bacteria.[554, 555] In case of tuberculosis, differentiation and recruitment of IL-22 producing Th cells was stimulated by pleural mesothelial cells in tuberculous pleurisy[556]. Additionaly antiparasite effect of IL-22 during intestinal infection was reported.[557]

IL-22 may also play a role in defense against viruses, although there are some inconsistencies. For example, IL-22 overproduction has been found in individuals with resistance to HIV-1 [558] and reduction of IL-22 production and Th22 cells depletion are important factors in HIV gut mucosa immunopathogenesis.[559] In viral hepatitis, hepatocytes upregulate IL-22.[560] Although no effect on virus replication has been observed in this disease, IL-22 might prevent and repair liver injury.[551] Another study with IL-22(-/-) mice suggests that IL-22 signalling exacerbates lethal West Nile Virus encephalitis by promoting virus neuroinvasion.[561] In influenza infection mouse model, a protective role of IL-22 was reported. [562] IL-22 produced by conventional NK cells provides signal for epithelial cells regeneration and protection against inflammation.

Finally, since chronic mucocutaneous candidiasis (CMC) was found to be associated with significant lower IL-22 levels, the inability to clear *Candida albicans* might be due to a defect in IL-22 production.[563] Taken together, these studies support an important role for IL-22 in the defense of different pathogens.

As keratinocytes are a major target for IL-22, its role in keratinocyte-associated diseases has been studied. Indeed, one study found an important role for IL-22 in

psoriasis by mediating dermal inflammation and acanthosis.[228] Consistently, in a mouse model of psoriasis, neutralization of IL-22 prevented development of the disease, reducing acanthosis (thickening of the skin), inflammatory infiltrates, and expression of Th17 cytokines.[564] In human, T cells isolated from psoriatic skin produced higher levels of IL-22, and supernatants of lesional psoriatic skin-infiltrating T cells induced an inflammatory response by normal human epidermal keratinocytes, resembling that observed in psoriatic lesions.[565] In vitro study using a living skin equivalent (LSE) model demonstrated that increased IL-22R expression and stronger IL-22 responsiveness of keratinocytes was due to IFN-α.[566] Another study investigates the influence of two different drugs on IL-22 and finds that etanercept but not acitretin is able to reduce IL-22 levels, accompanied by lower psoriasis area and severity index.[567] Moreover, human mAbs specific for IL-22 (fezakinumab/ILV-094) were tested in clinical trials for treatment of psioriasis.[568, 569]

Despite the fact that mainly CD4+ T cells contribute to the pathology of AD and psoriasis, recent studies suggest that CD8 (+) T cells are a significant and previously underestimated source of inflammatory cytokines in both diseases.[570] Large numbers of CD8 (+) T cells producing IL-22, IL-13 and IFN-γ were found in lesional and nonlesional skin of AD patients. Furthermore, in addition to Th17 cells, high percentage of IL-22 and IL-17 producing CD8+ T cells were observed in psoriatic skin lesions indicating potential role of those cells in AD and psoriasis.

Th17 cells are a major effector population in inflammatory bowel disease (IBD). As IL-22 is produced by this helper cell subset, its expression has been analyzed in IBD. Indeed, increased levels of IL-22 have been found in patients with inflammatory bowel disease, and intestinal epithelial cells (IEC) express functional receptors for IL-22.[571-573] On the other hand, in intestinal tissue of IBD patients, aryl hydrocarbon receptor (AhR) expression is down-regulated.[574] Since AhR signalling is necessary for IL-22 production, this data may suggest that decreased IL-22 expression may contribute to IBD development. Also it was found, that neutrophils producing IL-22 were able to reconstitute the colonic epithelial integrity during colitis.[545] Additionally, it was seen that IL-22 has importance for host health because it shapes the homeostatic balance between colonic microbiota and immunity.[575]

Although further investigations are needed to fully clarify the role of IL-22 in this disease, it seems to have adverse effects by contributing to the inflammation, but also beneficial roles by promoting wound healing. Such a repair effect of IL-22 is also

observed in hepatitis. Injection of recombinant IL-22 attenuated liver injury[551], while hepatocytes from mice deficient in IL-22 were highly sensitive to the detrimental immune response associated with hepatitis[576], suggesting IL-22 to serve as a protective molecule counteracting the destructive effects of the immune response and limiting tissue damage.

The other study describes presence of inducible IL-17 (+) IL-22 (+) memory T cells in lung draining lymph nodes of cystic fibrosis patients.[577] However, the role of pathogenic, double-positive IL-17 (+) IL-22 (+) cells responsive to *P. aeruginosa* and *Aspergillus* in cystic fibrosis require further investigation.

The results of studies addressing the role of IL-22 in cancer differ. One study observes prolonged survival of the hosts upon IL-22, although neither metastasis nor tumor growth was affected.[578] In another study, IL-22 treatment of mice with breast cancer lead to a decreased tumor size and a reduced tumor cell proliferation[579], while more recent studies suggest an adverse effect of IL-22 in cancer: Overexpression of IL-22 protected lung cancer cell lines from apoptosis induced by starvation and chemotherapeutic drugs, while administration of IL-22 RNAi plasmids significantly inhibited tumor cell growth.[580] Expression of IL-22 and IL-22R has been found on anaplastic large cell lymphoma (ALCL), and it was associated with proliferation of these cells.[581] Besides the anti-apoptotic and proliferative effects, IL-22 has been shown to induce inducible nitric-oxide synthase (iNOS) in colon carcinoma cells, a gene involved in inflammation and carcinogenesis.[582] Clinical relevance of IL-22 in patients with gastric cancer (GC) was investigated.[583] IL-22 producing T cells and Th22 are involved in establishing of tumor microenvironment, tumor progression and the presence of those cells predict poorer patient survival in GC. Differences in these results are most likely due to the different type of tumors analyzed. Further investigations are required to make conclusions about the type of cancer on which IL-22 might be a drug target.

Role in allergic disease

To date, only few reports investigated the role of IL-22 in allergic diseases. Inflamed skin of nickel-challenged allergic individuals was observed to contain infiltrating cells expressing IL-22 and IL-22R.[584] Another study reports that Th17 cells induce airway hyperresponsiveness in steroid-resistant asthma. It remains to be determined, whether this effect is due to IL-22 or due to other Th17 cytokines.[585]

Chronic skin inflammation due to infection and colonization with *S.aureus* in atopic dermatitis may be partially explained by increased IL-22 secretion by skin T cells.[586] In fact, fezakinumab has now entered phase 2 clinical trials for treatment of atopic dermatitis (www.ClinicalTrials.gov).

A recent study indicates that Th22 cells infiltrate the lung during asthma[587]. Authors showed that IL-22 and IFN-γ mediate antagonistic effects in lung epithelial cells. From one hand, by inhibiting IFN-γ induced expression of proinflammatory molecules, IL-22 reduced epithelial susceptibility to T cell mediated cytotoxity. On the other hand IL-22 mediated induction of the antimicrobial peptides was antagonized by IFN-γ. This data indicates a regulatory role for IL-22 in context of IFN-γ mediated lung inflammation.

To further investigate the role of IL-22 in onset and resolution of allergic asthma, patient samples and lung of control and IL-22 (-/-) mice immunized and challenged with OVA were investigated.[588] Since production of Th2 cytokines, chemokines, airway hyperreactvity, mucus production and eosinophil recruitment were reduced in IL-22 deficient mice, results indicate that IL-22 is required for initiation of allergic asthma. On the other hand IL-22 acts as negative regulator in established allergic inflammation because neutralization of IL-22 during antigen challenge increased Th2 cytokines along with enhanced allergic lung inflammation.

Conversely, it has been shown that antigen-induced airway inflammation may be attenuated by IL-22 via inhibition of IL-25 production by lung epithelial cells.[589] To conclude, IL-22 can exhibit both pro-inflammatory and anti-inflammatory properties depending on the stage of allergic lung inflammation.

Functions as demonstrated in IL-22-deleted mice, receptor-deficient mice and human mutations

The role of IL-22 in host defense is underlined by studies investigating IL-22- and IL-22R-deficient mice. IL-22 KO mice have an increased intestinal epithelial damage, systemic bacterial burden and mortality upon infection with *Citrobacter rodentium*, due to a defective induction of antimicrobial proteins belonging to the Reg family.[552] In contrast, the other IL-10 family members IL-19, IL-20 and IL-24 were all dispensable for host defense against this bacterium, suggesting a unique role for IL-22.

Six single nucleotide polymorphisms (SPN) have been found in the gene encoding IL-22.[590] Two of them seem to correlate with treatment response and viral clearance,

respectively, consistent with the reports suggesting a role for IL-22 in the defense of viruses. It remains to be elucidated, whether these or other SNP have an influence on the defense of other pathogens and whether they correlate with certain disease frequencies. A recent study with the use of IL-22 (-/-) mice defined a new role of IL-22 in skin repair by interaction between immune cells with fibroblasts.[591] In this study active IL-22 signaling was found in fibroblasts. Moreover after full-thickness wounding, IL-22 (-/-) mice exhibit major defects in skin‘s dermal compartments suggesting that IL-22 plays a role in restoration of epidermal barrier and tissue architecture during wound repair in skin.

Another study with mouse model indicates protective role of IL-22 in acute pancreatitis (AP) and involvement of AhR in this process[592]. Reduction of IL-22 (+) T cells and upregulation of IL-22R1 on epithelial cells was observed in mice with AP. From one hand, administration of recombinant IL-22 reduced AP symptoms but from the other hand, induction of IL-22 production required AhR signaling. This data suggest that AhR activation protects mice from acute pancreatitis by inducing expression of IL-22.

IL-23

Discovery and structure

IL-23 is a type I heterodimeric cytokine, which consists of a 19-kD 4-fold helical core α subunit (IL-23p19) that is disulfide-linked to an additional 40-kD distinct beta subunit (IL-12p40).[593] The IL-23p19 subunit has been mapped to the long arm of human chromosome 12 and on the mice chromosome 10. The protein shows 70% homology between mouse and human, and has an overall sequence identity of approximately 40% to the p35 subunit of IL-12.[593]

Receptor and signaling

Due to a common p40 subunit, IL-23 and IL-12 also share the IL-12Rβ1 subunit in their receptor complex. A second subunit (called IL-23R) is required for specific recognition of p19 and the heterodimer forms the high-affinity IL-23 receptors. The IL-23R gene has been localized on the human chromosome 1 and on the mice chromosome 6. Being a member of the IL-6/IL-12 receptor family, the IL-23R, consists of an extracellular N-terminal immunoglobulin-like domain and two cytokine receptor domains that bind to the IL-23p19.[594] The IL-12β1 subunit contains three membrane-proximal fibronectin type III and two cytokine receptor domains that

interact with IL-12/23p40.[595] The functional IL-23R is expressed on αβ and γδ T cells and innate leukocytes [594]. Stimulation of the receptor complex activates Jak2 and Tyk2, resulting in phosphorylation of the receptor complex, and formation of docking sites for STATs (1, 3, 4 and 5). The STATs are subsequently dimerized, phosphorylated and translocated into the nucleus, activating target genes.

Cellular sources and targets

The secretion of p19 depends on its ability to partner with IL-12p40 via a disulfide bond and therefore, coexpression of both subunits in one cell is required to generate the formation of the biologically active IL-23. IL-23 is mainly produced by phagocytic cells, macrophages and activated dendritic cells from peripheral tissues including the skin, intestinal mucosa and lungs. Production of both subunits of IL-23 is stimulated through activation of toll-like receptors by their ligands (including lipopolysaccharide, peptidoglycan, CpG DNA and poly I:C). Such interactions result in increased expression of p40 and p19, consequently enhancing the release of IL-23. Some evidence suggests that activation of DC through TLR2 preferentially induces IL-23 synthesis and an agonist of C-type lectin dectin-1, beta glucan curdlan, does so without inducing IL-12p70.[596] *S. pneumoniae* infection induces IL-23 production through MyD88-IRAK1/4-dependent TLR2 and Nod2 signaling in DCs. Bone marrow-derived DCs and macrophages treated with morphene and infected with *S.pneumoniae* or treated with TLR2 and TLR4 ligands produced significantly higher levels of IL-23, which could be blocked by MyD88 and IRAK1/4 inhibitors or TLR2 antibodies.[597] Other factors, such as prostaglandin E2, extracellular nucleotides and GM-CSF can modulate IL-23 production by antigen presenting cells both in mice and humans.[598] In EAE, Th17 cells stimulated with IL-23 are higly pathogenic and produce high levels of GM-CSF induced by IL-23, whereas Th17 cells stimulated with TGF-β and IL-6 are not pathogenic and have lower expression levels of GM-CSF. Thus, IL-23 leads to a positive feedback loop in Th17 cells and GM-CSF secreted by these cells stimulates the production of IL-23 by antigen-presenting cell.[599] Another study using IL-23R reporter mice showed, that γδ T cells were the first cells to respond to IL-23 during EAE. These cells produced Th17 related cytokines in response to IL-23, but they also prevented the development of Treg cell responses. This indicates that IL-23 is able to suppress Treg cell responses and promotes antigen-specific effector T cell responses via activating γδ T cells.[600] *Bordetella pertussis*, producing the pertussis toxin that blocks Gai linked Gprotein coupled

receptors and leads to an increase of cAMP, enhance IL-23. Additionally, IL-23 production can be enhanced via CD40-CD40L interaction, resulting in increased production of IL-23, and creating a potent positive feedback for augmenting IL-23 production by APC. However, such stimulation is dose and time dependent.[596] In spndyloarthropathis, it was very recently demonstrated that IL-23 serum levels are elevated and that polymorphisms in the IL-23R are associated with ankyosing spondylitis. The same study showed, that IL-23 is essential in enthesistis, as blocking of IL-23 reduced the clinical disease scores and the levels of entheseal inflammation in mice. IL-23 here acts on previously unidentified IL-23R^{+}, RORγt^{+}CD3^{+}CD4^{-}CD8^{-} Sca1^{+} entheseal resident T cells.[601]

Role in immune regulation and cellular networks

Contrary to IL-12 that stimulates both naïve and ~~activated~~ memory T cells, IL-23 acts only on memory and effector T cells.[602] In addition, to high levels of the IL-23 receptor complex expression on activated and memory T cells, the receptor is expressed on various cells populations including NK and NKT cells, eosinophils, monocytes, macrophages, DC and epithelial cells such as keratinocytes.[593, 594] Because TCR stimulation is not sufficient to induce IL-23R expression, additional stimulations are required to promote IL-23 responsiveness. Following IL-23 stimulation, several inflammatory molecules are produced including IL-17A, IL-17F, IL-6, IL-22, TNF, CXCL1, and α3 integrin. Thus, IL-23 has initially been identified as a Th17 cells promoting factor.[248, 603] Recent reports clarified this role of IL-23. It was shown that TGF-β and IL-6 are required for the differentiation of naive T cells into IL-23R-positive IL-17-producing T cells.[604-606] IL-6 induces the production of IL-21, which signals in an autocrine fashion to upregulate its own expression and to induce the expression of IL-23R in a STAT3 and RORγt-dependent manner.[487] IL-23, in synergy with TGF-β, further amplifies RORγt expression and production of IL-17. Despite this initial assumption, IL-23 is dispensable for the *in vitro* polarization of naïve T cells into Th17 effectors. However, following IL-6/TGF-β-mediated commitment of Th17 cells, subsequent exposure to IL-23 is necessary for full differentiation and effector function of Th17 cells. In a study using *IL23ra*$^{-/-}$mice, it was shown that IL-23 is tightly associated with Th17 cell-mediated inflammation and autoimmunity. IL-23R dependent signaling is required for the generation of normal Th17 cell effector responses. It was shown that IL-23 alone is not sufficient for Th17 development, but

is important to maintain the effector functions and IL-17 production of Th17 cells and is necessary for differentiation of activated T cells into effector Th17 cells.[607]

In addition to its role in Th17 cell development, IL-23 activates NK cells, enhances T cell proliferation and regulates antibody production.[608] IL-23/IL-17 pathway is associated with local tissue inflammation that produces swelling, heat, and pain, and sets up an environment with heightened immune responses. Therefore, it was proposed that IL-23 might play a critical role in driving an early inflammatory immune response to pathogens or injury by directly inducing IL-17 production and early neutrophil recruitment. Dysregulation of the IL-23/IL-17 immune axis has been linked to immunopathology and autoimmune inflammation and the generation of IL-23p19 KO mice indicated that IL-23, but not IL-12 plays a crucial role in the development of several autoimmune models. [193]

In a recent study with IL-23R reporter Knock-in mice and *IL23r*$^{-/-}$ mice, the role of IL-23R in the host response to intracellular pathogens was investigated. Macrophages, DCs, NK cells and neutrophils limit growth of the organism within the first 48h of infection and adaptive immunity involving $CD4^+$ Th1 and cytotoxic $CD8^+$ cells begins around 4 days after infection. IL-23 is produced very early by macrophages and DCs indicating that IL-23 might bind to IL-23R in early stages of infection. In addition, IL-23R regulated the function of specific IL-17-producing γδ-TCR^+ and αβ-$TCR^+CD4^-CD8^-$DN T-cells, which are two essential components of the early protective immune response against intracellular pathogens. [609]

Under physiological conditions, IL-23 is constitutively expressed in ileal mucosa, and IL-17 producing cells are highly enriched in intestinal tissues.[610] It is therefore not surprising that numerous studies have confirmed a role for IL-23 in contributing to the development of several intestinal diseases. Significant upregulation of local and systemic IL-23 production was observed in Helicobacter pylori-induced gastric ulcers and gastric cancer in human and in mouse models. In colo-rectal cancer IL-23 signaling promotes tumor growth and the development of tumoral IL-17 responses. IL-23 itself is produced by tumor-associated myeloid cells, which are activated by microbial products that penetrate the tumors but not the adjacent tissue. [611] In contrast to that study in pediatric B-acute lymphoblastic leukemia (B-ALL) cells, the antitumor activity of IL-23 was shown. IL-23R was upregulated in primary B-ALL cells in comparison to normal early B cells and IL-23 inhibited proliferation and induced apoptosis in tumor cells leading to a direct retardation of tumor growth. [612]

A 20-fold increase of Th17 cells and IL-17-expressing macrophages was observed in lesions of Crohn's disease patients compared to controls, which may be due to the increased expression of IL-23.[613] Furthermore, the development of spontaneous IBD in IL-10-deficient mice was completely prevented by crossing these mice to IL-23p19-deficient mice.[614] This demonstrates that IL-23 is required for the induction of colitis. In bacteria-driven innate colitis, IL-23 has an inflammatory effect on innate immune cells and pathogenicity is associated with an increased production of IL-17 and IFN-γ in the colon. After stimulation of colonic leukocytes with IL-23, type3 innate lymphoid cells (ILC3) expressing Thy1, SCA-1, RORγt and IL-23R exclusively induced the production of IL-17 and IFN-γ. In addition, these cells accumulated in the inflamed colon, indicating that these IL-23 responsive innate lymphoid population is able to mediate intestinal immune pathology. [615, 616]

In the pathogenesis of psoriasis it was shown that IL-23 predominantly stimulated dermal $CCR6^+$ γδ T cells to produce IL-17 and that the number of these cells was greatly increased in the affected skin.[617] IL-23 induced epidermal hyperplasia and inflammation by occurring in psoriasis were significantly reduced in T cell receptor δ-deficient mice and IL-17 receptor-deficient mice, but were normal in T cell receptor α mice indicating an independence of αβ T cells in pathogenesis and also IL-23 responsiveness in dermal γδT cells. [618] On the other hand, it was shown that frequency of circulating NKp44+ ILC3, which also produce IL-17A in response to IL-23, in the blood of psoriasis patients was significantly larger than that in the normal subjects or atopic dermatitis patients. Moreover, the significant increase in frequency of NKp44+ ILC3 in non-lesional psoriatic skin compared with normal skin was reported as well.[619] Future studies may uncover the relationship between γδ Tcells and ILC3 in the pathogenesis of psoriasis.

In addition, several clinical trials assess the suitability of IL-23 blocking antibodies, namely Ustekinumab, Guselkumab and Tildrakizumab, in treatment of systemic lupus erythematosus, graft versus host disease, psoriasis,[620-622] colitis [623] and crohn's disease, among others. [602]

Functions as demonstrated in IL-23-deleted mice and receptor-deficient mice.

The IL-23/IL-17 immune axis has also been implicated in the pathogenesis of experimental encephalitis and collagen-induced arthritis in mice. IL-23-driven IL-17-producing cells are highly potent at inducing CNS immune pathology.[248] The IL-

23p19-/- mice can still generate Th1 lymphocytes and IFN-γ, but are resistant to experimental autoimmune encephalitis (EAE), a model for human multiple sclerosis. Similarly, CIA studies revealed that the IL-23-deficient mice are resistant to the development of bone and joint pathology during exacerbated arthritis, due to the absence of CD4+ T cells that make IL-17.[624] High levels of IL-17 also correlated with the severity of disease in multiple sclerosis and rheumatoid arthritis patients.[613]

Multiple single-nucleotide polymorphisms are located in the IL-23R generation and show distinct correlation patterns to diseases. Polymorphisms in the IL-23R represent one of the strongest association in Crohn's disease, and it has also been linked to the pathogenesis of ulcerative colitis, psoriasis, ankylosing spondylitis and myocardial infarction.[625-627] The arginine residue at position 381 is the fifth amino acid internal to the transmembrane domain in the cytoplasmic tail of the IL-23R and is highly conserved between species. The glutamine allele of Arg381Gln is much less common than the arginine allele and it confers approximately threefold protection against the development of Crohn's disease. In addition to Arg381Gln, several other markers in IL23R and in the intronic region between IL23R and the adjacent IL12RB2, demonstrated independent evidence for association with the disease.[627] This suggests the presence of at least 2 independent risk alleles in the region.

Using *IL23r*$^{-/-}$ mice, the role of IL-23R signaling in T cells and their development in IBD was determined. Direct stimulation of IL-23R deficient CD4^{+} T cells resulted in intestinal, but not systemic, inflammation. IL-23 signaling in T cells led to an increased proliferation and accumulation of T cells in the colon and an eccess of IL-17A^{+}IFN-γ^{+} double-producing CD4^{+} T cells while inhibiting the induction of Foxp3^{+} IL-10 producing Treg cells in the gut. [628] In addition, protective effects for Arg381Gln in IL23R have been reported in psoriasis cohorts and a strong association with psoriasis was observed for SNPs within the p40 gene region.[626, 629] Recently, clinical trials using monoclonal anti-IL-23 therapy have shown promising results in the treatment of Crohn's disease.[630, 631]

IL-24

Discovery and structure

IL-24 was identified in 1995 through subtractive hybridization studies using cDNA libraries from human melanoma cells. It was shown to be expressed in healthy melanocytes, whereas its expression was abolished in melanoma cells. [632] As a

result, IL-24 was initially named melanoma differentiation-associated gene 7 (MDA-7).

The gene encoding IL-24 localizes (together with the genes encoding IL-10, IL-19 and IL-20) on chromosome 1q32 and is composed of seven exons and six introns. IL-24 shares 19% amino acid identity with IL-10 and like the other members of the IL-10 family and it has a predicted three-dimensional structure containing six α-helices. IL-24 consists of 206 amino acids and its predicted molecular weight is 23.8 kDa. [633] IL-24 possesses three consensus N-linked glycosylation sites and as a result of extensive N-linked glycosylation the apparent molecular weight of secreted human IL-24 is ~35 kDa. [634] Unlike most of the other IL-10 family members, human IL-24 must be glycosylated in order to maintain biological activity and solubility. Furthermore, a single unique disulfide bond is required for secretion and activity. [635] Mutation of lysine 123 resulted in enhanced stability of IL-24 by inhibiting its ubiquitination and degradation and it exhibited higher tumour suppression activity compared with the wild type form. [636]

Receptor and signalling

IL-24 is the ligand for two heterodimeric receptor complexes: IL-22R1/IL-20R2 or IL20R1/IL-20R2. These receptor complexes were identified through a screening experiment in which combination of putative R1 and R2 types of the IL-10 family (IL10R2, IL-20R1, IL-22R1 and IL-20R2) were expressed in transfected COS cells. IL-24 bound to cells that were transfected with the IL-20R2 and this binding was strongly enhanced when IL-20R2 was co-transfected with IL-20R1 and IL-22R1. [634] The binding of IL-24 to either receptor complex results in the activation of STAT1 and STAT3. Like IL-19- and IL-20-mediated STAT3 activation, IL-24-mediated STAT3 activation occurs at physiological concentrations whereas STAT1 activation occurs at much higher concentrations. [405] An indication for alternative signalling pathways for IL-19, IL-20 and IL-24 came from growth inhibition experiments with the carcinoma cell line NIH: OVCAR-3 which expresses all three receptor complexes involved in binding of these ligands. IL-19 and IL-24 induced growth inhibition in this cell line in a STAT-independent manner suggesting that other signalling pathways must be activated. [405]

Cellular sources and targets

IL-24 is expressed in normal melanocytes but is strongly downregulated in metastatic melanomas. [632] Furthermore, IL-24 was found to be expressed by T cells,

monocytes, NHEK cells as well as B cells. [404, 637, 638] IL-24 was also found to be produced by mast cells activated by T cell-derived microvesicles, but not FcεRI cross-linking.[639] A recent report showed that anisomycin- and IL-1β-induced IL-24 expression in normal human keratinocytes is regulated by p38 MAPK through mRNA stabilizing mechanisms. [640] In line with the initial concept of IL-24 as a tumour suppressor molecule, its expression in most human tumours is very low. Furthermore, a rare, functional, missense variant of IL-24 was associated with Juvenile idiopathic arthritis and IL-24 inhibited β-glycerophosphate-induced rat vascular smooth muscle cell calcification by inhibiting apoptosis, the expression of calcification and osteoblastic markers, and the Wnt/ β-catenin pathway. [456, 641] Also, IL-24 suppressed the growth of vascular smooth muscle cells by inhibiting H_2O_2-induced reactive oxygen (ROS) species production through the regulation of mitochondrial reactive oxygen species production and expression of antioxidant enzymes. [642]

Role in immune regulation and cellular networks

Monocytes secrete IL-24 after stimulation with concavalin A, LPS, and cytokines; T_h2 cells after TCR stimulation together with anti-CD3 and CD28 or PMA and Ionomycin; B cells after B cell receptor stimulation. [643] PBMCs stimulated with IL-24 produced high levels of IL-6, TNF-α and IFN-γ and low levels of IL-1β, IL-12 and GM-CSF within 48 hours. This pro-inflammatory response can be inhibited by addition of IL-10. [644] Therefore, IL-24 appears to play a role in an immunoregulatory loop. When added to B cell cultures, IL-24 strongly inhibits plasma cell differentiation and promotes CD40-induced proliferation indicating that it may play a role in the regulating the balance between plasma and memory B cell differentiation. [638] Furthermore, IL-24 induced the mitochondrial apoptotic pathway (Bax, Bid, Casp8, COX6C, COX7B) and inhibited expression of genes involved in DNA replication and metabolism in B cells. [645] Then, IL-24 was involved in immunity against *Salmonella typhimurium* and *Mycobacterium tuberculosis* by activating neutrophils and $CD8^+$ T cells. [646] Human $CD11b^+$ myeloid cells migration was induced by IL-24 in a G-protein coupled receptor dependent way. [647] Finally, Stat6 and c-Jun mediated IL-24 gene expression in T_h2 cells. [648]

Role of IL-24 as tumour suppressor

The first demonstration that IL-24 is a potent and specific inhibitor of cancer cell proliferation came from the same group that identified the IL-24 gene. They showed

that transfection of a number of different cancer cell lines containing both normal and mutated p53 and retinoblastoma genes with an adenoviral vector containing the IL-24 gene induced potent suppression of proliferation of all cancer cell lines tested. [649]

Increased levels of inducible nitric oxide synthase (iNOS) expression have been associated with melanoma progression. Treatment of malignant melanoma cells with recombinant IL-24 or transfection with an andenoviral vector encoding the IL-24 gene resulted in a marked reduction of iNOS, demonstrating a suppressive effect of IL-24 on iNOS expression which supports its role as a tumour suppressor. [650] More insight into the molecular mechanism by which IL-24 exerts cancer-specific apoptosis induction was recently gained. It was demonstrated that IL-24-mediated induction of cancer cell apoptosis depends on receptor binding but is independent of STAT3 activation. Furthermore, the treatment of tumour cells with recombinant IL-24 leads to increased expression of endogenous IL-24 through stabilization of IL-24 mRNA. Finally, rIL-24 treatment was shown to induce endoplasmic reticulum stress and reactive oxygen species production. [651] The authors concluded that the IL-24-induced endoplasmic reticulum stress and reactive oxygen species may specifically induce apoptosis in cancer cells. These cells are likely more susceptible to such signals than normal cells, because their endoplasmic reticulum stress and reactive oxygen species level are already elevated and therefore a slight increase in their production may tilt the balance towards apoptosis induction. This apoptotic effect of IL-24 on cancer cells was found to be mediated by Sigma 1 Receptor (SR1); a ligand-regulated protein chaperone. SR1; through interaction with IL-24 induces ER stress, p38/MAPK activation and production of ROS and caspase-3 activation in cancer cells. [652]

The first *in vivo* evidence of the potential therapeutic effects of IL-24 in the treatment of cancer was provided in 2002. In this study, an IL-24 encoding adenovirus was injected in subcutaneous lung tumour xenografts in nude mice. This treatment significantly inhibited tumour growth and induced extensive apoptosis of tumour cells. Furthermore, the expression of CD31 (an angiogenesis marker) was downregulated while TRAIL expression was increased in treated tumours. [653] From these results, it was concluded that treatment with an IL-24-encoding adenovirus may be a powerful therapeutic agent for the treatment of cancer. A phase 1 clinical trial in which and IL-24-encoding adenovirus was injected intra-tumorally in patients with advanced cancer demonstrated that this treatment is well-tolerated and induces

transient increased in IL-6, IL-10 and TNF-α as well as an increase in CD8+ T cells and induction of apoptosis in a large volume of the tumour. [654] Today, IL-24 is used in combination with other anti-tumour drugs. In human breast cancer cells, adenovirus mediated combined insertion of inhibitor of growth family member 4 and IL-24 together with radiotherapy resulted in suppression of growth, in promotion of apoptosis and in arresting of the cell cycle. [655] A recent study also showed that adenovirus mediated IL-24 overexpression in neuroblastoma cells [656] and hepatocellular carcinoma cells [657] inhibit cell migration and invasion capabilities of cancer cells. Adenoviral delivery of the IL-24 gene; was shown to be effective in killing of renal carcinoma cells when used in combination with histone deacetylase inhibitors. [658] A similar effect was observed in nasopharyngeal carcinoma cells, where adenoviral delivery of IL-24 proved effective at inducing apoptosis. [659]

Recent studies have identified that phosphorylation of IL-24 is essential for this cytokine to exert its anti-tumour and anti-proliferative effects on cancer cells. Phosphorylation of IL-24 is necessary for trafficking and subcellular localization inside cells. IL-24 exerts its cell cycle arresting function through activation of AKT/mTOR signalling pathway and phosphorylation of IL-24 is also necessary for the functional properties of IL-24. [660]

IL-24 also has the capability to reduce cell migration and invasion to other tissues. Lung cancer cell lines transfected with IL-24 encoding vector were found to reduce CXCR4 expression and possess reduced migration capability. This inhibition of CXCR4 expression is also mediated by activation of AKT/mTOR signalling. [661]

The micro RNA-205 was reduced in human oral cancer cells. Transfection of these cells with micro RNA-205 led to induced IL-24 production by targeting its promoter and increased cell cytotoxicity and apoptosis though activation of caspase-3/-7. [662]

Role in psoriasis

An IL-20R2-dependent mechanism for IL-23-induced skin inflammation and epidermal hyperplasia has been described. Intradermal treatment of mice with IL-23 induced epidermal thickening and mRNA expression of *IL-19* and *IL-20* whereas the expression of the subunits of their receptor complexes (IL-20R1, Il-20R2 or IL-22R1) was not affected. Intradermal injection of IL-23 into *il-20r2*$^{-/-}$ mice significantly inhibited epidermal thickening compared to WT mice while the skin phenotype of treated *il-19*$^{-/-}$ and *il-20*$^{-/-}$ mice did not differ from WT animals. This suggests a role for

IL-20R-mediated signalling in the IL-23-mediated initiation of psoriasis in which IL-19 and IL-20 appear to be functionally redundant. [663] Furthermore, etanercept improved psoriasis by suppression of gene expression of IL-19, IL-20, and IL-24. [410]

Recent studies show a more direct role of IL-24 in driving keratinocyte mediated skin inflammation. Keratinocytes stimulated with IFN-γ, IL-4, IL-6 or IL-22 show increased expression of IL-24. IL-24 in turn enhances expression of IL-8, PGE_2 and MMP-1 in keratinocytes through activation of JAK1-STAT3 and MAPK pathways, contributing to the inflammatory environment that induces IL-24 expression. [664]

Wound healing

IL-24 and its receptor were enhanced in chronic wound tissues. IL-24 promoted the chronicity in wound tissues by inhibition of the migratory behavior of human keratinocytes in an AKT dependent way. [665]

Functions as demonstrated in IL-24 transgenic mice

IL-24 transgenic mice share many of the phenotypic features with IL-20 and IL-22 transgenics including epidermal hyperplasia, neonatal lethality and abnormal keratinocyte differentiation. [666] This again indicates that there may be a certain degree of redundancy in the epidermal functions of these three related cytokines.

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IL-25

Discovery and structure

IL-25 was first described in 2001 by Hurst et al.[1] Due to its homology to the IL17 cytokine family (16-18% homology), it has also been named IL17E.[1, 2] The protein consists of 177 amino acids and has a molecular mass of 16.7 kDa in humans and 17.6 kDa in mice. It is encoded on chromosome 14q11.1 and little is known so far about its structure. The strongest identity exists at the C-terminal part (20-30%).

Receptor and signaling

IL-25 binds to the IL17RB and IL-17RA to form a heteromeric receptor complex.[3] It was previously shown that IL17RA$^{-/-}$ and IL17RB$^{-/-}$ mice are phenotypically normal. However, splenocytes from IL17RB$^{-/-}$ mice do not produce IL-5 or IL-13 in response to IL-25 stimulation, in contrast to wild type.[3] Intranasal challenge with IL-25 increases the numbers of eosinophils, neutrophils, lymphocytes, and expression of CCL2, CCL11, IL-5, -13, -9 and IL-10. This response in not visible in IL-17RA$^{-/-}$ and IL17RB$^{-/-}$ mice, since both receptors subunits are needed for IL-25 signaling.

IL-25 activates NF-kB and members of the MAP kinase transcription factor family.[4] TNFR-associated factor (TRAF) 6 directly associates with the cytoplasmic region of IL-17RB and mediates NF-kB, but not MAP kinase, activation upon ligand binding.[5] In contrast, IL-17RA does not contain a TRAF6-binding motif, but can recruit TRAF6 by directly associating with the adaptor protein Act1.[6] IL-17RA and Act1 interact through homotypic interaction of their SEFIR (similar expression to fibroblast growth factor genes and IL-17R) domains, which share residues with two of the three conserved motifs present in TIR (Toll/IL-1R) domains.[7] Act1 is also recruited to IL-17RB through the SEFIR domain, and Act1 deficiency reduces IL-25-mediated eosinophilia and Th2 responses in the airway.[8] There is an interaction interface (CC′ loop) in the SEFIR domains of several interacting SEFIR family members, including IL-17RA, IL-17RB, IL-17RC, and Act1. Deletion of the CC′ loop from either Act1 or IL-17RA disrupted the interaction between these two proteins.[9] IL-25 can directly activate STAT5 through a Act1-independent pathway.[10]

Cellular sources and targets

IL-25 is a product of several cell types and can regulate the function of both immune and non-immune cells. IL-25 is produced by Th2 cells[11], by *in vitro* cultured mast cells[12] and epithelial cells.[13, 14] Other cell types can also produce IL-25,

including alveolar macrophages after solid particle inhalation[15], intestinal epithelial cells[16] and brain capillary endothelial cells.[17] Eosinophil and basophil granulocytes from atopic individuals have also been described as sources of IL-25. RAG KO mice treated with IL-25 have the same hematological and histological changes as the WT mice. Because IL-25-treated RAG KO mice have increased gene expression of IL-5 and IL-13, it seems that there are non-T/non-B cells that responded to IL-25 by producing Th2-associated cytokines.[11] IL17RA and IL17RB are expressed on innate and adaptive immune cells such as CD4+ Th2 cells, fibroblasts, basophils, invariant natural killer cells (iNKT cells), macrophages and innate lymphoid cells type II (ILC2s). [18,20,19,20] Mucosal CD14+ cells, natural killer T (NKT) cells[21-24]are additional cell targets of IL-25. Th9 cells express IL-17RB and are able to respond to IL-25 by enhancing the production of IL-9.[25] Type 2 myeloid (T2M) cells have IL-25 receptor subunit IL-17RB, which is a key mediator of both innate and adaptive pulmonary type 2 immune responses.[26] IL-25 is found at very low levels in various tissues (brain, kidney, lung, prostate, testis, spinal cord, adrenal gland, trachea at an mRNA-level). Highest expression levels were detected in the gastrointestinal-tract and uterus.

Role in immune regulation and cellular networks

IL-25 initiates, promotes and augments Th2 cell-mediated immune responses, and inhibits both Th1 and Th17 cell responses.[11, 13, 16, 21] IL-25 seems to have two distinct functions in immune responses: one as an initiator of responses causing allergic diseases, by increasing the expression of IL-4, IL-5 and IL-13[11], and the other as an attenuator of the destructive inflammation found in diseases such as inflammatory bowel disease, diabetes and multiple sclerosis. Intra-peritoneal injection of IL-25 in mice leads to an increase in eosinophilia, splenomegaly and splenic plasma cell numbers. Moreover, IgE and IgG1 increase.[11] IL-25 induces Th2 associated cytokines (IL-13 all tissues; IL-4, IL-5 spleen). Nevertheless, it is important to mention that IL-25 leads to pathological changes solely in mucosal tissues, despite of gene expression in various other tissues. IL-25 administration induced epithelial hyperplasia in the esophagus and the non-glandular part of the stomach. Epithelial cells contained eosinophilic cytoplasmatic inclusions in gastric glands and pyloric epithelial cells. Furthermore, inflammatory infiltrates of eosinophils, neutrophils and mononuclear cells in epithelium and lamina propria of esophagus and stomach, sometimes in the serosa and submucosa are described. Within the small and large intestine: goblet cell hypertrophy and hyperplasia occurs and epithelia of the large

biliary tract in the liver and the large pancreatic ducts were often vacuolated and contained eosinophilic cytoplasmic inclusions.[11] Administration of IL-25 does not result in an increased IL-6 expression in the spleen, stomach or small intestine. No changes of IL-1α, TNF-α; IL-10; IFN-γ are described. In addition, IL-25 mRNA expression is not up-regulated upon IL-25 treatment. IL-25 had no impact on IL-4, IL-5 and IL-13 production of naïve T-cells or B-cells in the presence of LPS or CD40L.

IL-25 dependent actions are attributed to an IL-4, -5, -13 producing non T/non B-cell population (NTNB) that is ckit^{pos} FcεR1^{neg}. The NTNB ckit^{pos} FcεR1^{neg} cells were described as small agranular cells with limited cytoplasm with no marker expression of mature NK cells, mast cells, basophils or eosinophils. IL-25 has a key role in the initiation of Th2 type responses.[27] Saenz et al. reported a lineage negative multi-potent progenitor cell population they called MPP^{type2}. This subset is Lin^{neg} c-Kit^{int} Sca-1^{pos}, expands upon IL-25 administration in the gastric lymphatic tissue and can give rise to cells of the monocyte/macrophage and granulocyte lineage. MPP^{type2} cells lead to Th2 type responses and favor helminth expulsion.[28] A similar fraction that also responds to IL-25 has been described in the fat associated lymphoid cluster.[29] Epithelial-specific Act1 mediates the expansion of the Lin- c-Kit+ innate cell population through the positive-feedback loop of IL-25, initiating the type 2 immunity against helminth infection.[30]

Neill and Wong et al defined a Lin^{neg} ICOS^{pos}, ST2^{pos}, IL17RB^{pos}, IL7Rα^{pos}, MHCII^{pos} IL-13-producing leukocyte subset that expanded upon IL-25 and/or IL33 administration. They were named nuocytes according to their cytokine predominance. Nuocytes represent the predominant IL-13 producing subset 5 days after *N. brasiliensis* infection and are crucial for worm expulsion. Transfer of nuocytes into IL17RA$^{-/-}$ established features of IL-25-evoked Th2 type responses and established an IL-25 response in the recipient mice.[31]

Human lineage-negative CD127^{+} CD161^{+} and CRTh2+ type 2 innate lymphoid (ILC2) cells are able to respond to IL-25 with T helper type 2 cytokine production and play important role in the pathogenesis of allergic diseases.[20] Huang et al., described a different developmental pathway for ILC2 responsive to IL-25, they called it the inflammatory ILC2 pathway.[18]

A crucial role of IL-25 on Th9 cells has been suggested. IL-17RB is up-regulated on Th9 cells and IL-25 is capable of IL-9 induction in differentiated Th9 cells, but not naïve cells.[32] In addition, IL-25 may interact with the IL-17A pathway. IL25$^{-/-}$ mice did

not only display problems in reducing *T. muris* burden, but increased their IL-17A and IFN-γ levels.[33] Moreover, IL25$^{-/-}$ mice are highly susceptible to experimental autoimmune encephalomyelitis (EAE) most likely via an up-regulation of IL-23.[34] Treatment with IL-25 resulted in increased IL-13 secretion that opposed IL-17A induced EAE.

IL-25 directly inhibits LPS-induced IL-23 expression by macrophages and reduces the inflammatory cytokine response driven by toll-like receptor ligands in human blood monocytes and intestinal CD14+ cells.[16, 21, 23] IL-25 inhibits the production of Th1-associated cytokines, and prevents and cures experimental murine colitis mediated by luminal bacterial-driven Th1 cell responses.[21, 35]

The importance of IL-25 in the negative control of pathogenic cell responses is also seen in studies of murine diabetes and multiple sclerosis (MS).[17, 36] These results indicate that IL-25 may be an important counter-regulator of non-Th2-mediated inflammatory processes in various organs.

IL-25 has high anticancer activity without affecting nonmalignant mammary epithelial cells. Apoptotic activity of IL-25 is mediated by differential expression of its receptor, IL-25R, which was expressed in high amounts in tumors from patients with poor prognoses but was low in nonmalignant breast tissue. In response to IL-25, the IL-25R on the surface of breast cancer cells activated caspase-mediated apoptosis. Thus, the IL-25/IL-25R signaling pathway may serve as a new therapeutic target for advanced breast cancer.[37]

Role in allergic disease and other pathologic conditions

Recent data suggests a crucial role for IL-25 in asthma. IL-25 is expressed in the lungs of sensitized mice upon antigen inhalation. In contrast, administration of a sIL-25R inhibited antigen-induced eosinophil recruitment, CD4+T-cell recruitment, IL-5 and IL-13 production and goblet cell hyperplasia.[38] Administration of anti-IL-25 mAbs reduced IL-5 and IL-13 production, eosinophilic infiltration, goblet hyperplasia and AHR. Interestingly, this antibody successfully prevented AHR during allergen challenge.[9] Blocking of IL-25 before sensitization led to an abrogation of AHR after metacholine challenge.[39] In a transgenic model with exclusive expression of IL-25 in the lung there is increased recruitment of eosinophils and CD4+ T cells upon allergen-specific stimulation as compared to allergen-challenged wild type, while the neutrophil and macrophage cell counts are similar. IL-4, IL-5 and IL-13 are increased in the BALF, whereas INF-γ is undetectable. Mucus secretion, TARC and eotaxin

levels are also enhanced. However, IL-25 expression itself does not induce airway inflammation. Recently, IL17RB expressing $CD4^+$ NKT cells were described to be responsible for airway hyperreactivity in an asthma model in mice.[19, 24]

IL-25 is elevated in asthma and contributes to angiogenesis, at least partly by increasing endothelial cell VEGF/VEGF receptor expression through PI3K/Akt and Erk/MAPK pathways.[40]

IL-25 plays an active role in driving the airway remodeling. IL-25 was shown to act directly on human fibroblasts to induce collagen secretion. Recruitment of endothelial progenitor cells to the lung and subsequent neovascularisation was also IL-25 dependent, demonstrating a direct role for IL-25 during angiogenesis in vivo. IL-25 appears to play a critical role in the induction of AHR regardless of the model used to induce allergic airways disease, and this has been shown to be independent of Th2 cytokine production.[41]

Epithelial overexpression of Smad2 can specifically alter airway hyperreactivity and remodeling in response to an aeroallergen challenge.[42]

Allergen exposure upregulates IL-25 and induces type 2 cytokine production in a previously undescribed granulocytic population, termed type 2 myeloid (T2M) cells. High-dose dexamethasone treatment did not reduce the IL-25–induced T2M pulmonary response. Similar IL-4– and IL-13–producing granulocytic population was identified in peripheral blood of human subjects with asthma. These data establish IL-25 and its receptor IL-17RB as targets for innate and adaptive immune responses in chronic allergic airway disease and identify T2M cells as a new steroid-resistant cell population.[26]

Clinical studies have shown reduced numbers of NK cells in infants suffering from a severe RSV infection. The authors demonstrated that NK cell deficiency during primary RSV infection of BALB/c mice results in the suppression of IFN-γ production and the development of an RSV-specific Th2 response and subsequent allergic lung disease. The outgrowth of the Th2 responses was dependent on airway epithelial cell-derived IL-25, which induced the upregulation of the notch ligand Jagged1 on dendritic cells. This study identifies a novel pathway underlying viral-driven Th2 responses that may have functional relevance to viral-associated asthma.[43]

IL-25 expression is present in nasal polyps of patients with chronic rhinosinusitis. Anti-IL-25 treatment is also suggested to be an effective treatment in this disease,

since it reduced the number of polyps, inflammatory infiltrating cells and tissue remodeling in a murine model.[44]

IL-25-producing cells have been identified within the dermis of AD patients and propose that these cells are dendritic cells (DCs). IL-25 produced by DCs could have dual role as both an inducer of the TH2 response and as an inhibitor of filaggrin synthesis, thereby directly affecting skin barrier function in AD patients.[45]

Functions as demonstrated in IL-25-deficient mice, receptor-deficient mice and transgenic models

IL-25-deficient mice display a rather normal phenotype. Th2 type effector functions are normal with the exception of eosinophils. However, $IL25^{-/-}$ mice fail to expel *Nippostrongylus Brasiliensis* efficiently due to subtle changes in the onset of Th2 type cytokine responses.[27] In wild type animals, the increase of a non T/non B-cell effector cell population (NTNB) that is $ckit^{pos}$ $Fc\varepsilon R1^{neg}$ precedes the increase in Th2 type CD4 cells. Due to the prolonged presence of high Th2 cytokine levels, IgE is higher and the number of mast cells in mice with parasitic infestation is higher in IL-25 $^{-/-}$ deficient mice. IL-25 deficiency does not lead to a delay in goblet cell hyperplasia and has no effect on basophil counts. However, there is a deficit in circulating eosinophils (NBNT, CCR3+, SSC high). The delayed onset of Th2 type response to worms can be restored upon addition of IL-25, but IL-25 itself is not sufficient to expel the worms by its presence in IL-$4^{-/-}$, -$5^{-/-}$, -$9^{-/-}$, -$13^{-/-}$ mice. Response to the parasite is characterized by a delayed onset and permanently high levels of these Th2 type cytokines due to persistent parasitic burden in IL-25-deficient mice.[27]

IL-25-deficient mice infected with *Trichuris muris* develop more severe intestinal inflammation than wild-type mice, accompanied by exaggerated production of IL-17A and IFN-γ.[33] IL-25-deficient mice exhibit accelerated experimental autoimmune encephalomyelitis onset and enhanced disease severity compared with wild-type mice.[34] Eosinophil cell counts and the levels of proinflammatory mediators in bronchoalveolar lavage fluid, airway hyperresponsiveness to methacholine, and the OVA-specific IgG1 and IgE levels in the serum are all significantly suppressed in IL-25–deficient mice during OVA-induced allergic airway inflammation.[46]

IL-25 over-expressing mice displayed splenomegaly, lymphadenopathy and a strong increase of eosinophils and B-cells in peripheral blood.[47] Due to the fact that B-cells decrease in parallel in the bone marrow, it could be assumed that IL-25 contributes to the release of premature B-cells into the periphery. These B-cells do

not proliferate upon IL-25 exposure, but they up-regulate their IL-17E receptor expression. In accordance with the increased B-cell frequencies in the periphery, IgM, IgG and IgE levels are elevated. In addition, the levels of various cytokines are substantially increased (IL-2, IL-4, IL-5, IL-6, IL-10, INF-γ, G-CSF, GM-CSF and eotaxin).[47] Pan et al. reported similar results. However, their transgenic mice showed marked growth retardation and a more pronounced inflammation of organs.[48] Experiments with adenovirus expressing IL-25 or IL-25 alone resulted in Th2-like reactions with elevation of mRNA of IL-4, -5, -13 and production of the chemokines LIX, TARC and eotaxin. In addition, vascular changes (rather distal) in the lung with moderate media hypertrophy, presence of eosinophils in the lumen and infiltrates with eosinophils and monocytes beneath the endothelium within the vessel wall and adjacent to the vessels were described. Bronchi and larger bronchioles epithelium is thickened and contains large amounts of mucus. Epithelial cells sometimes contained eosinophilic inclusions in the cytoplasma.[1]

In conclusion, IL-25 promotes Th2 cytokine-based immunity, causing asthma and allergy, and at the same time is responsible for airway remodeling and also capable of limiting inflammation associated with debilitating human diseases, such as inflammatory bowel diseases, diabetes and multiple sclerosis.[11, 13, 17, 21, 36] This dual role of IL- 25 is strictly linked to its ability to be immune-stimulatory for Th2 type responses and suppressive for the development and/or amplification of Th1/Th17-associated immunity.[11, 13, 16, 21] IL-25 responses are impaired in Traf4-deficient cells, showing implications in allergic airway inflammation. [49]

IL-26

Discovery and structure

IL-26 was discovered in a study investigating the phenotypic changes of T cells after transformation by *Herpes saimiri* virus. IL-26 was identified and initially termed AK155 by using the technique of subtractive hybridization for cloning cDNA transcripts that are specifically present in transformed human T cells and not in untransformed cells. [50] IL-26 shows 24.7% identity to IL-10 and is suggested to have a closely related structure consisting of six α-helices. The observed molecular weight of monomeric IL-26 is 19 kDa. Gel electrophoresis under native conditions revealed that IL-26 spontaneously forms dimers.

The gene encoding IL-26 is located on chromosome 12q15, in close proximity to the genes for IFN-γ and IL-22. Therefore, common regulatory mechanisms can be expected. Interestingly, several groups failed to identify a murine homolog of IL-26 and apparently this gene is missing in mice and rat. Only for exon 5, a section sharing weak homology with human IL-26 could be detected. This sequence is disrupted by several stop codons. Unexpectedly, IL-26 has been found in zebra fish, chicken and frog, suggesting an evolutionary conservation despite the lack of IL-26 in rodents. [51, 52]

Receptor and signalling

The receptor for IL-26 consists of two chains. [53, 54] One chain is the IL-10R2, which also belongs to other receptor complexes of this cytokine family, namely the receptors for IL-10, IL-22, IL-28 and IL-29. The second chain is the IL-20R1, which is also required for binding the cytokines IL-19, IL-20 and IL-24. As IL-26 is suggested to form dimers, it is likely to bind to two IL-10R2 and two IL-20R1 chains, although this has not been proven yet. IL-26 seems to bind first to IL-20R1, thereby inducing dimerisation of the receptor chains. This dimerisation activates the Jak/STAT signalling pathway, resulting in rapid phosphorylation of STAT1 and STAT3.

Cellular sources and targets

IL-26 expression has been found to be restricted to memory T cells after T cell receptor stimulation, and to NK cells. [55] Among the T cells, $CD4^+$ cells produced higher levels of IL-26 than $CD8^+$ cells. Recently, IL-26 has been found to be specifically expressed by the T_h17 subset of T cells [56,57], a subset involved in many inflammatory and autoimmune disorders. The finding that IL-26 is expressed by these cells expands the research of T_h17-dominated diseases and underlines a difference between human and mouse T_h17 cells, as IL-26 is not present in mice. Similar things have been observed in NK cells. A recent study identified a distinct subset of human NK cells that specifically express IL-22, and that have therefore been termed NK-22 by the authors. [58] This subset, located in mucosa-associated lymphoid tissues, such as tonsils and Peyer's patches, also produces IL-26, but in contrast to T_h17 cells no IL-17A and IL-17F. The co-expression of IL-22 and IL-26 is therefore commonly observed and not surprising, considering the close chromosomal location of these genes.

As the IL-10R2 chain is ubiquitously expressed, fitting to its role as common part of several cytokine receptors, it is likely that the IL-20R1 chains account for the cell

specificity of IL-26 signalling. [55] In contrast to IL-10R2, IL-20R1 is not detected in immune cells, but on several epithelial cell lines and many tissues like skin, testis, heart, placenta, salivary gland, and prostate. [59, 60] Activation of STAT1 or STAT3 upon IL-26 stimulation has been observed for example in the colorectal adenocarcinoma cell line HT-29 or the epithelial keratinocyte line HaCaT. [53, 54] Therefore it seems that while immune cells are major producers of IL-26, its targets are non-immune cells like epithelial cells from various tissues.

Role in immune regulation and cellular networks

To date, only few studies addressed the role of IL-26 in immune regulation. One report describes IL-26 to enhance secretion of IL-8 and IL-10 as well as surface expression of CD54 by epithelial cells. [53] Another study investigated the influence of on B cells and found an inhibition of IgG and IgA production. [61] More recently, IL-26 has been shown to induce pro-inflammatory cytokines like TNF-α, IL-6 and IL-8 in intestinal epithelial cell lines and to inhibit proliferation of these cells. [62] However; IL-26 was also shown to have elevated levels in gastric cancer lesions and was found to contribute to the proliferation and survival of human gastric cancer cells via the initiation of STAT1 and STAT3 pathways. [63] Further analyses are required to get a clear picture of IL-26's role in immune regulation and cellular networks.

Role in host defence or other immune regulatory conditions

The lack of IL-26 in mice makes functional investigations more difficult, as the role of IL-26 cannot be studied in KO mice. The finding that IL-26 is expressed by T_h17 cells lead to the hypothesis that IL-26 might be involved in inflammatory diseases, as T_h17 cells play a key role in many of these disorders. One study analyzed the infiltration of various inflamed tissues by T_h17 cells by isolating $CD4^+$ T cells from lesions of patients with various chronic inflammatory diseases. [64] The tissues analyzed include samples from patients with psoriasis vulgaris, rheumatoid arthritis, Crohn's disease, multiple sclerosis as well as bronchial biopsies taken from patients with severe asthma. [65] T cells from all of these tissues were characterized by the expression of T_h17-specific genes, among them IL-26. Supernatants of the cells induced expression of genes associated with inflammation in primary keratinocytes. Whether IL-26 contributed to this effect remains to be determined. Another study investigates the function of IL-26 in Crohn's disease and reports expression of both IL-26 receptor subunits IL-20R1 and IL-10R2 by several intestinal epithelial cell lines. [62] IL-26 decreases proliferation of these cells and increases expression of pro-

inflammatory cytokines. Furthermore, IL-26 serum protein expression was higher in patients with Crohn's disease compared to controls, suggesting a role of IL-26 in this disease, although IL-26 expression might also just indicate a high number of T_h17 cells, without having a direct effect. In patients with rheumatoid arthritis the concentrations of IL-26 were higher in the sera and synovial fluid compared to healthy subjects. Synoviolin$^+$ fibroblast-like synoviocytes and CD68$^+$ macrophage-like synoviocytes were the main IL-26-producing cells in rheumatoid arthritis joints. IL-26 induced the production of IL-1β, IL-6, and TNF-α by human monocytes and IL-26 primed monocytes promote the generation of RORγt$^+$ T_h17 cells. [66] IL-26 levels were also shown to be higher in the peripheral blood of multiple sclerosis patients compared to controls, and were modulated by the treatment of patients with IFN-β; along with other T_h17 cytokines. [67]

IL-26 was found to differentially modulate *in vitro* infection of enveloped viruses. IL-26 enhances the binding, infection and replication capabilities of viruses like vesicular stomatitis virus and inhibits the infection of human cytomegalovirus; while having no effect of the infection capabilities of herpes simplex virus type 1. This effect was also observed in various cell types not expressing IL-10R1; and is thought to be independent of IL-26R complex. [68]

Direct anti-microbial effects of IL-26 were discovered with recent studies. IL-26 was found to be capable of killing extracellular bacteria by pore formation; a function arising from amphipathic and cationic properties of IL-26 protein. The anti-bacterial effect of IL-26 also contributes to the DNA sensing capability of plasmocytoid dendritic cells (pDC) enabling pDCs to mount an immune response by sensing both human DNA from dying cells and bacterial DNA. IL-26 also promotes entry of foreign DNA into intracellular vesicular structures in pDCs by forming IL-26/DNA complexes; contributing to the activation of TLR9 signalling in pDCs. [69]

Human mutations

In human, the genomic region for the genes encoding IL-26, IL-22 and IFN-γ is polymorphic. Two microsatellite polymorphisms have been found at the IL-26 locus. [70] The first is located in the third intron and the second in the 3' region of the gene. Therefore, these polymorphisms do not affect the amino acid sequence of the protein, but they can be used as genetic markers. Further studies revealed an association between the polymorphisms in this region and the protection of some

male individuals from multiple sclerosis. [71, 72] One marker located 3 kb 3' from the IL-26 gene was significantly associated with rheumatoid arthritis in women. Therefore, polymorphisms in the 12q13-15 region may contribute to sex-based differential susceptibility to this disease. Interestingly, the original reason why a correlation with inflammatory disorders has been analyzed was the presence of the IFN-γ gene in this chromosomal region. Only later, it became apparent that T_h17 cells, as a main player in inflammatory diseases, express IL-26, which is also located to this region.

IL-27

Discovery and structure

IL-27 is a member of the IL-12-related cytokine family. This heterodimeric cytokine consists of the p28 protein and Epstein-Barr virus-induced gene 3 (EBI3) subunits. The IL-27 p28 chain (also named IL-27A or IL-30), as a member of the long-chain four-helix bundle cytokines, is homologous to the helical p35 subunit of IL-12. The EBI3 subunit (IL-27B) is related to IL12p40 and structurally resembles the soluble IL-6R. [73] The IL-27 p28 gene is located on chromosome 16 in human and on chromosome 7 in mice and contains 202 residues. The EBI3 gene is on human chromosome 19 and mice chromosome 17 and contains 229 amino acids. IL-27 differs from other cytokines in that its subunits are not linked by a disulfide bond, which theoretically allows the production of the two subunits by distinct cells, followed by extracellular association.

Receptor and signaling

IL-27 mediates its effect through an heterodimeric receptor composed of a WSX-1 subunit (also termed IL-27Ra or TCCR for T cell cytokine receptor), which is an orphan class 1 cytokine receptor that is homologous to the 2 chain of the IL-12 R, and gp130 that is shared by several cytokines (e.g. IL-6, IL-11, CNTF, LIF, CLC, OSM and CT-1. WSX-1 confers ligand specificity and the gp130 signaling subunit that activates the Jak-STAT signal transduction pathway. [74] Consistent with the actions of IL-27 on T cells, WSX-1 is highly expressed on T cells. However, WSX-1 and gp130 are co-expressed on a variety of cells and tissues. Furthermore, the generation of Tr-1 cells is promoted by IL-27. These cells produce IL-10 by inducing expression of the activator protein-1 family transcription factor c-Maf. c-Maf directly trans-activates the *Il10* promotor [75, 76, 77] and is binding to the *Il21* promotor [78],

inducing IL-21 production to maintain IL-10 production. [79] Moreover, IL-27 signaling up-regulates expression of the aryl hydrocarbon receptor (AhR), which together with c-Maf optimizes interaction with the *Il10* and *Il21* promotors, resulting in Tr-1 cell development. [80]

The pattern of STAT activation by IL-27 depends on the cell type and the activation state. In resting lymphocytes IL-27 activates STAT1, STAT3, STAT5, and low amounts of STAT4. [81, 82] Decreased activation of STAT1 was observed in fully activated relative to resting CD4+ T cells. [83] In myeloid cells, IL-27-induced phosphorylation of STAT1 and STAT3 has been observed. [74, 84] Function of IL-27 also depends on the STAT activation. STAT1 plays a key role in early regulation of T_h1 cells differentiation [85] and is also necessary for mediating the suppressive effects of IL-27 on T_h17 [86-88] and Th2 differentiation.[82] Both STAT1 and STAT3 are required for IL-27-induced IL-10 production in T cells, but their activation has not been linked to IL-27 function in the myeloid lineage. [89, 90] STAT3 and p38 signaling is activated by IL-27 which starts phosphorylation cascade of ERK and p38 MAPKs as well as Akt and is able to induce expression of the anti-bacterial gene deleted in malignant brain tumor 1 (DMBT 1). In contrast, the activation of indoleamine 2, 3-dioxygenase, an anti-inflammatory and anti-bacterial gene is dependent on STAT1 signal transduction. [91]

IL-27p28 has been highlighted to be able to act as a gp130 cytokine-signaling antagonist. gp130 signaling is known to be involved in a wide range of immunological functions and to be an important regulator of inflammation in many diseases, including IBD, asthma, cancer, and auto immune diseases. [92] This indicates that IL-27p28 may be a promising drug target for many different diseases. More recent studies suggest that IL-27p28 has a biological function even in the absence of EBI3. There is no initiation of STAT signaling without EBI3 [73], exposure to Il-27p28 antagonizes IL-27-mediated STAT1 signaling and INF-γ production from CD4+ T cells *in vitro*. Expression of IL-27p28 can abrogate anti-tumor effects of IL-27 and suppresses graft rejection mediated by IL-27, suggesting that p28 can antagonize pro-inflammatory effects of IL-27 *in vivo*. [93] Additionally, a mutation in p28 subunit generates an IL-27 heterodimer antagonizing wt IL-27 signaling, indicating that this amino acid residues are crucial in interaction with the receptor to inhibit a normal IL-27 signaling. [94] Furthermore, it has been shown that IL-27p28 is able to act as a low-affinity antagonist for IL-6, IL-11 and IL-27 signaling, by interacting with gp130. The

blocking of the biological effect of IL-6 by IL-27p28 is independently from EBI3, too. Physiological relevance was demonstrated by overexpression of IL-27p28, which resulted in antagonizing gp130 dependent B-cells responses. [95]

Recently; a study aimed to identify mechanisms by which IL-27 might exert its immunosuppressive effect. They showed that IL-27 priming of naïve T cells upregulated expression of programmed death ligand 1 (PD-L1) and its activator in a STAT1 dependent manner. Co-culturing of IL-27 primed T cells with naïve T cells inhibited T_h17 differentiation through PD-1-PD-L1 interaction. [96]

Cellular sources and targets

IL-27 is expressed predominantly by APCs, including DCs and macrophages, and by endothelial cells. The production of both subunits can be induced by TLR-ligands such as LPS, polyriboinosinic:polyribocytidylic acid (Poly I:C) and by intact *Escherichia coli*. [73] In bacterial infections TLR4 is upregulated in a STAT3- and NF-kB-dependent manner by IL-27 [97] and LPS induced NO-production is enhanced by IL-27 via activation of STAT1, NF-κB and MAPKs. [98] Additionally, signaling via CD40L and IL-1β can up-regulate the EBI3 subunit, whereas p28 has been shown to be up-regulated by IFN-γ. [99] Furthermore a mechanism has been identified by which IFN- γ limits Th9-mediated auto-immune inflammation through DC modulation of IL-27. [100]

The source and regulation of IL-27 promoting IL-10 production *in vivo* remains unclear, but there are evidences that DCs [101, 102, 103] and migroglia [104] are involved. But finally it is still not clear whether the same mechanism is working in other cell types such as macrophages [105] and CD8+ T cells. [106]

A recent study has shown that IL-27 modulates the function of conventional DCs (cDC) by lowering the expression of MHC class II, co-stimulatory molecules CD40, CD80 and CD86. IL-27 in parallel decreases the expression of cytokines IL-12, IL-6 and IL-23, which play pivotal role in T_h1 and T_h17 differentiation. Another inhibitory effect of IL-27 on cDCs is mediated through the upregulation CD39. CD39 is an ectonucleodase that catalyzes the turnover of extracellular ATP to ADP, and its increased expression limits the ATP-dependent activation of the NLRP3 inflammasome activation in cDCs. Previous studies have determined the activation of the NLRP3 inflammasome in APCs have a direct control on T_h1, T_h2 and T_h17 differentiation. This potent effect of IL-27 returning DCs into an inactive state has the

potential to lead to new therapeutic approaches for various autoimmune disorders. [107]

In contrast; IL-27 was recently described to have an opposite effect on DCs when they are differentiated in the presence of IL-27. DCs differentiated in the presence of IL-27 may show increased bacterial clearance ability characterized by acidification of phagosomes and Cathepsin D accumulation. DCs were also shown to have increased levels of MHC II expression, as well as higher expression of surface molecules like DC-SIGN and CD40. IL-12 was also described as having higher expression in DCs differentiated with IL-27. [108] This dual role of IL-27, depending on the maturation phase of the cells it reaches gives a good view of how IL-27 can be an immune activator and immune suppressor in different disease phenotypes.

Role in immune regulation and cellular networks

IL-27 was first described as a T_h1 polarizing cytokine because of its action, alone or in synergy with IL-12, to promote IFN-γ production in a STAT1-Tbet dependent manner. Mice genetically deficient in WSX-1 were shown to be impaired in IFN-γ production and T_h1 differentiation, with higher susceptibility to infection with intracellular pathogens such as *Leishmania major* or *Trichuris muris*. [109, 110] This leads to the conclusion that IL-27 was essential for the development of T_h1 immunity. In addition it has been found in study of human visceral leishmaniasis that IL-27 is associated with response in which T cells produce effector cytokines and IL-10. [111] A recent study identified a link between severe asthma phenotype and higher levels of IL-27 in asthma patients with a Th2 cytokine profile. IL-27 induced the production of airway CXCL9 from human bronchial epithelial cells (HBECs), and was augmented by IL-13. This augmentation of IL-27-derived CXCL9 by IL-13 was found to be due to an increase in STAT1 activation and decreased STAT 3 signaling in HBECs. [112]

However, other reports indicated that IL-27 could also act as an inhibitor of the Th2 immunity. A strong and accelerated Th2 response was developed in WSX-$1^{-/-}$ mice challenged with *Trichuris muris*. [113] In asthma and glomerulonephritis models, the absence of IL-27 signaling led to an exacerbated T_h2 response. [114, 115] Inhibitory role of IL-27 on the Th2 response may in part be due to its capacity to inhibit expression of the Th2 lineage-specific transcription factor GATA3.[82] Recently; experiments with WSX-1 deficient mice showed that these animals have impaired IL-21 levels, decreased numbers of T_{fh} cells (a T helper subset crucial in assisting B

cells for class switching and high affinity antibody production), and due to this reduced production of high-affinity antibodies indicating that IL-27 servers as a survival factor for these T_{fh} cells. [116]

Stimulation of human monocytes with histamine resulted in significant down-regulation of TLR ligand induced IL-27 production. On RNA level subunits, p28 and EBI3 were influenced. The down-regulation occurs by histamine receptors 2 and 4 (H2R, H4R). DCs isolated from H4R deficient mice produce more IL-27 after TLR stimulation. The down-regulation of IL-27 by histamine might be a new mechanism in the pathogenesis of inflammatory skin diseases such as chronic eczema and psoriasis where increased histamine concentrations are present on site of inflammation. [117]

Studies to determine the natural antagonists of T_h17 cell activity, lead to the discovery that IL-27 can directly antagonize the development of T_h17-cell responses and limit IL-17-cell-driven inflammation in the central nervous system. [87, 88] The lack of IL-27-signaling resulted in an increase in the number of IL-17 producing CD4+ T cells in the CNS and was associated with exacerbated clinical disease. IL-27 also limits T_h17-cell-mediated uveitis and scleritis and was suggested to contribute to immune privilege. [86] IL-27 inhibition of the development of T_h17 cells was also shown in vitro. [83, 118]

A new study focused on the role of IL-27 in HIV infection and investigated gene expression of IL-27 induced genes during HIV infection. During HIV infection IL-27 induced gene expression is impaired, providing evidence for new viral pathogenic mechanisms contributing to the widespread impairment of immune response observed in HIV pathogenesis. [119] IL-27 was recently shown to modulate monocyte to macrophage differentiation via down-regulating spectrin β nonerythrocyte 1 (SPTBN1) via TAK-1/MAPK signaling pathway. SPTBN1 is a required host factor for HIV-1 infection; and IL-27 modulated macrophages are modulated to be HIV resistant. [120] IL-27 was also shown as a cytokine that promotes the accumulation of antiviral CD4+ T cells during chronic lymphomeningitis virus infection (LCMV) and rapidly induces IL-21 for viral clearance. IL-27R signaling was also found to be critical for the control of LCMV *in vivo*. [121] In addition another study identified IL-27 by a genome-wide expression analysis as a novel candidate diagnostic biomarker for predicting bacterial infection in critically ill children. [122]

Functions as demonstrated in IL-27-deleted mice and receptor-deficient mice.

IL-27 is a pleiotropic cytokine with a wide range of activity on the T cell responses that are not limited to a precise T_h cell subset. It is known that IL-27 has the capacity to regulate T cell proliferation and this might explain why IL-27 can act on diverse subsets of T cells. CD4+ T cells from IL-27R-/- mice show enhanced proliferation following activation *in vitro*. [109, 123, 124] This inhibition of T cell proliferation might be due to inhibition of IL-2 production as increased expansion of CD4+ T cells has been observed during acute infection with *T. gondii*, and was associated with high production of IL-2. [124, 125] IL-27 has been shown to directly regulate the production of IL-2 by CD4+ T cells *in vitro*.[124, 126]

In addition to controlling the production of the cytokine IL-2, recent studies underlined a role of IL-27 in promoting IL-10 synthesis. [89, 90] *In vitro*, supernatant of IL-27 activated CD4+Tcells contained higher levels of IL-10 than the unstimulated cells, and *in vivo T gondii* infected IL-27R-/- mice displayed a reduced capacity to produce IL-10. Furthermore, it seems that IL-27-mediated inhibition of EAE depends on IL-10 production.

In line with the regulatory function of IL-27, the IL-27R is highly expressed on regulatory T cells (T_{reg}), which are known to play a prominent role in limiting inflammation. [127] However, the role of IL-27 is not clearly defined and seems to be species specific. IL-27R $^{-/-}$ mice display normal number of regulatory T cells and the expression of the specific transcription factor for regulatory T cells, FOXP3, is inhibited by IL-27 in *in vitro* stimulated mice CD4+T cells. [118, 127] In contrast, TGF-β-induced FOXP3 expression is enhanced by IL-27 in *in vitro* differentiated human T_{reg} cells. During a colitis model transfer of IL-27RA$^{-/-}$ cells leads to reduced symptoms and upregulation of FoxP3+ cells, indicating the important pathogenic, pro-inflammatory role of IL-27 in this model. It was also shown in another study that IL-27RA$^{-/-}$ TCRβ$^{-/-}$ mice have impaired T_h17 differentiation by APCs that are producing low levels of IL-6 and IL-1β in a colitis model. [128] An oral tolerance model has been used to show that higher T_{reg} frequencies in transferred IL-27RA$^{-/-}$ cells are due to increased T_{reg} conversions, indicating IL-27 is a potent agonist of differentiation of iT_{regs}. [129] This could be a result of the suppressive effect of IL-27 on IL-2, which might hamper the growth of T_{regs}. [130] Another study with IL-27RA$^{-/-}$ mice showed in a model of staphylococcal enterotoxin and lipopolysaccharide injection, that IL-27RA$^{-/-}$ FoxP3^{+}

T_{regs} produce more IL-17 and less IL-10 than wt T_{regs} do, suggesting IL-27 is affecting T_{reg} cytokine production. [131]

Another key regulatory function of IL-27 might be to regulate early inflammatory events during acute infections, as IL-27 neutralization protects mice against lethal septic peritonitis by enhancing the influx and oxidative-burst capacity of neutrophils. [132] Due to its similarity to other members of the IL-6/IL-12 family, IL-27 was also though to a role in inflammatory bowel disease (IBD). In fact, overproduction of IL-27 was observed in patients with Crohn's disease or ulcerative colitis and IL-27R was required for the induction of experimental DSS-induced colitis. [133-135] In a recent study was shown that IL-27 is an mediator of intestinal epithelial barrier protection mediated by transcriptional activation of anti-inflammatory and anti-bacterial target genes in a mouse model of DSS-induced colitis. [91] Due to the knowledge that *Bifidobacterium breve* induces development of IL-10 producing Tr1 cells mediated by CD103+ DCs, Jeon et al. treated CD103+ DCs with *B.breve* and co-cultured them with IL-27ra-/- T cells and observed failure to induce IL-10 production. Performing a colitis mouse model they proof that *B.breve* activates intestinal CD103+ DCs to produce IL-10 and IL-27 via the TLR2/MyD88 pathway. [136] However, another study showed that EBI3 was dispensable for TNBS-induced colitis. [137] In contrast to the IL-10-/- mice that are highly susceptible, the double IL-10/IL-27-/- mice were resistant to spontaneous and helminth-induced colitis. [138] IL-27 promoting effect on the onset of IBD was due to its function on both T_h1 and T_h2 responses.

DC-derived IL-27 was recently found to contribute to the recruitment and activation of NK and NKT cells; indicating that IL-27 is important in the control of immune response against tumors. IL-27p28 conditional knockout mice were showing high susceptibility to methyl-cholanthrene-induced fibrosarcoma and reconstitution of IL-27 restored the number of NK and NKT cells in tumor sites. [139] IL-27 also stimulates IFN-γ from NK cells, as well as increased expression of T-bet and surface markers such as CD25 and CD69. NK cells stimulated by IL-27 also display higher cytotoxic activity, characterized by higher expression of perforin and increased levels of granule exocytosis. [140]

IL-27 was additionally found to have a direct effect of prostate cancer tumors. IL-27 was described to have a downregulating effect on pro-angiogenesis related genes such as FLT1, PTGS1/COX1 and FGFR3; effectively inhibiting proliferation of human prostate cancer cells and reduces their angiogenic potential. [141]

Both IL-27$^{-/-}$ (EBI3$^{-/-}$) and IL-27R$^{-/-}$ mice have been generated to investigate the function of IL-27 in vivo. However, the phenotypes of both mice lines are not exactly similar. The discovery of the new IL-35, which shares the EBI3 subunit with IL-27, may explain this discrepancy. [142]

Four SNPs were identified in the IL-27p28 sequence; -964A/G, 2905T/G, 4603G/A and 4730T/C. [143, 144] Polymorphism at position -964A/G is most likely to be associated to asthma. [143] Both -964A/G and 2905T/G gene polymorphism may have a protective action against chronic obstructive pulmonary disease. [144] The AG genotype of -964A/G had a 2.2-fold decrease risk, and the TG genotype of the IL-27p28 2905T/G had a2.85-fold decrease risk of chronic obstructive pulmonary disease. However, further studies are needed to characterize the molecular mechanism involved in susceptibility to these diseases.

A recent study demonstrated that IL-27 promotes expression of T-bet and CXCR3 in T_{reg} cells. During an infection with *Toxoplasma gondii* transfer of T_{regs} ameliorated infection-induced pathology in Il-27$^{-/-}$ mice, dependent on their ability to produce IL-10. Furthermore they conclude that IFN-γ and IL-27 have key roles in development of T_{reg} cells and IL-27 is specialized to control T_h1 mediated immunity at local sites of inflammation. [145]

During experimental models of arthritis IL-27 has been shown to reduce inflammation [146] and suppresses osteoclastogenesis, mediated by the induction of IFN gamma. [147]

IL-28 A and B, IL-29 (Type III Interferons)

Discovery and structure

The most recent discovery of the subfamily within the IL-10 family of cytokines (type II cytokine superfamily) is a result of a genomic screening process and comprises 3 distinct, but closely related cytokines designated as IL-28A, IL-28B and IL-29, based on their homology in gene and protein structure, and receptor usage.[148, 149] These cytokines display profile of biological activity resembling type I interferons (IFNs)-like antiviral and antitumor activity *in vitro* and *vivo.* Therefore, they have been alternatively designated as type III IFNs or IFN-lambdas (IFN-λs), and refer to IFN-λ1 (*IFNL1*, IL-29), IFN-λ2 (*IFNL2*, IL-28A) and IFN-λ3 (*IFNL3*, IL-28B), respectively.

Human *IFNL2*, *IFNL3* and *IFNL1* map to the chromosomal location 19q13.[149] Genes *IFNL2* and *IFNL3* share high homology (96% aa identity) and both contain six exons, whereas *IFNL1* contains five exons.[149] This gene structure is common for IL-10 family of cytokines and distinct from genes encoding type I IFNs, which contain only one exon. In 2013 a new gene upstream of *IFNL3* was discovered and it was designated *IFNL4*. This gene encodes IFN-λ4 and is similar to IFN-λ3.[150]

Receptor and signaling

All IFN-λs mediate their effects by high-affinity binding to the heterodimeric IL-28R1/IL-10R2 receptor complex, distinct from those used by type I and type II IFNs. The receptor complex is composed of IL-28R1 chain, alternatively named IFN-λR1 (IL-28R1, IL-28RA, CRF2/12 or LICR2) coded by *IFNLR1* and unique for IFN-λ ligands, and IL-10R2 chain (*IL-10RB,* CRF2-4), constitutive part of receptors for IL-10 and IL-22, as well.[148, 149, 151, 152] The IL-28R1 consists of 200-aa extracellular domain, transmembrane domain and 223–aa intracellular domain. Three alternatively spliced forms of IL-28R1 have been identified, one translated into full length receptor, and other two resulting in putative secreted form of the extracellular domain, or a form that is incapable of signaling.[149]

Signaling through IL-28R1/IL-10R2 complex requires Jak/Stat signaling pathway. Binding of IFN-λ to the receptor elicits activation of JAK1, subsequent phosphorylation of STAT1 and STAT2 (on Tyr residues 343 and 517) on the IL-28R1 chain (like type I IFNs receptor), recruitment of transcription factor complex IFN-stimulated gene factor 3 (ISGF3) and induction of OAS and Mx expression.[148, 151, 153, 154] On the other hand, their use of the IL10-R1 chain and their ability to phosphorylate STAT3, STAT4 and STAT5 suggest that they may also exhibit immunoregulatory activity.[155] It is proven that IFN-λ activates the p90 ribosomal protein S6 kinase 1 (RSK1) and its downstream effector, initiation factor eIF4B. Factor eIF4B is essential for up-regulation of p21 (WAF1/CIP1) expression, suggesting a mechanism for generation of growth-inhibitory responses.[156] Although type I IFNs and IFN-λs signal through distinct receptors, they induce expression of the similar repertoire of interferon-stimulated genes (ISGs).[157]

Cellular sources and targets

IFN-λs are produced by the variety of nucleated cell types, particularly dendritic cells, in response to viral infection or/and activation with the bacterial components,

and, unlike IFN-α/-β, by direct stimulation with IFN-α or IFN-ª.[158] Stimulation of PBMC with TLR3-L or encephalomyocarditis virus (EMCV) results in massive production of IFN-λs (and type I IFNs). [158, 159] A rare subset of human BDCA3+ myeloid dendritic cells, also called mDC2 cells, are a potent producers of IFN-λ in response to hepatitis C virus via TLR-3 – dependent pathway. These cells showed tendency to accumulate in the liver, recognize HCV in CD81-, endosome- and TRIF-dependent manner and produce substantial amounts of IL-28B/IFN-λ3.[160] Similarly, mouse CD8α+ conventional dendritic cells were shown to be the major producers of IFN-λ in response to TLR3-L *in vitro* and upon infection with HSV-1 and parapoxvirus *in vivo*.[161] In addition to type III IFNs, viral infection elicits strong inflammatory chemokine and cytokine response, which usually correlates with viral load during infection. When infected with influenza A pneumonia virus, alveolar type II epithelial cells secrete IFN-β, IL-29/IFN-λ1 (the major IFN protein secreted), IL-28A/IFN-λ2, as well as IL-8, IL-6, MCP-1, RANTES and MIP-1β, but not TNF-α (which is the hallmark inflammatory cytokine produced by alveolar macrophages). Administration of IL-29 and IFN-β before infection significantly reduced the release of infectious viral particles and CXC and CC chemokines and was accompanied with an increase in antiviral genes *MX1, OAS,* and *ISG56,* but not IFN-β, and negatively correlated with the viral load. These data suggest that IL-29 can exert IFN-β-independent antiviral protection.[162] These results also strongly implicate regulation of types I and III IFN genes by a common mechanism. *IFN-ª*1 gene is regulated by virus-activated IRF3 and IRF7 (resembling that of the *IFN-* gene), whereas *IFN-ª*2/3 gene expression is mainly controlled by IRF7 (resembling those of *IFN-~* genes).[163, 164]

Cis-regulatory element in *IFN-ª*1 gene was described to include a cluster of interferon regulatory factor-binding sites and additional NF-κB-binding site, all shown to be essential for gene activation by viruses in functional assays.[159] Furthermore, c-REL/p65 NF-κB heterodimer and IRF-1 were defined as key transcriptional activators, and ZEB1 (selective for type III IFNs), B lymphocyte-induced maturation protein 1 and the p50 NF-κB homodimer as key repressors of the *IFN-ª1* gene. Therefore, a model for *IFN-ª1* regulation has been proposed, in which IRF and NF-κB activate gene expression independently via spatially separated promoter

elements suggesting implication of independent evolution of the promoters for *IFN-ª1* and *IFN-* and transposable elements in the regulation of the *IFN-ª1* by NF-κB.[164, 165]

Unlike receptors for type I IFNs being broadly expressed, expression of IFN-λ receptor is largely restricted to hepatocytes, the cells of epithelial origin and some types of immune cells, suggesting important role of IFN-λs eliciting early innate antiviral immune response at epithelial-environmental interface. Immune cells express high levels of a short IFN-λR splice variant (sIFN-λR1/sIL-28R1), which codes for a secreted, glycosylated protein. This form of receptor binds IFN-λ1 with a moderate affinity and is able to inhibit IFN-λ1 effects.[166]

Despite the fact that IFN-αs and IFN-λs induce expression of the similar repertoire of interferon-stimulated genes (ISGs), *in vivo* IFN subtypes show clear differences with respect to their kinetics of action and to their spatial activation pattern: while the type I IFN response is strong in liver, spleen, and kidney, type III IFN reactivity is most prominent in organs with mucosal surfaces.[167] Restricted patterns of type III IFN receptor expression in contrast to ubiquitously expressed IFN-α/β receptors suggest that type III IFNs may have limited cytotoxicity to normal cells.[168]

Role in immune regulation and cellular networks

Based on their similarity with type I IFNs, it was expected that IL-28 and IL-29 may play a role in the defense against viral infection. Accordingly, IL-28 and IL-29 gene expression was very low in untreated PBMCs, whereas a marked increase in their expression could be induced after infection with a wide variety of viruses, as well as with poly-IC, both *in vitro* and *in vivo.*[148] IL-28- and IL-29-mediated antiviral activity has been confirmed against a broad range of viral infections.[148, 149, 158, 162] IL-28A is able to restrict neutrophils recruitment, limiting IL-1β expression and thus reducing inflammation.[169] IL-28A and IL-29 are found predominantly up-regulated in HCV patients and similarly effective in inducing antiviral genes and inhibiting hepatitis B and C viral replication.[170, 171] This suggests potential of their therapeutic use for the treatment of HBV and HCV infections.

Lambda interferons render epithelial cells of the respiratory tract and**,** unlike type I IFNs, of gastrointestinal tract resistant to viral infections.[162, 172] Hepatitis B virus (HBV) induces an inflammatory network involving high expression of three inflammatory factors, that regulate each other in the order IL-29/IL-8/COX-2, through positive regulation and negative feedback. In HBV-transfected human lymphocytes

and hepatocytes, IL-29 activates the production of IL-8, which in the same time enhances the expression of COX-2 and attenuates the expression of IL-10R2. COX-2, in turn, decreases the production of IL-8, which leads to attenuated expression of IL-29. Furthermore, it appears that HBV infection–dependent elevation of IL-29 inhibits HBV replication and that highly expressed IL-8 attenuates anti-HBV activity of IL-29, which favors the establishment of persistent viral infection.[173] A novel antiviral effect of IL-29 has been described to involve the suppression of IRES-mediated translation. [174] Production of IFN-α and IFN-λ was found to be linked: IFN-λ increased production of IFN-α by pDCs, and IFN-α significantly increased production of IFN-λ.[175]

IL-28 and IL-29 can be produced by virus-infected cells, maturing dendritic cells (DCs), and regulatory T-cells in the skin, and they mainly influence keratinocytes and melanocytes. In keratinocytes, IL-28 and IL-29 induce growth inhibition, upregulate expression of viral and microbial sensing cellular receptors (TLR-3) and melanoma differentiation associated gene 5, and strengthen the cellular response to these receptors' ligands.[176]

The importance of type III IFNs activity in antiviral defense is additionally suggested by the evolutionary conserved mechanisms employed by viruses in order to escape antiviral immunity and assure persistence of infection. Both nonstructural proteins NS1 and NS2 of mice pneumonia virus are found to be inhibitors of the interferon type I and type III responses *in vivo* mediated through their antagonism of (IFN-α/β) and IFN-λ.[177] Similar strategy is used by HCV whose NS3/4A protease activity mediates inhibition of HCV genomic RNA-induced IL-28 expression through interference with minimal IL-28 promoter region consisting of putative NF-κB and IRF3-binding sites.[178]

In addition to IL-19, IL-20 and IL-24, monocytes, but not macrophages, are well-known source of IL-29. During their maturation to macrophages production of all of these cytokines are either strongly reduced or completely abolished. During monocyte differentiation to DC upon bacterial stimuli IL-20 and IL-28A are produced in addition to IL-29. The co-expression of IL-20, IL-28 and IL-29 in maturing DCs supports their role in the amplification of the innate immune response in tissue resident cells like keratinocytes. The effect is mediated through IL-20-dependent

expression of antimicrobial proteins and IL-28/IL-29-dependent upregulation of TLRs (mainly TLR-2 and TLR-3).[179, 180]

Furthermore, type III (like type I) interferons enhance IL-10R expression on human monocytes and macrophages, resulting in IL-10-mediated suppression of TLR-induced IL-12 in APCs.[181] Interestingly, IL-29 up-regulated whereas IFN-α down-regulated the surface expression of the IFN-γR1 chain on macrophages, which results in differential responsiveness of TLR-triggered macrophages to IFN-γ. This may implicate a complex network among different IFNs in regulating immunity to pathogens.[182] IFN-λ4 is associated with hepatitis C virus clearance.[150]

IFN-λ members have shown multi-faceted immunomodulatory and immunoregulatory capacity that may provide tremendous opportunities for the treatment of broad range of allergic diseases and autoimmune disorders. They include: immunomodulation of Th2 response in an IL-29-dependent manner by preferential inhibition of Th2-derived IL-13 secretion indirectly through the action of conditioned mDC,[155] by inhibition of IL-4, IL-4Rα, IL-13 and GATA3 expression directly on Th2 differentiated CD4+ cells,[183] by IL-4–induced feedback inhibition of Th2 response indirectly via monocyte derived IL1ra inducing IFN-λ secretion from pDCs, [184] and by induction of IL-4 and IL-13 release, but not histamine, from mast cells.[185]

Immunomodulation in an IL-28-dependent manner is induced by conditioning of lung CD11c+ dendritic cell (DC) function to promote Th1 differentiation;[186] delayed-type hypersensitivity (DTH) in a murine model for autoimmune uveitis in human.[187]

IFN-λR-mediated immunoregulatory actions can be summarized as: apoptosis of T cells, generation of tolerogenic DC phenotype and induction of regulatory CD4+ cells *in vitro* and *in vivo*,[188] and differentiation of MDDC into low T cell stimulatory capacity, and further promotion of expansion of existing regulatory T cells.[189, 190]

Role in allergic disease and other pathologic conditions

Along with extensive role in antiviral immunity, IFN-λ members have been associated with allergy, asthma and autoimmune diseases.

IL-29 appears to play a role modulating Th1/Th2 response. Naive T cells co-cultured with allogenic IL-29-conditioned mDCs showed strong decrease in IL-13 secretion with no change in IFN-γ production.[155] Furthermore, both naive and memory human $CD4^+$ T cells were found to express IL-28Rα mRNA and to be

responsive to IFN-λ1. Expression of Th2 cytokines (IL-4 and IL-13) was suppressed in naive and memory CD4+ T cells upon IFN-λ1 stimulation, without affecting their proliferation. This effect was accompanied by inhibition of both IL-4Rα and GATA3 expression as well as decreased expression of surface markers delineating differentiation of "central memory" T cells into "effector memory" T cells.[183] Taken together, IL-29 was shown to have capacity to lower expression of Th2-mediated cytokines from memory CD4+ cells acting directly (leading to a decrease in intensity of Th2 phenotype), or indirectly via conditioned mDCs (causing preferential IL-13 inhibition). This feature gives IL-29 a potential to be beneficial for the treatment of Th2-skewed disorders. In addition to mDC2 as a source of IFN-λ *in vitro* and *in vivo*, it has been reported that pDCs are major IFN-λ producers among peripheral mononuclear cells.[191] Furthermore, while IL-4 enhances IFN-λ1 (IL-29) production by pDCs via monocyte secretion of IL-1Ra, IFN-λ1 exerts a powerful inhibitory effect over the T-helper 2 (Th2) response by antagonizing the effect of IL-4 on $CD4^+$ T cells and inhibiting the production of Th2-associated cytokines.[184] In the same time, IL-29 caused release of IL-6 and TNF-α from $CD4^+$ cells.[192] This represents a novel mechanism for regulation of both IFN-λ1 production and pDC function, and suggests an expanded immunomodulatory role for Th2-associated cytokines.

There has been an evidence of impaired innate anti-viral response (insufficient production of IFN-β and IFN-λ) in asthmatic bronchial epithelial cells (EC) upon stimulation with rhinovirus (RV) and polyIC *ex vivo when* compared to EC of non-allergic healthy control children.[164, 193] Deficient interferon responses to rhinovirus infection are present in childhood in asthmatic subjects irrespective of their atopic status and in atopic patients without asthma. These findings suggest that deficient immune responses to viral infections are not limited to patients with atopic asthma but are present in those with other T(H)2-oriented conditions.[194] A carriage of the T allele of the tagging single nucleotide polymorphism rs12979860 3 kb upstream of IL28B, encoding flanking IL-28B (IFN-λ3), has been associated with allergic disease.[195, 196]

Virus – primed CD3+ cells upregulate IFN-λ receptor. Interaction of IFN-λ with its receptor leads to T cell apoptosis, subsequent phagocytosis by DC and their tolerogenic phenotype capable to generate regulatory T cells *in vitro* and *in vivo*. Passive transfer of IFN-λ-primed CD3+ cells inhibited Th2 cell-mediated intestinal

inflammation in mice indicating that IFN-λ has a role in the development and maintenance of oral tolerance.[188] This gives IFN-λ a potential to be beneficial suppressing antigen-specific Th2 cell-mediates inflammation in patients, as well. Furthermore, recombinant IFN-λ alone promotes differentiation of monocyte-derived dendritic cells (MDDCs) into a phenotype with low T cell stimulatory capacity and high PD-L1 expression, which further promotes expansion of existing regulatory T cells.[189, 190]

Up to 60% of human tonsil, colon and lung mast cells express IL-29. Stimulation with LPS and poly (I:C), as well as allergens, can induce the release of IL-29, while extrinsic IL-29 induces mast cells to release IL-4 and IL-13, but not histamine. These findings indicate an additional role for IL-29 in the pathogenesis of allergic inflammation.[185] IL-29 and IL-28Ralpha mRNA expression in PBMC, as well as circulating IL-29, were significantly increased in patients with rheumatoid arthritis (RA) compared with healthy controls. Increased IL-29 levels were detected in RA synovial fluid (SF) when compared with osteoarthritis SF and mostly expressed by macrophages and fibroblasts in the lining region of RA synovium. RA synovial fibroblasts exposed to IL-29 specifically upregulated IL-6, IL-8 and MMP-3 but down regulated IL-10 suggesting RA pathology-related IL-29 disregulation.[197, 198]

Administration of a vaccine containing a portion of the encephalitogenic proteolipid protein ($PLP_{139-151}$) coupled to OVA-peptide and reovirus pσ1 conferred protection against $PLP_{139-151}$-induced experimental autoimmune encephalomyelitis (EAE) via induction of IL-10 producing FoxP3+ Treg cells and IL-4-secreting FOXP3+ Th2 cells. However, after depletion of Treg cells the pσ1-based protection against EAE was associated with an increased expression of FOXP3 on CD25-CD4+ T cells producing IL-28. IL-28 could have a protective role in EAE and may therefore be a alternative therapy candidate for multiple sclerosis.[199] This was supported by the finding that expression of IL-28 was dysregulated in patients with SLE suggesting its contribution to some of the SLE pathogenesis.[200]

Lung cancer cell lines were reported to express both IFN-λ receptor chains. Upon IFN-λ2 treatment with lung cancer cells with epidermal growth factor receptor (EGFR) mutations underwent growth suppression and apoptotic cell death by STAT1 phosphorylation and were more sensitive to treatment compared with cells with KRAS mutations. The effect was dependent on caspase-3/7 and was confirmed as

anti-tumor effect in a cancer cell transplant animal model.[201]Therefore, IFN-λ2 would be a new therapeutic agent for lung cancers with EGFR mutations in humans.[201]

Preclinical studies by several groups indicate that IFN-λ may exert strong antitumor therapeutic potential.[202] Improving the potency of immune responses is a key feature among issues concerning vaccines against deadly pathogens and tumors. IL-28B with its strong adjuvant-like property may be a good candidate for the development of the vaccine capable of robustly enhancing adaptive immunity.[203]

IL-28B/IFN-λ3 displays particularly interesting activity not shared by two other IFN-λs. IL-28B, like IL-12, is capable of robustly enhancing adaptive immunity. IL-28B reduces regulatory T-cell populations during DNA vaccination, whereas IL-12 increases this cellular subset. In addition, IL-28B is able to increase the percentage of splenic CD8+ T cells and their granularity (through granzyme B loading) in vaccinated animals, which leads to higher antigen-specific cytolytic degranulation compared with cells taken from animals that received IL-12 as an adjuvant. IL-28B treatment was shown to induce 100% protection from mortality after a lethal influenza challenge. These data suggest that IL-28B is an excellent candidate for the development of the new class of vaccines against fatality-causing pathogens as well as enhancing the immunity to tumors.[203, 204]

Restricted patterns of type III IFN receptor expression in contrast to ubiquitously expressed IFN-α/β receptors suggest that type III IFNs have limited cytotoxicity IFN-λ and therefore the IFN-λ therapy could be less toxic and suitable for certain types of malignancies as not all cells are responsive to this cytokine. [168, 202]

The importance of functional IL-28B/IFN-λ3 in antiviral response against HCV infection is even more enhanced by identification of a genetic polymorphism near the IL28B gene which turned to be associated with an approximately twofold change in response to the treatment with pegylated-IFN-α in combination with ribavirin.[205]

Three landmark genome-wide association studies identified single nucleotide polymorphisms near the interleukin 28B (IL28B) region, which were more frequent in responders to the treatment. Favorable variants of the two most widely studied IL28B polymorphisms, rs12979860 and rs8099917, are strong pretreatment predictors of early viral clearance and sustained viral response in patients with genotype 1 HCV infection. This suggests that IL28B may be a key factor involved in host immunity against HCV.[206] IFN-α preparations are now a critical component in the treatment of

chronic Hepatitis C infection and IFN-β therapy is now the first line treatment for relapsing remitting multiple sclerosis.[207]

Clinical studies assessing safety and efficacy in the treatment of HCV with exogenous IFN-λ3 are currently underway. Early results suggest that IFN-λ3 treatment inhibits HCV replication and is associated with a limited side effect profile.[208] Several large genome-wide association studies have identified single nucleotide polymorphisms (SNPs) linked to *IFN-ª3* associated with the spontaneous resolution and successful treatment of HCV infection. Therefore, there is hope that IFN-λ3 genetic variants may serve as important predictive biomarkers of treatment outcome.[209]

IFN-λ can prevent and cure persistent enteric viral infection.[210] A study showed that after murine norovirus infection, IFN-λ was found to act on non-hematopoietic cells and the antiviral effect was independent from the adaptive immune responses.[211] Similarly, in tick-borne encephalitis (TBE), IFN-λ3 plays a protective role. Most patients with TBE are carriers of an interferon genetic polymorphism.[212] Furthermore, a single-nucleotide polymorphism of IFN-λ4 is indicative of both viral and non-viral liver fibrosis.[213]

In addition, the IL-28R1 and IL-10R2 are expressed on a wide range of melanoma cell lines as well as primary melanoma tumors. Their incubation with IL-29 resulted in subsequent induction of IFN-regulated transcripts. IL-29 was shown to synergistically enhance bortezomid- and temozolomide-induced apoptosis.[154] Although constitutive expression of mouse IFN-λ2 in melanoma cells did not affect their proliferation *in vitro*, the growth of B16.IFN-λ2 cells, when injected s.c. into mice, was either retarded or completely prevented, showing antitumor activities of IFN-λs *in vivo.*[214]

Functions as demonstrated in Type III Interferon-deleted mice, receptor-deficient mice and transgenic models

Abrogation of endogenous IL-28 cytokine function in IL-28Rα-/- mice exacerbated allergic airway inflammation by augmenting Th2 and Th17 responses, and IgE levels. The immunomodulatory effect appeared to be mediated through IL-28-dependent conditioning of lung CD11c+ dendritic cell (DC) function to down-regulate OX40L, up-regulate IL-12p70 and promote Th1 differentiation.[215]

Using IL-28RA$^{-/-}$ and IFNAR$^{-/-}$ mice and bone-marrow chimeric mice it was shown that TLR-3 - and TLR-9 - activated antiviral defense requires expression of IL-28Rα

only on non-hematopoietic cells. Thereby, epithelial cells respond to IFN- and directly restrict virus replication. Additionally, type I IFN receptor system has been shown to mediate positive feedback on both IFN-α/β and IFN-λ expression, while no such an effect was obvious for IFN-λR. [215]

The important role of IFN-λ in the defense against several human pathogens that infect the respiratory tract (influenza A virus, influenza B virus, respiratory syncytial virus, human metapneumovirus, and severe acute respiratory syndrome (SARS) coronavirus), gastrointestinal tract and the brain was shown in mice lacking functional receptors for type I IFN, type III IFN, or both. [216, 217]

IL-30

IL-30 is p28 subunit of IL-27

IL-31

Discovery and structure

IL-31 is a four helix bundle cytokine of the IL-6 family closely related to the IL-6 type cytokines oncostatin M, leukemia inhibitory factor and cardiotrophin 1. It was first cloned in 2004[218] and is encoded on chromosome 12q24.31 in humans. The mature protein has a molecular mass of 24 kDa.[219]

Receptor and signaling

IL-31 signals through a heterodimeric receptor complex, which consist of the IL-31receptor alpha (IL-31RA) and oncostatin M receptor β (OSMRβ). IL-31 receptor interactions occur through different binding sides.[220] Four splice variants of IL-31RA have been described so far (v1-4) in humans.[218] The short isoform (v2) displays strong inhibitory functions. IL-31RA belongs to the GP130 family, has a single trans-membrane domain with a box1 motif (proline rich motif) considered to be essential for signal transduction. In addition three tyrosine residues exist that account for STAT1 activation and dependent in the residue for STAT3 and STAT5 activation[218, 219, 221].

IL-31RA is constitutively expressed in keratinocytes and epithelial cells, but expression is consistently lower than those of OSMRβ in keratinocytes and epithelial cells from other sources. Loss of IL-31RA upon keratinocyte differentiation has been described.[222] IL31 RA is also expressed on $CD14^+$ cells and dendritic cells, STAT1

dependent, and up-regulated upon stimulation with INF-γ and LPS.[223] Moreover eosinophils, [224] skin-infiltrating macrophages (CD68+), intestinal epithelial cells and in a subset of small sized neurons express the receptor. Some IL-31RA expression has been described on CD4 T-cells. However, these cells lack the expression of OSMRβ.[218]

Upon stimulation with IL-31, primary cells natively expressing IL-31RA mainly signal via the STAT 3 pathway, whereas diverse human epithelial cell lines display activation of various signaling pathways including STAT1, STAT3, STAT5 and the PI3 kinase with a preferential engagement of STAT3, ERK1/2, JNK and AKT-pathways.[218, 222, 225-228] In general the mode of activation resembles those of the IL-6 receptor-specific signal transduction. A negative feedback loop via SOCS3 is suggested.

Cellular sources and targets

Messenger RNA and protein expression of IL-31 has been detected in humans in activated $CD4^+$ T-cells, which are in most cases of the Th2 type and, at lower levels in CD8+ T-cells, mast cells [229-231], monocytes, macrophages and dendritic cells.[218, 232] Recently, it was reported that IL-4 can induce IL-31 expression from not only Th2 cells, but also Th1 cells[233]. In addition, mRNA is detected in various tissues. [218] The main target cells of IL-31 are keratinocytes, epithelial cells dorsal root ganglia, eosinophils, basophils, mast cells and monocytes.

Role in immune regulation and cellular networks

IL-31 induces the release of IL-6, IL-8, CXCL1, CXCL8, CCL2 and CCL8 by eosinophils[234], upregulates chemokine mRNA expression (CCL1, 4, 17, 19, 22, 23, 25, CXCL1) in keratinocytes, induces β-endorphin[235] and leads to the expression of growth factors like VEGF and chemokines in epithelial cells[218]. In patients with atopic dermatitis IL-31 down-regulates CCL2 expression after TLR2 ligand stimulation and subsequent IL-31RA up-regulation.[228] In line with this observation human β-defensins and LL37 lead to the secretion of IL-31 in mast cells.[231] Moreover, staphylococcal endotoxins induced IL-31RA expression on monocytes, macrophages and responded with the generation of pro-inflammatory cytokines like IL-1β, IL-6 and IL-18.[236] In human skin models, keratinocytes differentiation factors like filaggrin are repressed by IL-31. This effect is partly IL-20 and IL-24 dependent.[237] UVB or reactive oxygen species can induce IL-31 in the skin of mice and in human T-cells, monocytes and

monocyte-derived dendritic cells.[232] In epithelial cells changes in cell morphology, inhibition of proliferation and inhibition of apoptosis takes places. Thus, IL-31 may play a part in attenuation of proliferation and the induction of regeneration if inflammation takes place. Its impact on dorsal root ganglia remains to be investigated in detail.

Role in allergic disease

IL-31 expression is increased in skin biopsies of patients with atopic dermatitis, allergic contact dermatitis,[238] mastocytosis[239] and prurigo nodularis.[240] Serum IL-31 levels are higher in chronic spontaneous urticaria [241] and AD patients and correlate with SCORAD scores.[242] In addition IL-31 is significantly higher expressed in anti-CD3 or SEA stimulated T-cell from allergic and healthy donors and is mainly restricted to CD45RO CLA+ cells.[243] A common IL-31 haplotype that is associated with a higher risk to develop non-atopic eczema is a reported,[244] and a genetic association with the IL-31 gene is reported with atopic and non-atopic dermatitis in a Taiwanese population.[245] IL-31RA is expressed on a sensory neuron and IL-31 induce itch. [246] In the context of seasonal allergic rhinitis allergen nasal challenge resulted in a local up-regulation of IL-31 five hours after intranasal application of the allergen.[247] In patients with Japanese cedar pollinosis, IL-31 was induced in PBMC of allergic individuals upon allergen specific stimulation but not in patients that underwent specific immunotherapy.[248]

Anti-IL-31 antibody treatment in NC/Nga mice suggests an impact on initial scratching behavior, which is lost upon chronification. IL-31 blocking did not impact severity of dermatitis, weight gain or histological findings.[249] First clinical trial aiming to assess the effects of anti-IL31 mAbs (BMS-981164) administration in healthy and atopic dermatitis patients has been already performed. To date though, the results have not been reported.[250]

In the context of asthma an up-regulation of IL-31mRNA in PBMCs and of IL-31 in the serum is reported.[251] IL-31 increased protein expression of EGF, VEGF and MCP1/CCL2 in a bronchial epithelial cell line.[252] Two mouse models (BALB/c, C57BL/6) of airway hyperresponsiveness, displayed IL-31mRNA up-regulation upon antigen challenge in the lung.[218]

IL-31 has been linked to inflammatory bowel disease. LPS, TNF-α, IL-1β and IFN-γ up-regulated IL-31 at an mRNA and protein level in a colon cancer cell line, which in turn served responsible for IL-8 induction. In line with this findings IL-31 mRNA

expression is higher in patients with Morbus Crohn and ulcerative colitis and correlated with IL-8 expression in lesions.[226] However, another publication failed to detect a correlation between IL-31 and colitis ulcerosa.[253]

Functions as demonstrated in IL-31-deleted mice and receptor-deficient mice

IL-31RA-deficient mice do not display apparent pathologies. Importantly, they do not have a dermatitis-like phenotype. In parasite mouse models with *S. mansoni* egg- and *trichuris*-induced inflammation IL-31RA$^{-/-}$ mice have enhanced Th2-type responses, granuloma formation and accelerated worm expulsion. Thus, rather Th2 counter-regulatory properties of Il-31 were suggested initially.[254, 255] Recently an enhanced response to OSM leading to up-regulated OSM-induced cytokine induction was reported in IL-31RA$^{-/-}$ mice, which may account for the observed enhanced Th2-type responses.

Transgenic over-expression of IL-31 results in alopecia, chronic pruritus that induces skin lesions, conjunctivitis and swelling around the eye due to excessive scratching.[218] An inverse T/B-cell ratio with a relative increase of activated memory T-cells was reported, whereas IgE and IgG concentrations remained unchanged. This resembles nonatopic dermatitis with similar histology (hyperkeratosis, acanthosis, inflammatory cell infiltration, an increase in mast cells). Intra-dermal injection of IL-31 induces inflammatory infiltrates filled with eosinophils, neutrophils, monocytes and lymphocytes and enlarged lymph nodes within days. This nonatopic dermatitis like phenotype could also be achieved in RAG1 -/- and mast cell-deficient mice.

In conclusion, IL-31 is partially associated with a Th2 type response and there is numerous evidence for a linkage with atopic dermatitis, in particular in the context of pruritus. However, the role of IL-31 in other diseases, its exact mechanisms and its physiological role remains to be evaluated in detail.

IL-32

Discovery and structure

IL-32 was originally described as natural killer cell derived transcript 4 (NK4) found in activated NK cells and T cells.[256] On expression of the recombinant form of the NK4 transcript, it became clear that NK4 encoded for a protein with many characteristics of a cytokine. Therefore, the name was changed to IL-32, although IL-32 lacks sequenced homology to presently known cytokine families. The gene

encoding IL-32 is located on human chromosome 16p13.3 and is organized into 8 exons. Six isoforms of IL-32 exist because of mRNA alternative splicing. The isoforms α, β, γ and δ are expressed in several tissues and cell types, whereas the two isoforms ε and ζ were abundantly expressed only in activated T cells.[257] IL-32γ is the most potent isoform, which can be secreted since it harbours a helical transmembrane structure. This isoform can be spliced into the less active IL-32 beta, which appears to be a salvage mechanism to reduce inflammation. [258]

Receptor and signalling

Although a specific receptor for IL-32 is not known so far, a recent study demonstrates that IL-32 has a structure similar to focal adhesion targeting region (FAT) of focal adhesion kinase (FAK-1), which shows that IL-32 is involved in integrin signalling and procaspase-3 activation. It binds to integrins, paxillin and FAK-1. [258] Recombinant IL-32 induces various pro-inflammatory cytokines such as human TNF-α, IL-8, MIP-2 in many cells, especially in monocytes, macrophages and PBMCs by activating the signal pathway of nuclear factor-kappa B (NF-κB) and p38 mitogen activate protein kinase (MAPK).[259] In this context, it has been recently demonstrated that silencing endogenous IL-32 by short hairpin RNA impairs the induction of the pro-inflammatory cytokines TNF-α and IL-1β in monocytes suggesting that IL-32 acts in the same cells where it is produced. [260]Furthermore, it was shown, that IL-32 mediated activity is dependent on TNF-R1. An increased phosphorylation of TNF-R1 as well as a phosphorylation of p300 and death-associated protein kinase-1 (DAPK-1) was detected after stimulation with IL-32 and IL-17, suggesting that there are overlapping inflammatory networks of IL-32 and IL-17, and that these proteins affect both TNF-R1-dependent and –independent pathways. [261]

Cellular sources and targets

IL-32 is found in several tissues and cell types. Moderate constitutive levels of mRNA are present in the thymus, small intestine, and colon. High steady state levels of mRNA could be detected in the spleen and peripheral blood leucocytes.[259] Activated T lymphocytes and NK cells produce high levels of IL-32, whereas primary human B cells stimulated with IgM or anti-CD40, do not.[257] Dominant and widespread source of IL-32 are epithelial cells. IL-32 was expressed in human lung epithelial cell lines and intestinal epithelial cell lines upon stimulation with TNF-α, IFN-γ, IL-1β and IL-18.[259,262] Recently, IL-32 was detected in endothelial cells stimulated with IL-1β and keratinocytes stimulated with TNF-α and IFN-γ.[263, 264] In addition, a subset of

immature monocyte-derived dendritic cells constitutively expressing IL-32 was identified suggesting a role of IL-32 in the immune response mediated by dendritic cells.[265] Besides, IL-32 is able to induce monocytes to rapidly differentiate into DCs, which are then able to increase the production of the Th1- and Th17 polarizing IL-12 and IL-6. [266, 267] Primary human T cells stimulated with anti-CD3 synthesize IL-32 with a molecular weight of 25 kDa, which on Western blot is found in lysates, but not in supernatants. Similar findings were reported for 293T cells transfected with either IL-32γ or IL-32β.[257] In contrast, it was reported that over-expression of IL-32α or IL-32β in COS cells resulted in secreted IL-32.[259] It was shown, that IL-32γ can be spliced into the less proinflammatory IL-32β. By overexpression of a splice resistant IL-32γ in synovial fibroblast, IL-32γ can be secreted.[268] This becomes more evident since it was shown, that induced IL-32 is associated with membrane structures. After proteinase K treatment of IL-32-containing vesicles, native IL-32 is released via a non-classical secretory route involving multi-vesicular bodies and exosomes. [269] A MyD88-dependent IRAK1/p38/PI3K pathway and an independent Fgr/PKCdelta/PI3K pathway regulate the expression and secretion of IL-32α in IL-1beta-stimulated human alveolar epithelial cells. [270]

Role in immune regulation and cellular networks

Over-expression of IL-32β in HeLa cells induces apoptosis. Co-transfection of the same HeLa cells with short-hairpin RNA coding for IL-32 resulted in a 50% decrease in the expression of the IL-32 protein in parallel with decreased cell death. Furthermore, the expression of IL-32 is upregulated in activated T cells suggesting that IL-32 is specific for T cells undergoing apoptosis and could be involved in activation-induced cell death in T cells, probably via its intracellular actions.[257] Moreover, high levels of IL-32 were observed in stroma cells from patients with myelodysplastic syndrome (MDS) and low levels in patients with myeloproliferative disorder (MPD). Co-transfection of stroma cells with IL-32 small interfering RNA, which resulted in a decreased expression of the IL-32 protein, reduced significantly apoptosis in leukemia cells, suggesting that IL-32 in stroma cells appears to deliver pro-apoptotic signals to leukemia cells.[271] Recently, the role of IL-32 in keratinocyte apoptosis in the context of atopic dermatitis was demonstrated.[264] Down-regulation of IL-32 by IL-32 siRNA in human primary keratinocytes and artificial skin equivalents could decrease apoptosis markedly. Moreover, IL-32 was detected in chronic atopic dermatitis skin lesions, which are characterized by infiltrations of activated T cells

inducing keratinocyte apoptosis. In THP-1 cells infected with Mycobacterium tuberculosis IL-32 can influence the production of pro-inflammatory cytokines as well as apoptosis via its intracellular actions suggesting that this cytokine has a dual-function, induction of pro-inflammatory cytokines and induction of apoptosis.[272] In an attempt to isolate a putative IL-32 receptor, proteinase 3 (PR3) has been identified as a specific IL-32α binding protein. The binding of IL-32α to PR3 is independent of its enzymatic activity. PR3 cleaves IL-32α resulting in the formation of two peptides of 16 kDa and 13 kDa. These two cleavage products of IL-32α showed enhanced biological activity in the induction of macrophage inflammatory protein-2 (MIP-2) and IL-8 from mouse and human monocytes.[273] Recently the biological activity between the four isoforms α, β, γ and δ was compared. The γ isoform of IL-32 showed the highest activity in inducing TNF-α, MIP-2 and IL-6, although all isoforms were biologically active.[274] Moreover, IL-32 is synergizing with nuclear oligomerization domains (NOD) for the release of IL-1β and IL-6 in PBMCs.[275] Although a mouse homolog of IL-32 has not been reported so far, IL-32 induces TNF-α and MIP-2 in a mouse macrophage cell line.

Role in allergic disease

IL-32 is present in many inflammatory diseases and it is assumed that IL-32 also has important functions during allergic inflammation. So far, the role of IL-32 in atopic dermatitis is described. IL-32 contributes to the pathophysiology of atopic dermatitis its expression in keratinocytes and serum levels correlated with disease severity of atopic dermatitis independent of the atopy status.[264] In allergic rhinitis, the IL-32 protein and mRNA in the nasal mucosa tissue from AR patients is significantly increased. IL-32 is involved in inflammation and IL-1β, IL-18 and granulocyte-macrophage colony stimulating factor (GM-CSF)-release. [276]

Role in host defense or other immune regulatory conditions

Proinflammatory cytokines can be induced by bacterial products via pattern recognition receptors. Two important families of microbial receptors are the cell-surface TLR and the intracellular nuclear oligomerization domain (NOD) receptor family. IL-32 has the property to amplify the release of IL-1β and IL-6 induced by the intracellular pattern recognition receptor NOD2.[275] *Streptococcus pyogenes* cell wall (SCW) fragments contain TLR-2/NOD2 ligands, which are upregulated in SCW-induced arthritis aggravated by IL-32γ, which leads to severe joint erosion in an IL-1-dependent manner. [277] IL-32 was specifically induced by mycobacteria through a

caspase-1 and IL-18 dependent production of IFN-γ[278] and enhances the clearing of THP-1 cells infected with mycobacteria.[272] Furthermore, the expression of IL-32 is increased in response to human immunodeficiency virus infection (HIV). IL-32 plays an important role in suppressing HIV because a significant increase in HIV replication was observed by knockdown of IL-32 in HEK 293T cells.[279] IL-32 not only contributes to host responses through the induction of pro-inflammatory cytokines, it also directly affects specific immunity by differentiating monocytes into macrophage-like cells mediated through a caspase-3-dependent mechanism. In addition IL-32 reversed GM-CSF-/IL-4-induced dendritic cell differentiation to macrophage-like cells.[280]

IL-32 plays an important role in autoimmune disease. It is highly expressed in rheumatoid arthritis synovial tissue biopsies and is associated with disease severity.[278, 281] Synovial staining of IL-32 also correlated with indices of synovial inflammation as well as synovial presence of TNF-α, IL-1β and IL-18. Moreover, in synovial biopsies from patients with rheumatoid arthritis, the level of IL-32 staining correlated with systemic inflammation. Injection of recombinant human IL-32 into the knee joints of naïve mice resulted in joint swelling, infiltration and cartilage damage. However, in TNF-α-deficient mice, IL-32 driven joint swelling was absent and cell influx was markedly reduced suggesting that IL-32 activity is TNF-α dependent. Transgenic mice over expressing human IL-32 demonstrated that splenocytes from such mice produced more TNF-α, IL-1β and IL-6 in response to lipopolysaccharide stimulation and contained more TNF-α in serum. In these mice, exacerbation of the collagen-induced arthritis was observed, which could be negated by TNF-α blockade. This finding supports the proposed TNF-α dependence of IL-32 activity.[282]. Furthermore, it was shown, that TNF-α induces IL-32γ in fibroblast-like synoviocytes (FLS). Overexpression of IL-32γ and an additional stimulation with LPS in THP-1 cells resulted in increased TNFα, IL-1beta, IL-6 and CXCL6 production. Thus, TNFα is a potent inducer of endogenous IL-32 expression and IL-32 contributes to prolonged TNFα production revealing an autoinflammatory loop. [283]

IL-32 plays also important roles in Crohn's disease and inflammatory bowel disease, which are chronic intestinal disorders unknown etiology. Both are characterized by disruption of epithelial barrier, and the formation of epithelial ulceration. One reason of the epithelial damage is insufficient bacterial killing based on genetic factors such as mutation in the NOD2 gene. IL-32 acts in a synergistic manner with NOD2-specific muropeptides for the release of pro-inflammatory

cytokines. This effect was absent in colon cells of patients with Crohn's disease having a NOD2 gene mutation, suggesting a pivotal role of IL-32 in the pathogenesis of Crohn's disease.[275] In addition, it was demonstrated that IL-32α expression was enhanced in colon cells upon stimulation with IFN-γ, TNF-α and IL-1β. There was a markedly enhanced expression of IL-32α in colon epithelial cells of patients with inflammatory bowel disease compared to healthy controls or samples of ischemic colitis.[262]

Recently, it was shown that IL-32 is able to inhibit angiogenesis in asthma. After knockdown of IL-32 in normal human bronchial epithelial (NHBE) cells by siRNA transfection, a significantly increased secretion of the pro-angiogenic factor VEGF and platelet-derived growth factor was observed. Human umbilical vein endothelial cells cultured in supernatants from IL-32 siRNA-transfected NHBE cells showed enhanced *in vitro* angiogenesis. Furthermore, it was shown that IL-32 serum levels were significantly higher in asthmatic patients compared with healthy control subjects. [264] However, a recent study reported that IL-32 promotes angiogenesis in the settings of pulmonary arterial hypertension and neoplastic diseases.[284] The effect of IL-32 to angiogenesis may depend on each tissue or disease situation.

The regulation and expression of IL-32 was recently examined in chronic rhinosinusitis (CRS) revealing that there is a potential role for IL-32 in the pathogenesis in CRS especially in sinus tissues from CRS patients with nasal polyps. It was shown that IL-32 mRNA levels were up-regulated by TNF-α and IFN-γ in primary sinus epithelial cells. Moreover IL-32 mRNA levels were significantly higher in human primary sinonasal epithelial cells cocultured with Th1 cells. [285]

The roles of IL-32 are also reported in various cancer including colon, gastric, lung, prostate, and thyroid carcinoma. However, the question whether IL-32 promotes or regress cancer is not yet settled. IL-32 is related to acquirement of metastatic phenotype of gastric and lung cancer. [286-288] On the other hand, IL-32 inhibited tumor cell growth through inactivation of NF-κB and STAT3 signals and increasing cytotoxic CD8+ T cells or NK cells numbers in cultured colon cancer cells. [289, 290]

IL-32 in mouse models:

Although IL-32 is only present in tissues from humans and absent in rodents, there is an IL-32 over expressing mouse model available. In transgenic mice over expressing human IL-32, splenocytes produced more TNF-α, IL-1β and IL-6 in response to lipopolysaccharide stimulation and contained more TNF-α in serum. In

these mice, an exacerbation of the collagen-induced arthritis was observed that could be negated by TNF-α blockade.[282] Recently, it was demonstrated in the context of vascular inflammation that over expressing of IL-32 in mice leads to increased inflammatory cell infiltration, vascular leakiness and tissue damage in lungs that resulted in a significant acceleration of animal death compared to wild type control.[291] In mice overexpressing human IL-32γ, it was shown, that these TG mice are healthy, but the constitutive TNF-α levels were elevated in serum and colonic tissue. These mice exhibited a moderate exacerbated acute inflammation, but also less colonic inflammation, reduced tissue loss, and improved survival rate, upon dextran sodium sulfate (DSS)-induced colitis, compared to WT mice. This was accompanied by significantly reduced constitutive levels of IL-32γ, TNF-α and IL-6 levels and elevated IL-10 levels compared to WT, showing, that IL-32γ can worsen as well as protect intestinal integrity. [292]

IL-33

Discovery and structure

IL-33 was first reported in 2003 by Baekkevold et al. as nuclear factor from high endothelial venules (NF-HEV).[293] It belongs to the IL-1 cytokine family and is a potent inducer of Th2 type responses via its receptor, the IL1 receptor related protein ST2.[294]

IL-33 is a β-trefoil fold protein with a molecular weight of 30 kDa. The protein contains a highly conserved N-terminal homeodomain-like helix-turn-helix DNA-binding domain.[293] It localizes to the nucleus, associates with heterochromatin and mitotic chromosomes and exhibits potent transcriptional repressor activities.[295, 296] This N-terminal domains show homology to the transcription factors *engrailed* and *pou.* IL33 is encoded at chromosome 9p24.1 (human) or 19qC1 (mouse).[294] Human and mouse IL33 share 48% homology.

Initially, cleavage by caspase 1 into an active 18 kDa cytokine was considered to take place.[295, 297] However, it became evident that full length IL33 is active via its IL-1-like domain at the carboxyterminus and inactivation takes place mainly via cleavage by the caspases 3 and 7.[298-300] Recent data suggests an amplification of IL33 activity via neutrophil-derived elastase and cathepsin G.[301]

Receptor and signaling

IL-33 binds to its receptor ST2, which was initially described as an orphan receptor and is expressed on T-helper cells, DCs,macrophages, mast cells, basophils, eosinophils and innate lymphoid cells.[302-306] ST2 belongs to the IL-1R family and is encoded on Chr 2 q 12 and is highly conserved across species. The glycosylated form has a molecular weight of 60-70kD that corresponds to the secreted form. Four isoforms have been described so far: sST2, ST2L, ST2V, STLV.[307-309]

The trans-membrane form ST2L displays a similar structure as the IL-1RI that consists of three extracellular immunoglobulin domains and an intracellular Toll interleukin 1 receptor domain (TIR-domain).

ST2-dependent signals induced via IL-33 result in a modulation of the NFκB activation or activation of MAPKs.[294, 310, 311, 312] Binding to ST2 down-regulates TLR signaling via competitive inhibition through binding to MyD88. This may be an important mechanism to counter-regulate overshooting immune responses and have been linked to LPS tolerance.[313, 314] Signaling occurs via recruitment of a co-receptor, the IL1-receptor accessory protein (IL-1RacP) or via T1ST2-homodimerization.[315, 316] IL-1RacP knockout mice do not respond to externally administered IL-33.[315] In vitro, IL33/ST2 signaling has been demonstrated both in ST2-transfected 293 cell line, which resulted in phosphorylation of IκBα and activation of Erk 1/2, p38 and JNK and on mouse mast cells that naturally express ST2. The signaling patterns were similar to IL-1 stimulation through IL-1R.

The soluble form of ST2 (sST2) is released by cardiac myocytes, lung alveolar epithelial cells, fibroblasts, macrophages and monocytes in the presence of LPS, TNF-α, IL1ß, or Th2 clones. It is actively involved in negative regulation of IL-33 induced actions via inhibition of binding of IL-33.[317-319] Consequently, administration of sST2 fusion protein attenuates inflammation in an asthma model in mice.[303] In addition, sST2 levels are elevated in autoimmune diseases, inflammatory bowel disease, cardiac diseases, lung diseases, metabolic diseases, infectious diseases, trauma and allergic diseases.[318, 320-332]

Role in immune regulation and cellular networks

IL-33 is assumed to act as an “alarmin” that is considered to be up-regulated in response to inflammation, released by necrosis of cells and inactivated during apoptosis.[298-300] Aside from necrosis-related release, fibrolasts release IL-33 in a nuclear pore complex dependent fashion upon mechanical stress without cell death *in vitro* and *in vivo* in a model that induces acute pressure overload of the left

ventricle.[333] However, mechanisms of release need further investigation. In general stromal cells in inflamed tissue are considered to be the source of IL-33 upon cells damage.

Target cell populations are classically considered to be basophils, mast cells, eosinophils, dentritic cells, macrophages, NK cells, NKT cells, T lymphocytes, B lymphocytes, endothelial cells, epithelial cells, fibroblasts, (osteoclasts, microglia, and recently discovered innate lymphoid cells. [31, 294, 334-336] In concert with TSLP and IL-25, IL-33 is one of the most potent inducers of Th2 type inflammation on mucosal tissues and involved in helminth infection and allergic pathology.[337] However, recent findings suggested that IL-33 also worked as a regulator of inflammation through contribution to Treg development, maintenance and expansion by direct or indirect mechanisms and have a role in tissue homeostasis.[338-340]

Group 2 innate lymphoid cells were first defined as effector cells of IL-33 in fat associated lymphoid clusters (FALC) as a population of non T-, non B-cell and named as natural helper cells. These cells proliferated in response to IL-2, produced large amounts of IL-13 in response to IL-33 and lead to goblet cell hyperplasia thereby leading to worm repulsion.[260] Following this report, other groups also found similar populations in mice and named as nuocytes and innate helper 2 cells.[335, 341] These cells are defined as group 2 innate lymphoid cells according to proposed classification.[342, 343] All of these lymphoid cells have no lineage marker neither antigen-specific receptors and produce large amounts of Th2 cytokines in response to IL-33.

IL33 acts as a maturation factor for Bone marrow-derived DCs accompanied by the release of pro-inflammatory cytokines, such as IL-6, IL-1β, TNF-α and TARC/CCL17. IL-33-pre-treatment of DCs increases the potency to induce allergen-specific Th2-type cells. Intra-tracheal administration of OVA-pulsed DCs with IL-33 significantly enhances eosinophil numbers and mucous secretion. [336, 344]

In vitro polarized Th2 cells produce enhanced amounts of the Th2 type cytokines IL5 and IL13 in the presence of IL33.[294] Naïve T-cells do not express the receptor ST2 per se. Evidence is suggesting that a STAT5 inducer may be required for ST2 up-regulation.[345]

In mast cells also numerous pro-inflammatory cytokines like IL-1β, IL-6, IL-13 and TNF-α are induced by IL-33. Basophils and eosinphils respond to IL-33 via activation enhanced integrin expression.[346-349] In addition, bone marrow derived mouse

dendritic cells express low levels of ST2 on their surface. IL-33 up-regulates MHCII and CD86 and induces IL-6 in the absence of IL-12. These IL-33 treated dendritic cells are able to elicit a robust Th2 phenotype in naïve T-cells with high IL-13 and IL-5 production.[334]

In conclusion, IL-33 represents a cytokine that bridges innate and adaptive immunity to elicit inflammatory and counter-regulatory signals in the context of allergic disease, autoimmune diseases and parasite infections.

Role in autoimmunity and other diseases

Several mouse model systems like auto-antibody induced arthritis[350, 351], IL-13 dependent cutaneous fibrosis[352], psoriasis[353], hepatic fibrosis[354] and ulcerative colitis[355] link IL-33 and autoimmune diseases. In experimental colitis models, $ST2^{-/-}$ and $IL\text{-}33^{-/-}$ (ref. 356) improved colitis and the absence of ST2 on non-hematopoietic cells protected against DSS-induced colitis. Blocking of ST2 via neutralizing antibodies resulted in a reduction of inflammation and disease activity. Administration of IL-33 on the other hand lead to enhanced disease activity, increased gut permeability and impaired epithelial healing.[357]

IL-33 is abundantly expressed in synovial fluid of rheumatoid arthritis-patients.[295] Administration of sST2-Fc fusion protein reduced the severity of collagen-induced arthritis and resulted in lower serum INF-γ and TNF-α levels without an up-regulation of Th2 type cytokines.[358] Recently, a potential anti-inflammatory and beneficial role of IL33 has been reported in serum-induced arthritis.[359]

Soluble ST2 levels are also elevated in case of severe trauma or sepsis.[319] External application of sST2 induced a down-regulation of pro-inflammatory cytokines and increased survival in mice.[360] This is in line with the observation that ST2-deficient mice fail to develop endotoxin tolerance.[313]

IL-33 and in particular its ligand ST2 has been linked to cardiovascular disease.[361] Cardiac fibroblasts and cardiomyocytes express IL-33 and sST2 when exposed to biomechanical strain or angiotensin II. Mice that undergo myocardial infarction display elevated sST2 in the serum and ST2 mRNA in cardiomyocytes. Levels decrease within the next days. Soluble ST2 represents an independent risk factor for 30-day mortality after myocardial infarction in human. Thus, it may act as a biomarker for myocardial infarction. Interestingly, sST2 levels are also significantly higher in patients with chronic heart failure and seem to be an independent marker for dyspnea related to acute congestive heart failure. IL-33 may serve as a rescue factor

since cardiac hypertrophy was reduced and survival prolonged in mice after aortic constriction.[361] In addition, IL-33 administration led to a reduced aortic atherosclerotic plaque formation in mice with a germline deletion of ApoE. The opposite effect was observed in case of sST2 application.[362]

Role in allergic disease

Initial experiments demonstrated that IL-33 administration leads to lymphocyte-independent airway hyper-reactivity and goblet cell hyperplasia in mice. [260, 335, 363], [294] Repeated treatment with IL-33 resulted in mRNA up-regulation of IL-4, IL-5 and IL-13 (strongest up-regulation) in the thymus, the spleen, the liver and the lung in vivo. This treatment also induced eosinophilia, increased numbers of mononuclear and plasma cells, splenomegaly with elevated serum levels of IgA, IL-5 and IL-13, whereas IL-1α, IL-2, IL-10, IL-12, INF-γ and TNF-α were not altered. Epithelial hyperplasia (esophagus, small intestine) has been described in the gastro-intestinal tract. Eosinophilic and monocytotic infiltration together with hypertrophy and enhanced mucous secretion in bronchi and larger bronchioles occurs. In addition, media hypertrophy of small and medium arteries of the lung has been reported.[294] Genome wide association studies in humans suggested a role of IL-33 in the context of asthma[364-366]

Novel data on the IL-33/ST2 system has changed the understanding of fundamental mechanisms and target populations in allergic diseases. Although further characterization and understanding of innate lymphoid cells and precursor populations is needed, it became evident that they respond to IL-33 and are able to induce allergic inflammation in the absence of adaptive immunity. Lung ILC2 produced large amounts of IL-5 and IL-13 in response to IL-33 and TSLP in a model of papain-induced airway inflammation in the absence of T and B cells.[367] Moreover IL-33 has been linked to Influenza induced and glycolipids driven (source allergens) airway hyperreactivity.[363, 368, 369] Intra-tracheal administration of OVA-pulsed DCs with IL-33 significantly enhanced eosinophil numbers and mucous secretion. [336, 344] IL-33 amplifies alternative macrophage activation in the lung of mice in an IL-13 and IL-4Rα-dependent manner and thereby increases airway inflammation.[370] In line with these findings significantly higher levels of IL-33 were found in bronchoalveolar lavage fluid[371] and a role in airway remodeling via its effect on human fibroblasts and airway smooth muscle cells is suggested.[372, 373] The number of IL-33-positive epithelial cells was significantly higher in lung epithelial cells of asthmatic

individuals[370]. IL33-IL1RL1 pathway polymorphisms are associated with asthma and specific wheezing phenotypes; with most of the SNPs are associated with intermediate-onset wheeze, a phenotype closely associated with allergic sensitization. [374]

In atopic dermatitis IL-33 is upregulated in skin biopsies of patients with atopic dermatitis.[311, 375, 376] Moreover, IL-33 may contribute to the Th2-linked down-regulation of human beta defensin 2 in primary human keratinocytes.[377] And it also directly contributes to the down-regulation of human filaggrin.[378] Overexpression of IL-33 gene in skin elicits atopic dermatitis-like skin inflammation in mice.[379]

A recent publication in mouse hypothesized that IL-33 may even play a more prominent role than TSLP and IL-25 in the context of house dust mite induced allergic asthma, peanut allergy and anaphylaxis.[380]

Although contradictory data are available[381], several studies have shown the blocking of Th2 type inflammation in asthma in mice either by transfer of sST2 or administration of neutralizing antibodies.[293, 295] As an immune tolerance breaking role of IL-33, infection of the respiratory epithelium with rhinovirus can antagonize tolerance to inhaled antigen through combined induction of TSLP, IL-33, and OX40 ligand. [382]

Pre-exposure with sST2 in mice reduced allergen specific proliferation of T-cells.[317] Interestingly sST2 levels in serum of patients with acute eosinophilic pneumonia or acute exacerbations of asthma are elevated as compared to healthy controls.[324, 325] A recent report suggested potent sST2 production by lung alveolar epithelial cells and lung bronchus epithelial cells in response to IL1α, IL1β, TNFα and in a human endotoxin model.[319]

Functions as demonstrated in IL-33-deficient mice and receptor-deficient mice

IL-33$^{-/-}$ mice showed attenuated eosinophilic pulmonary inflammation compared to wild-type mice in OVA-induced asthma model. However, serum OVA-specific IgE levels were comparable in these two groups.[356, 383-385] IL-33$^{-/-}$ mice also showed attenuated eosinophilic pulmonary inflammation in protease-induced asthma model which is independent of T cells and B cells. These results indicated that IL-33 is important for inducing local eosinophilc inflammation, but not for antigen-specific Th2 cell differentiation in asthma model.

In myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis, IL-33$^{-/-}$ showed comparable inflammation compared to wild type mice. IL-33$^{-/-}$ showed attenuated intestinal inflammation in dextran sodium sulfate-induced colitis compared to wild type mice. Moreover, IL-33$^{-/-}$ mice were resistant to LPS-induced septic shock in comparison with wild type mice. These observations indicate that IL-33 seems to play a crucial role in innate-type inflammation rather than acquired immune responses.[356]

However, it has been reported that the phenotypes of ST2$^{-/-}$ mice did not completely correspond with those of IL-33$^{-/-}$ mice in certain disease models such as OVA-induced airway inflammation[356, 383-385], collagen-induced arthritis[350, 386] and LPS-induced septic shock.[313, 356] In addition, it was also reported that full-length IL-33 can induce inflammation in an ST2-independent fasion. Those findings suggest that IL-33$^{-/-}$ mice, rather than ST2$^{-/-}$ mice, should be used to clarify the role of IL-33 in disease model.

IL-34

Discovery and structure

IL-34 was newly discovered in 2008 by Lin et al. whose unique role, already described, is its action as a regulator of myeloid lineage differentiation, proliferation and survival, acting via c-fms. IL-34 uses the second and functional ligand for the proto-oncogene *c-fms* products and receptor tyrosine kinase (fms) and biological effect of macrophage colony-stimulating factor (M-CSF) that is main ligand for c-fms, is required for osteoclastogenesis. [387, 388] IL-34 also shares that topology characterized by a four-helix bundle. Although there remains the fact that IL-34 lacks all of the cysteines forming the distinctive intrachain disulfide bonds in CSF-1 have only one or two intra-chain bonds and yet, have that same four-helix bundle topology. [389] Although IL-34 and M-CSF shared Fms as common receptor, M-CSF and IL-34 shared no homology in their amino-acid sequences[387]. IL-34 has more restricted species cross-reactivity; with the human and mouse ligands much less active on the other species. [390] IL-34 is lacking discernible sequence similarity to MCSF, has been recently identified as the second functional ligand for MCSFR in mammals and birds. [387, 389, 391]

Receptor and signaling

IL-34 mRNA is widely expressed in tissues, including heart, brain, lung, liver, kidney, thymus, vascular endothelial cell, neurons and spleen. [387, 392-394] In embryonic life IL-34 is expressed by neocortical neurons in layers II–V, as well as by meningeal cells. [395] Mammalian IL-34 has a distinctive antiparallel four-helix bundle cytokine core structure consisting of long aA, aB, aC, and aD helices as with MCSF. [396, 397] N-glycosylation site is conserved in helixa1 in mammalian and bird IL-34 molecules. The glycan serves to fill he cavity between the helices α1 and αC and is critical for IL-34 stability in solution.[396] IL-34 stimulates proliferation of monocytes and macrophages through the colony-stimulating factor 1 receptor (CSF1R), which is also shared by colony-stimulating factor 1. [387, 392, 398] MAPK is involved in the induction of IL-34 but not MCSF, by IL-1β and TNF-α. [399] IL-34 stimulates FMS-dependent phosphorylation of extracellular signal regulated kinase-1 and -2 (ERK1/2), and promotes the formation of the colony forming unit-macrophage in human bone marrow cultures. [387, 400] IL-34 plays an important role in receptor activator of nuclear factor-κB ligand RANKL-induced osteoclastogenesis in mouse and human. [388, 392] Additionally IL-34 in combination with RANKL can induce bone marrow cells from splenocytes. [392] Both human and mouse IL-34 were also able to activate the feline CSF-1R in vitro; again the mouse ligand was less active. IL-34 is more species-specific than CSF-1 as identified by the reduced activity of human IL-34 on the mouse CSF-1R. [390, 391] The identities of teleost IL-34 were further confirmed with human, chicken, zebrafish and fugu. [401] The fish IL-34 molecules only share low identities to IL-34s from birds (27.2–33.8%) and mammals (22.2–31.4%). Identities with in birds (76.7%) and mammals (67.8–71.9%) are relatively high. [401]

Role in immune regulation and cellular networks

Macrophage phenotype and function were differently regulated even at the level of the single receptor Fms, by using IL-34 and M-CSF. [398] IL-34 was specifically expressed in splenic tissues, predominantly in the red pulp region. Systemic administration of IL-34 to mice increases the number of monocytes/macrophages and reduces bone mass in vivo. [392]

IL-34 is produced by neuronal cells and promotes microglial proliferation. [394] IL-34 enhanced proliferation of microglia that expressed CSF1R. Neuronal cells primarily produced IL-34 too. [394] Predominant expression of IL-34 reduced expression of CSF-1 and minimal expression of the CSF-1R in adult brain in mice. [395] FMS-deficient mice had a more severe phenotype in the deficiency of monocytic lineage cells

compared with the CSF-1-deficient (op/op) mice. Blocking CFR1 with anti-CSF-1 antibody may produce quantitatively and/or qualitatively different biological effects compared with strategies that target signaling due to both CSF-1 and IL-34. [400, 402] IL-34-deficient mice lack microglia and Langerhans cells. [403] IL-34 induced proinflammatory cytokines and chemokines in human whole blood in the same manner as M-CSF and the elevation of these mediators was inhibited by M-CSF soluble receptor or GW2580, c-FMS kinase inhibitor, confirming that IL-34 functions as new ligand of c-FMS and its function is quite similar to M-CSF in the induction of proinflammatory mediators in human whole blood. Some proinflammatory cytokines and chemokines elevated by M-CSF and IL-34, IP-10, IL-8, and MCP-1 levels were significantly increased by M-CSF and IL-34. Although level of IP-10, IL-8, and MCP-1 was dramatically increased by M-CSF and IL-34, the level of increase was variable among donors. [404]

Role in autoimmunity and other diseases

Microglia treated with IL-34 attenuate oligomeric amyloid-alpha neurotoxicity in primary neuron-microglia co-cultures. The neuroprotective effect of IL-34 was mediated via microglial clearance of oligomeric amyloid-alpha and antioxidant functions via through up-regulation of insulin-degrading enzyme and heme oxygenase-1. [394] In addition, IL-34 is able to protect against excitotoxin-induced neurodegeneration through CSF1R in neurons. [405] TNFα and IL-1β increase IL-34 gene expression in rheumatoid synovial fibroblasts. The expression of IL-34 was associated with the severity of synovitis and rheumatoid arthritis. [406] [407] IL-34 was also overexpressed in the inflamed salivary glands of patients with Sjögren's syndrome and correlated with IL-1β and TNF-α expression. [408] IL-34 and its receptor are upregulated in ischemia-incited human inflamed kidneys and IL-34 promotes macrophage-mediated persistent ischemia-incited acute kidney injury. [409]

IL-35

Discovery and structure

First described in 2007, IL-35 is the latest member of the IL-12 family. It is composed of the p35 subunit of IL-12 and the EBI3 subunit of IL-27.[410, 411] The gene encoding p35 is located on chromosome 3 in humans and on chromosome 6 in mice and contains 197 a.a. With its four-helix bundle structure p35 has homologies to

other single chain cytokines of the IL-6 superfamily. The EBI3 subunit is related to IL12p40 and structurally homologous to soluble IL-6R, a class I receptor chain for cytokines. The EBI3 gene is located on human chromosome 19 and mouse chromosome 17. It and contains 229 amino acids. In contrast to IL-12 and IL-23, and similar to IL-27, the subunits of IL-35 are not covalently linked by disulfide bonds.

Receptor and signaling

IL-35 signals through the IL-12Rβ2 and gp130 receptor subunits. Therefore it is not only shares the cytokine subunits, but also the receptor subunits with IL-12 (IL-12Rβ2) and IL-27 (gp130). Gp130 is a common receptor chain shared by several members of the IL-6 superfamily. Surprisingly, IL-35 is not only signaling through the IL-12Rβ2/gp130 heterodimer, but also mediates its effects through IL-12Rβ2/ IL-12Rβ2 and gp130/gp130 homodimers.[412] IL-12Rβ2 is mainly expressed on natural killer cells and activated T cells, while gp130 is expressed quite ubiquitously. The receptors do not have an intrinsic kinase activity but associate with JAK1 (gp130) and JAK2 (IL-12Rβ2), which lead to the activation of STAT4 and STAT1.[412] STAT1/STAT4 heterodimers form after activation, which do not occur in IL-12 signaling. This might distinguish the anti-inflammatory signal of IL-35 from the pro-inflammatory signal of IL-12.[413] The heterodimer is necessary for the positive feedback loop on the expression of p35 and EBI3, but seems to be partially dispensable for the suppressive function of IL-35.[412]

Cellular sources and targets

The main source of IL-35 is CD4+ regulatory T cells including the iTr35, a new inducible regulatory T cell type induced by IL-35.[410, 414-416] Unlike constitutively expressed regulatory cytokines like TGFβ, IL-35 is only expressed after induction.[417] The induction of the IL-35 subunits p35 and EBI3 are better described with their other partners forming IL-12 or IL-27 (see IL-12 and IL-27 section in this paper), but not well characterized as the induction of IL-35. The major known stimulus so far, besides artificial TCR signaling, is the self-induction of IL-35.[414, 415] The subunits of IL-35 can also be induced by stimulation with LPS or proinflammatory cytokines in monocytes, vascular endothelial cells, smooth muscle cells and epithelial cells.[417] In addition, stimulated human peripheral blood T cells of healthy donors produce high amounts of IL-35 protein.[418] Recently, Olson et al. reported the existence of a CD8+CTLA+ tumor specific regulatory T cell that expresses IL-35.[419] *In vivo* IL-35 expression could be induced by intestinal infection with *Trichuris muris* and in the

tumor beds of melanoma and colorectal adenocarcinoma in mice.[415] IL-35-producing B cells as well as $CD138^+$ plasma cells are also involved in the negative regulation of immunity. During experimental autoimmune encephalomyelitis (EAE), $CD138^+$ plasma cells are the main source of B-cell-derived IL-35 and IL-10.[420] In humans, IL-35 could be induced by virus-infected DCs, dependent on PD-L1 and CD169.[421]

Role in immune regulation and cellular networks

IL-35 belongs to the latest of immune regulatory cytokines. It is shown, that IL-35 can reduce proliferation of effector T cells and increase IL-10 production and proliferation of regulatory T cells.[410, 414] Furthermore, it can induce it's own inducible regulatory T cell type: iTr35.[415] IL-35 seems to directly suppress Th17 development and to have a suppressive role in several Th17-related diseases.[411, 415, 422-425] The functions of IL-35 on other cell types needs to be clarified. So far, mainly roles of IL-35 on immune responses were shown, but recently it was indicated that IL-35 might not only influence the anti-tumor immune response, but directly increases apoptosis and decreases cell proliferation in tumor cell lines.[426] On the contrary, high levels of IL-35 in colorectal and pancreas cancer tissues and peripheral blood are correlated to the extent of colorectal cancer malignancy and clinical stage, suggesting that IL-35 implicates in tumor pathogenesis.[427, 428]

Role in allergic disease

In mice, IL-35 overexpression in lungs could reduce allergic airway inflammation and IgE production in mice that received HDM specific Th2 cells and were challenged with HDM.[429] Reversion of IL-17-dependent AHR over time after repeated challenges was dependent on IL-35.[424] In humans, several polymorphisms in p35 and EBI3 were associated with increased susceptibility to asthma,[430] atopic dermatitis,[431] allergic rhinitis[432] and celiac disease.[433-436]

Functions as demonstrated in IL-35-deleted mice and receptor-deficient mice.

Neither the p35 nor the EBI3 knockout mice show overt signs of autoimmune disease or developmental abnormalities.[137, 437] Both knockout mice show a variety of changes in the pathologies of many diseases. Since it is not possible to distinguish between the effect of IL-12 and IL-35 or IL-27 and IL-35 the focus should be here on mouse models with clear IL-35 effect.

IL-35 has been shown to have suppressive effects on a lot of autoimmune diseases.[438] The majority of studies of the effects of IL-35 have been carried out

using mice and experimental models of arthritis.[439] It was first described as being protective against collagen-induced arthritis.[411, 440] IL-35 depleted regulatory T cells failed to suppress colitis in RAG knockout mice after T cell transfer,[410] while adoptively transferred iTr35 could suppress colitis in the same model.[415] The treatment with recombinant IL-35 led to the a reduction in colitis development in several models of experimental colitis.[441] Additionally, iTr35 ameliorated systemic autoimmunity in Foxp3 -/- mice and almost abolished peptide-induced experimental autoimmune encephalitis.[415] In mice infected with HSV recombinantly expressing IL-2, IL-35 was able to reduce demyelination induced by the viral infection. The ectopic expression of IL-35 in the pancreas could prevent the development of type I diabetes.[442] These data suggest a possible therapeutic use of IL-35 in autoimmunity. However, the importance of the cytokine in human autoimmunity has not yet been established.[439]

As mentioned earlier, IL-35 was able to reduce allergic airway inflammation in a mouse HDM asthma model and to revert AHR in an IL-17-dependent mouse model.[424, 429] The expression of IL-35 was found in the bed of melanoma and colorectal adenocarcinoma, where it might have immune suppressive activity, since the transfer of iTr35 led to an increase in B16 melanoma growth.[415] On the other hand, IL-35 might also have direct suppressive influence on the cancer cells by inducing apoptosis and suppressing proliferation.[426]

In humans, little is known about the influence of IL-35 on the pathogenesis of diseases. So far, IL-35 was found in the serum of ALM patients and being expressed in CD4+ T cells in patients with chronic Hepatitis B infection.[443] For both, p35 and EBI3 several genetic variations were associated with increased risk in autoimmune diseases, allergic diseases and cancer,[432, 444, 445] but whether IL-35 or IL-12 and IL-27 influence the risks can only be speculated on according to the biological data available. More recently, serum IL-35 levels were related to the pathogenesis of childhood asthma as well as inflammatory bowel diseases.[446] [447]

IL-36

Discovery and structure

IL-36α, IL-36β, and IL-36γ (formerly IL-1F6, IL-1F8, and IL-1F9 respectively) and IL-36Ra (previously IL-F5) [448, 449] are IL-1 family members and were identified

approximately 10 years ago through DNA searches for homologues and probing of genomic libraries [450-453]. They are clustered on chromosome 2q [451, 453, 454]. A crystal structure of mouse IL-36Ra revealed a β-trefoil structure, similar to IL-1β and IL-1Ra, although the loops connecting the β- strands were substantially different [455].

Interestingly, IL-36 Ra, α, β and γ lack a hydrophobic leader peptide found in most secreted proteins [450, 451, 456] however, N-terminally truncated forms of the cytokines show much higher activity but it is uncertain how this truncation is performed in the cell [457]. Investigations with IL-36α demonstrate that release from bone marrow-derived macrophages is dependent on treatment with LPS and ATP [458].

Receptor and signaling

The orphan receptor IL-36R (formally IL-1RL2 or IL-1Rrp2) was identified as the receptor of agonists IL-36α, β and γ and antagonist IL-36Ra [459, 460]. Similar to members of the IL-1R family, the IL-36R receptor has three extracellular immunoglobulin domains and an intracellular Toll-iL-1R domain [460].

The IL-36 family of cytokines activate several proinflammatory signaling pathways. IL-36 α, β and γ bind and activate NF-κB through IL-36R which also requires the accessory protein IL-1RAcP. In addition to NF-κB activation, IL-36 α, β and γ activate mitogen-activated protein kinase pathways JNK and ERK1/2 and the secretion of cytokines IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor [460].. IL-36Ra antagonism works in a manner similar to IL-1Ra where binding of N-terminally truncated IL-36Ra to the receptor prevents IL-36R association with the accessory protein IL-1RAcP [457].

Cell sources and targets

IL-36 cytokines α, β and γ are mainly expressed in internal endothelial tissues and in skin [453]. Specifically, IL-36α is expressed in the trachea, thymus, fetal colon, spleen [460] and BMDCs [461]. IL-36β is most highly expressed in skin but also in fetal colon, skeletal muscle [460] and Th0 cells [461]. IL-36γ is expressed in embryonic tissue and in tissues containing epithelia, most highly in skin and at lower levels in uterus, trachea [459, 460] and BMDCs [461].

IL-36R is expressed predominantly in keratinocytes and other epithelial barriers as well as in lower levels in prostate, ovary, thyroid, uterus, liver, kidney, lung and trachea as detected by quantitative PCR [460]. IL-36R is also expressed at lower levels

on dendritic cells [462], naive $CD4^+$ T cells, differentiated Th1 and Th2 cells and at very low levels on Th17 cells [453].

Role in immune regulation and cellular networks

High IL-36R and IL-36 cytokines α, β and γ expression is observed in keratinocytes and other epithelial barriers of the body skin [453, 459, 460] and the double stranded RNA analogue poly(I:C) was shown to strongly induce IL-36γ expression in keratinocytes [463]. IL-36 cytokines and their receptor may have a role in promoting the early inflammatory response to tissue injury or infection [453, 461, 462] and may constitute a distinct but analogous IL-1 signaling system active in epithelia [464].

IL-36R is expressed at lower levels on naive $CD4^+$ T cells [453] and dendritic cells [462], and even lower levels on Th1 and Th2 cells. Addition of IL-36 to activated CD4+ T cells induced production of IL-2, IFN-γ and IL-4 which could be significantly inhibited with the addition of IL-Ra [453, 461]. The cytokine environment influences the selectivity of the effect of IL-36 on Th cell polarization [461]. IL-36 can strongly induce the production of IL-2 and in combination with IL-36β and IL-12 can induce Th1 differentiation [461]. IL-36 cytokines have been also shown to regulate and enhance the function of Th17 cytokines suggesting a role in the TH17 related mucosal host defense [465]. IL-36Ra also interacts with the orphan receptor SIGRR and downregulates IL-1β- and LPS-induced inflammation in the brain, characterized by an increase in IL-4 production [466].

Based on work with mice, IL-36R signalling is crucial in controlling the pathogenic IL-23/IL-17/IL-22 immune pathway when psoriasiform dermatitis is induced through TLR7 or TLR3 signalling [467, 468]. Addition of IL-36α intradermally in mice led to an induction of IL-17A, IL-23, TNF, and IFN-γ transcripts supporting the role of IL-36 in the IL-23/IL-17/IL-22 pathway [468]. Furthermore, TNF, IL-17A, IL-23, and IFN-γ were able to induce IL-1F6 mRNA creating a positive feedback loop [468].

Role in host defense and autoimmune diseases

An important role of the IL-36 cytokines has been identified in lesional psoriasis skin where the expression of IL-36Ra, α and γ, and their receptor IL-36R are all significantly increased relative to skin from a healthy individual. [459, 464, 469, 470] Furthermore, individuals with generalized pustular psoriasis, a rare and more severe condition, were found to have mutations in IL-36Ra. [470-472]

Role in allergic diseases

Work by Ramadas *et al.* [473, 474] with asthma hyper-responsive (A/J) and asthma hypo-responsive (C3H/HeJ) strains of mice showed an increase in IL-36γ (but not Ra, α or β) transcript level in lungs following allergen treatment. Parafilm sections of lung showed IL-36γ expression predominantly in airway epithelial cells and addition of IL-36γ led to an increase in NF-κB, neutrophil recruitment, chemokine production, and increased airway hyperresponsiveness. [474] IL-36 α, IL-36 γ and IL-36RN was found to be upregulated in lesional atopic dermatitis skin transcriptome analyses. [475]

IL-36 in mice and IL-36 mutations

Similar to humans, mouse IL-36 α, β and γ are expressed predominantly in epithelial barriers, specifically, in mouse paw and esophagus.[460] IL-36R mRNA was found expressed in bone marrow-derived dendritic cells, splenic $CD4^+$ T cells, bone marrow–derived macrophages and bone marrow-derived neutrophils. IL-36R was not found in $CD8^+$ T-cells and B-cells. [453]

A mouse model of psoriasis has been developed and shows some similarities to the human disease, however, it is difficult to model in the mouse because of profound structural and developmental differences between mouse and human skin. [468] The transgenic expression of IL-36α in basal keratinocytes resulted in cutaneous inflammation sharing some features with psoriasis which resolved by P21 with the silencing of the transgene expression, but then recurred in mice at 6 mo of age. [453, 469] This inflammation phenotype was dependent on the IL-36R receptor, and IL-1RAcP and TNF-α modulated (but did not eliminate) the inflammation phenotype. [469] Deletion of IL-36Ra led to a much more severe phenotype and neonatal lethality. [469]

Mutations in IL-36R were found in people with generalized pustular psoriasis [470, 472] and keratinocytes from patients had an overproduction of IL-8 not only in response to IL-36α, β and γ but also after poly-IC (specific to TLR3) stimulation. This suggests that the IL-36 pathway may play a role in an innate immune response to pathogens. [470, 472]

IL-37

Discovery and structure

IL-37 was first described in 2000 by Kumar et al. as IL-1 family member 7 (IL-1F7).[456] It maps to the IL-1 family cluster of genes on chromosome 2.[476] IL-37 has five different splice variants (IL-1F7a-e) with a molecular weight of 17 to 24 kDa.[452,

[454] The major splice variant IL-37b (IL-1F7b) which is the largest and includes five of the six exons shares significant sequence homology with IL-18. Only IL-37b and IL-37c containing exons 1 and 2 express an N-terminal prodomain, which includes a potential caspase-1 cleavage site.[477]

Receptor and signaling

IL-37b (proIL-37b) precursor is cleaved by caspase-1 into mature IL-37b. Both of them bind to the IL-18 receptor α-chain (IL-18Rα) with 50 times lower affinity compared to IL-18 itself.[478] However, the binding of IL-37 to IL-18Rα does not function as a receptor antagonist of IL-18.[477] IL-37b also binds to IL-18 binding protein (IL-18BP), which is the natural antagonist of IL-18, and enhances the IL-18-neutralizing capacity of the IL-18BP.[479] Recently, IL-1R8 was found to act as the co-receptor for IL-37- IL-18Rα and this interaction was required for the anti-inflammatory function of IL-37.[480, 481]

IL-37 has to be cleaved by caspase-1 to be activated.[477] After this procession m ature IL-37b translocates into the nucleus by caspase-1 and forms a functional complex with Smad3, which affects gene transcription.[482] The phosphorylation of STATs 1-4, which are involved in signal transduction for proinflammatory cytokines, are suppressed by IL-37b. IL-37b also suppresses both c-Jun, which is a part of the IL-1-inducible proinflammatory transcription factor AP-1, and phosphorylation of p38 MAPK, which contributes to several proinflammatory signaling cascades. Moreover, IL-37b increases phosphorylation of GSK-3α/β, which renders this kinase inactive.[483-487]

Cell sources and targets

The IL-37 transcripts are detected in human tissues such as liver and subcutaneous, visceral fat of obese patients,[488] lymph node, thymus, bone marrow, placenta, lung, testis, uterus and colon tumor, and in human cell lines such as THP-1, U937, A431, IMTLH, KG-1, HL60, HPBMC, HPT-4 and NHDC.[489] The protein is found in monocytes, tonsil plasma cells, breast carcinoma cells, some colon carcinoma cells, melanomas and lung carcinomas. Isoform-specific expression studies reveal, that IL-37a is the only present isoform in brain, IL-37b is a kidney specific isoform, IL-37c is only expressed in heart and IL-37d, IL-37-e are only expressed in bone marrow and testis [477, 479]. IL-37 acts by an intracellular mechanism in translocating to the nucleus by forming a functional complex with Smad3.[482, 485] It suppresses TLR-induced proinflammatory cytokines and DC activation.

Role in immune regulation and cellular networks

IL-37 is a recently identified cytokine that has evolved to permit tolerance to components of self as well as the eradication of pathogens with minimal collateral damage to the host. [490] TGF-β and several TLR ligands such as LPS and Pam_3CSK_4 highly induce IL-37 in PBMC. Inflammatory stimuli and cytokines, TLR agonists, IL-18, IFN-γ, IL-1β, the dinucleotide CpG[491] and TNF moderately increase it, whereas it is inhibited by IL-4 plus GM-CSF.[485]

The siRNA knockdown of LPS-induced IL-37 results in two to threefold increase of mature IL-1β, IL-6 and TNF in human PBMC. The treatment with sIL-37 does not affect the expression of the anti-inflammatory cytokines IL-10 and IL1Ra.[491] Meanwhile, the TLR-induced proinflammatory cytokines are reduced both in mouse macrophage RAW cell line stably expressing the human IL-37b (RAW-IL-37) and in human monocyte cell line THP-1 and epithelial cell line A549 overexpressed by IL-37b.[485]

The IL-1 family members are expressed in airway epithelial cells. TNF and IL-17 weakly increase IL-37 levels in Primary normal human bronchial epithelial cells (NHBE).[492]

IL-37b-overexpressing THP-1 cells show not only the suppression of cellular adhesion and migration regulators such as focal adhesion kinase (FAK), proline-rich tyrosine kinase 2 (Pyk2) and paxillin, but also the reduction of kinases, which affect cellular proliferation and differentiation, including the MAP kinase p38α, multiple STAT transcription factors. In addition, IL-37b-overexpressing RAW-IL-37 cells show the striking morphological differences such as loss of pseudopodia and vacuolization. Thus, IL-37b also regulates post-receptor signal transduction in a specific fashion.[485]

Role in host defense and autoimmune diseases

IL-37 is not constitutively expressed in tissues from healthy subjects. However, it is highly expressed in synovial tissue from individuals with active rheumatoid arthritis, suggesting that IL-37 mediates a negative feedback mechanism to suppress excessive inflammation.[485] Furthermore IL-37 level is significantly increased in patients with systemic lupus erythematosus (SLE) compared with healthy controls and is down regulated after treatment with glucocorticoids.[493] In patients with atopic dermatitis, serum IL-37 was significantly high but independent of the diverse phenotypes (mild, severe AD).[494]

Functions as demonstrated in IL-37 transgenic mice and Smad3 knockdown *in vivo*

IL-37b transgenic mice are protected from LPS-induced shock and from conA (concanavalin A) induced hepatitis. They show lower serum and tissue concentrations of IL-2, IL-4-IL-6, IL-9, IL-12, IFNγ, and have less LPS-induced DC activation. Serum IL-10 levels are unaffected.[495]

Furthermore, IL-37 plays a significant anti-inflammatory role in a mouse model of colitis. IL-37tg mice are less susceptible to dextran sulfate- induced colitis, compared with wild-type mice.[495, 496] The expression of human IL-37 protects transgenic mice (hIL-37transgenic) from clinical signs of colitis and from DSS-induced intestinal damages. This effect is associated with decreased TNFα, IL-1β-Release and increased IL-10 levels. This protective effect is not caused by the induction of IL-10 because blockage of IL-10 receptor does not reverse the IL-37-mediated protective effect.[496]

Another protective effect is described in a mouse model of hepatic ischemia/reperfusion. Treatment with recombinant IL-37 has a protective effect on liver inflammation through reduction of proinflammatory cytokines and chemokines (TNFα, MIP-2, KC). TNFα-induced neutrophil activation is significantly suppressed.[497]

The siRNA knockdown of Smad3 shows the reduction of the anti-inflammatory function especially in IL-37 transgenic mice, indicating the functional link between IL-37 and Smad3.[485]

IL38

Discovery and structure

IL-38 was first described as a member of the IL-1 family (IL-1HY2) in 2001.[498] It was mapped to the IL-1 locus on human chromosome 2 which occupy an 500-kb interval. The gene consists of five coding exons and encodes a protein with a predicted molecular mass of 17 kDa with a characteristic IL-1 signature motif (Amino acids 119-137). IL-38 shares a significant sequence similarity with other members of the IL-1 gene family. [499] The genomic structure, the amino acid sequence and the predicted three-dimensional structure of IL-38 resembles that of the receptor antagonists IL-1Ra and IL-36RN (FIL1δ).[498, 499] In contrast to other IL-1 family

members, neither a signal pro-peptide nor a caspase-1 cleavage site has been identified. [451, 456, 498] The maturation and the mechanism of the secretion remain unclear.

Receptor and signaling

IL-38 is secreted in transiently transfected CHO cells and binds to the soluble type I IL-1 receptor (IL-1R1) with low affinity.[498] Furthermore this protein is also able to bind the immobilized IL-36 receptor (IL-36R; IL-1Rrp2). The binding is comparable to IL-36 receptor antagonist (IL-36Ra) binding to the same receptor. Increased IL-38 concentration results in a lost of this inhibitory effect. These findings led to the conclusion, that IL-38 as well as IL-36a is a partial receptor antagonist. [500]

Cell sources and targets

In immunohistochemical analysis, IL-38 transcripts are detected in basal epithelia of skin, in spleen and in proliferating B cells of the tonsils. [498] Multitissue cDNA PCR analysis shows an expression in fetal liver, spleen, placenta, thymus, tonsil and in the human cell-line THP-1. [499]

Role in immune regulation and cellular networks

IL-38 shows similar biological effects on immune cells as IL-36Ra. In *Candida albicans* stimulated peripheral blood mononuclear cells, IL-38 inhibits the production of characteristic cytokines of the Th17-respose, IL-17A (reduced by 37%) and IL-22 (reduced by 39%). Therefore, the same effect could be observed after IL-36 receptor (IL-36R) blockage with the antagonist IL-36Ra. There is no effect on IFN-γ production or induction of cytokine production. The IL-36-driven production of IL-8 in stimulated PBMCs decreases after treatment with IL-38 (reduced by 42%) as well as IL-36Ra. IL-38 has also an effect on other immune cells. In LPS stimulated monocyte derived dendritic cells (DCs), the IL-6 level is significantly increased (twofold) in presence of IL-38. [500]

The transcription factor NF-KB plays a key role in regulating immune responses and is linked to autoimmune and inflammatory diseases. In contrast to other members of the IL-1 family, IL-38 does not activate the NF-KB pathway via IL-1Rrp2 (IL-1R-related protein 2) in Jurkat cells.[501]

IL-38 polymorphism and autoimmune diseases

IL-38 polymorphism plays a role in the pathogenesis of autoimmune diseases The IL-38 polymorphism rs3811058 is associated with ankylosing spondylitis (AS) in Taiwanese Chinese [502] and psoriatic arthritis in a Caucasian population. [503] The

same SNP and also rs7570267 are significantly associated with rheumatoid arthritis in a Korean population. [504]

IL-38 in mice and human mutations

At present, the effect of IL-38-gene deletion in a knock-out mouse model is still unknown.

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Interferon alpha and beta

Discovery and structure

Type I interferons (IFN-I) comprise a wide class of structurally related cytokines, mostly recognized by their pivotal role in antiviral responses.[1] The most extensively studied members of IFN-I are interferon-α (IFN-α) and interferon-β (IFN-β). IFN-I regulate lymphocyte development, immune responses and the maintenance of immunological memory of cytotoxic T cells. In addition, they have a protective role in various pathophysiologic processes, but also detrimental effects on several autoimmune diseases. [2]

At the end of 1950s interferon (IFN) was first described as a substance inducing the antiviral state in cells. [3] Later, interferons were grouped as type I IFNs (acid-stable at pH 2 and heat-stable) and type II IFNs, which are acid-labile, but so far there is only one member in this group – IFN-γ. (Reviewed in [4]). More recently, type III IFNs were described, IFNs-ʎ (lambda).

Type I IFNs are structurally related proteins that act on a common cell-surface IFN-α receptor (IFNAR). Members of this family include: IFN-α (alpha), IFN-β (beta), IFN-κ (kappa), IFN-δ (delta), IFN-ε (epsilon), IFN-τ (tau), IFN-ω (omega), and IFN-ζ (zeta, also known as limitin).

All human type I IFN genes are clustered in the same locus on the short arm of chromosome 9. Homology between human IFN-α and IFN-β is about 30% and 45% at the amino acid and nucleotide level, respectively. IFN-α, and β (IFN-αβ) genes lack introns; this feature allows a more rapid transcription which is particularly convenient in defense against viral infections.[4]

Thirteen genes code for structurally different forms of IFN-α but only a single gene codes for human IFN-β. IFN-α subtypes are - IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNA10, IFNA13, IFNA14, IFNA16, IFNA17, IFNA21. All eutherians produce IFN-I, but IFNA2, the first discovered and prototypical member of the family, is restricted to humans and closely related hominids.[5]

Human IFN-α subtypes are composed of 165 or 166 amino acids and murine IFN-α subtypes consist of 166 or 167 amino acids. Human and murine IFN-β have 166 and 161 amino acids, respectively. [6]

IFN-α and IFN-β are 15–21 kD and 22 kD in size respectively. IFN-α and IFN-β have a globular structure composed of five a-helices. Their receptors, IFNAR1 and

IFNAR2, belong to the class II cytokine receptor family for a-helical cytokines. [6]

Receptors and signaling

IFN-α and β bind both to a specific cell surface receptor complex – IFNAR- on both, the virus infected cell and nearby uninfected cells. IFNAR is present in low numbers (100 – 5000 molecules/cell) on the surface of all vertebrate cells. The receptor complex consists of two known subunits, IFNAR-1 and IFNAR-2.

Mature human IFNAR-1, resulting from removal of the peptide leader sequence, is a 530 amino acid residue integral membrane protein. It is composed of an extracellular domain of 409 amino acid residues, a transmembrane domain of 21 residues and an intracellular domain of 100 residues. Mature human IFNAR-2 has been isolated as three forms. The full length receptor chain comprised of 487 amino acids, is referred to as IFNAR-2c and is 115 kDa in size.[7]

Antiviral activity mediated by the IFNAR requires induction of an enzyme 2'–5'-oligoadenylate synthetase (2', 5'-AS), a double-strand RNA dependent protein kinase (PKR), as well as a myxovirus (influenza) resistance (MxA) protein. These molecules inhibit viral replication and degrade viral components. Induction of 2'–5'-AS activates ribonuclease (RNase) L, a latent cellular endoribonuclease that mediates antiviral activity[8].

Type I IFNs signaling pathways are initiated by Janus kinase (Jak) phosphorylation of downstream proteins. The canonical route involves STAT1 and STAT2 activation by Jak (JAK-STAT pathway). Other alternative networks have been discovered, such as the activation of the pleiotropic mTOR pathway through PI3K, or MAPK p38 activation by *vav* or another GTP exchange factor. In addition to operate through transcriptional control, type I IFN can directly influence translation through the mTOR pathway.[9, 10]

IFN-αβ strongly activates STAT1 and STAT2 and induces the formation heterotrimeric transcription factor complex interferon-stimulated gene factor 3 (ISGF3).[11] ISGF3 translocates to the nucleus and induces the transcription of hundreds of IFN-stimulated genes involved in the generation of the antiviral state.

Negative regulation of type I IFN signaling is accomplished by various mechanisms, including receptor internalization and degradation, dephosphorylation of JAKs and STATs by several phosphatases, induction of suppressors of cytokine signaling (SOCS) and repression of STAT-mediated gene activation by protein

inhibitors of activated STATs (PIAS).[12]

In summary, the overall IFNαβ signaling involves five major steps: (a) IFN-driven dimerization of the receptor outside the cell which leads to (b) initiation of a tyrosine phosphorylation cascade inside the cell, resulting in (c) dimerization of the phosphorylated STATs, activating them for (d) transport into the nucleus, where they (e) bind to specific DNA sequences and stimulate transcription.[13]

Cellular sources and targets

Small amounts of IFN-I are produced under healthy conditions (IFNα by leukocytes and IFNβ by fibroblasts) but their production increases enormously by viral infections or exposure to double-stranded nucleic acids.[14]

Basically, all nucleated cells can produce IFN-αβ in response to viral infection, but plasmacytoid dendritic cells (pDCs), or “natural IFN-producing cells” (NIPCs) produce up to 1000-fold more IFN-αβ (and IFN-λ) than other cell types. [15, 16]

Even though pDCs express constitutively all protein machinery for rapid IFN-I production, they are mostly dispensable for driving local anti-viral responses.[17] Initially, local infected cells are the main source of IFN-I, but after systemic viral spread, pDCs on the spleen becomes the most important source. Mast cell can also secrete IFN-I. Due to their tissue localization, their importance as local sentinels of viral infections should be further evaluated.

The relative biologic activities of the different IFN-α subtypes vary markedly, and, for example, on a molar basis, IFN-α8 and IFN-β are more efficient antiviral agents than are many other IFN-α subtypes. [18]

Different stimuli trigger IFN-I expression. Viruses and double-stranded RNA are the most efficient natural inducers of type I IFNs, but other infectious agents, such as protozoan parasites, may induce their production. [19, 20] Besides, pathogen-associated molecular patterns, danger signals and cellular stress induced by viral infection can initiate synergistic pathways that promote IFN-I production[21].

Probably, all cells in the organism can produce type I IFNs, but in the absence of viral infection IFN synthesis is shut off, and most cells do not release measurable amounts of it.[4]

Beside pDCs it seems that relevant levels of type I IFNs are also produced by conventional myeloid DCs (CD11chiB220−Ly6C−)[22, 23] especially when infected with certain types of DC-tropic dsRNA viruses.[24]

It is remarkable that the induction of most IFN-α genes is dependent on IFN-β signaling and IFN-β-induced interferon regulatory factor 7 (IRF7).

The type I IFN gene induction is initiated by the recognition of double-stranded (ds) RNA that is produced by many viruses during their replication cycle. These patterns can be roughly divided as being “cytosolic” or “endosomic”.

“Cytosolic” receptors, such as RIG-I, MDA5 and LGP-2 , are expressed ubiquitously and are localized to the cell’s cytosol where they detect viral nucleic acids produced upon infection.[25, 26]

The first identified cytosolic sensor is dsRNA dependent protein kinase (PKR), whose catalytic activity is stimulated by its binding to dsRNA. However, although PKR contributes to type I IFN production in response to the synthetic dsRNA analog poly(I:C), gene targeting in mice has shown that it is superfluous for IFN responses to viral infection. [27, 28] MDA5 recognizes mainly dsRNA, RIG-1 can detect single stranded RNA (ssRNA) of viral origin, but also short dsRNA fragments. [29] Host ssRNA cannot be recognized through this receptor because of the presence of the methyl guanosine cap or a monophosphate at the 5’ end.

“Endosomic” receptors consist of members of the Toll-like receptor [TLR] family, which detect viral nucleic acids in endosomes and only in specialized cell types.

Nine TLRs have been identified in humans, of which three (TLR3, TLR7 and TLR9) recognize nucleic acid components and stimulate type I IFN production. Interestingly, TLR expression is also regulated by IFNs, further highlighting the amplifying principle of the IFN response.[30] The TLR “endosomic” mode of recognition does not require that the IFN-producing cells are infected themselves and hence does not need to be ubiquitous. [31]

Four IRF family members (IRF1, IRF3, IRF5 and IRF7) are positive regulators of type I IFN production. These molecules regulate transcription at distinct type I IFN loci, thereby determining which type I IFN subtypes are expressed in the initiation and propagation of the IFN response.[32]

Type I IFN induction is mediated by an initial complex composed minimally of TRAF3, NEMO (IKKγ) and TANK; this complex controls the activity of noncanonical kinases TBK1 and IKKε that specifically phosphorylate transcription factors IRF3 and IRF7, leading to their dimerization and nuclear translocation, and transcriptional activation of type I IFN genes.

IRF3, but not IRF7, is produced constitutively in nucleated cells; IFN-B activates IRF7 transcription promoting a positive feedback loop that ends up with stimulation of all types of IFN-alpha and also IFN Beta. Plasmocytoid DCs express IRF7 constituvely, explaining why they are a potent source of IFN-I.

Both IRFs and NF-κB bind to the IFNβ promoter in a temporally coordinated fashion to drive its transcription. Secreted IFNβ then binds to and activates the type I IFN receptor (a heterodimer of IFNAR1 and IFNAR2) in an autocrine or paracrine manner.

Role in immune regulation and cellular networks

Type I IFNs are the main players in defense against viral infection. Their effects go beyond directly killing viral-infected cells; they also orchestrate also adaptive immune responses. IFN-inducible genes (about 1000) participate in different biological processes, such as cell metabolism, cell survival, proliferation and tissue repair. [33] Particularly, production of IFNβ is very important because it induces other cells (infected or non-infected) to make IFNα, thus amplifying and maintaining the IFN response.

The regulatory effects of type I IFNs on innate immune cells occur at several stages of differentiation, including the pluripotent HSC, immature and mature DC. Type I IFNs do not only regulate innate but adaptive immune responses too. IFN-I can directly influence immune cells through IFNAR or, indirectly, by inducing chemokines for recruitment of immune cells to the site of infection. IFN-I induce secretion of a second wave of cytokines like IL-15 that regulate NK and memory CD8+ T cell numbers and activities. NK cells show low responsiveness to IFN-I, instead, they are stimulated by IL-15-trans presented by IFN-I activated DCs.[34, 35] Also, type I IFN - dependent release of IL-15 leads to rapid and efficient memory CD8+ T cell response in a TORc1 dependent manner.[34]

IFNs are critical for the stimulation DCs, enhancing its capability to present antigens, and for the activation of naïve T cells.[22] Beside immune cells, type I IFNs can regulate the lifespan of various other cell types. For example, IFN-I have been reported to trigger apoptosis of tumor cells as well as virus-infected cells.

On the one hand, cytotoxic T cells are induced to proliferate by type I IFNs. Additionally, IFNs also stimulate production of the chemokines CXCL9, CXCL10 and CXCL11, which attract CTL (cytotoxic lymphocytes) to the sites of infection. The

expression of MHC class I molecules is increased on all types of cells due the type I IFNs – so making the recognition of infected cells more easy.

In contrast, IFN-αβ seem to have a potent antiproliferative and proapoptotic effects on T cells[36], which is contradictary to the clonal expansion of effector T cells during infection when large amounts of IFNs are produced. It can be that early in the antiviral response, T cells are under the control of regulatory processes that downregulate the transcriptional response to IFNs, thereby facilitating proliferation of effector cells.[37]

Type I IFNs regulate CD4+ T helper cell development. IFN-αβ contributes to various functions of T helper type 1 (Th1) cells, particularly the secretion of interleukin-2 (IL-2) by memory cells. Conversely, IFN-αβ restricts the development of alternative populations such as Th2 and Th17. [38]

The antiproliferative and proapoptotic effects of IFN-αβ are associated with a variety of molecular changes, including increases in both cyclin kinase inhibitors and several proapoptotic molecules (Fas/FasL, p53, Bax, Bak) as well as with activation of procaspases 8 and 3. [36]

Type I IFNs also exert a variety of effects on the development and function of B cells. Thus, IFN-αβ enhance BCR-dependent mature B2 cell responses and increase survival and resistance to Fas-mediated apoptosis.[39]

Signaling by IFNAR, acting directly or indirectly through other cytokines/chemokines, is also required for normal development and proliferation of the B1 subset[40], which is thought to be a major producer of autoantibodies. Moreover, type I IFNs, acting indirectly through DC activation, exert strong adjuvant effects by markedly enhancing antibody responses and promoting Ig isotype switching.[41]

IFNs-I also affect monocyte and/or macrophage function and differentiation. Thus, IFNs-I markedly support the differentiation of monocytes into DC with high capacity for antigen presentation, stimulate macrophage antibody-dependent cytotoxicity, and positively or negatively regulate the production of various cytokines (e.g., TNF, IL-1, IL-6, IL-8, IL-12, and IL-18) by macrophages [42]In addition, autocrine IFN-I is required for the enhancement of macrophage phagocytosis by macrophage colony-stimulating factor and IL-4 [43]and for the lipopolysaccharide-, virus-, and IFN-γ–induced oxidative burst through the generation of nitric oxide synthase 2.

Role in host defense and autoimmunity

Type I IFNs are critical for the host innate and adaptive immune responses against several pathogens, mainly viruses. Its relevance as a defense mechanism varies according to host (genetics) and pathogen factors. IFN-I are necessary for eradication of most viral infections, but dispensable in some cases[44]. A negative effect on elimination of some intracellular bacteria, fungi and, surprisingly, in some chronic viral infections have been described (Reviewed in[45]). Novel pathways of type I IFN-mediated immunoregulation are being discovered. Deficient mice of the IFN-stimulated gene cholesterol 25-hydroxylase overproduce inflammatory interleukin-1 (IL-1) family cytokines and are more resistant to infection by the intracellular bacteria *Listeria monocytogenes.*[46]

Several lines of evidence strongly suggest that these cytokines are directly activating cells and effector pathways of pathogenic significance in systemic autoimmune disease. Type I IFNs promote DC activation and, then, enhance its capability of antigen presentation to autorreactive T cell clones. Thus, viral infections may boost autoimmune responses under an inflammation context.

Compelling evidence supports raised levels of type I IFN in systemic autoimmune diseases, but also in organ-specific conditions. Elevated type I IFN levels in the serum of patients with systemic autoimmunity were described in 1970th [47] but were largely ignored. The involvement of INF-α in autoimmunity was first suggested by Rönnblom and colleagues. They demonstrated that elevated serum IFN-α levels could be driven by immune complexes.[48,49] IFN was produced, when immunoglobulin from patients with systemic lupus erythematosus (SLE) was combined with plasmid DNA or apoptotic cells and added to peripheral blood mononuclear cells (PBMCs),

Subsequently, Blanco and colleagues[50] demonstrated that serum from patients with SLE was capable of inducing the maturation of monocytes into DCs in an IFN-α-dependent manner. Chronic DC maturation in the presence of increased IFN levels might have a central role in autoimmunity by activating autoreactive T cells to drive the autoimmune destruction of target tissues. The capacity of self-antigen-containing immune complexes to stimulate IFN production further contributes to a self-propagating loop of tissue damage.

Recently, novel immune mechanisms that lead to IFN-I release in response to host nucleic acids have been discovered, wherein, these cytokines set up an appropriate

scenario for antigen presentation and proliferation of auto-rreactive lymphocytes. In psoriatic patients, it has been demonstrated that antimicrobial peptide secretion, secondary to skin infection, promotes autoimmune responses. Coupling of LL-37 with host nucleic acids enhance pDC stimulation and IFN release.[51] As demonstrated in this first study, other types of antimicrobial peptides linked to self-RNA or -DNA can enhance autoimmune responses in systemic diseases.[52, 53] Structural features of antimicrobial peptides, which share cationic properties, permit to activate TLR9[54]

In some patients treatment of chronic viral disease or malignancy with high-dose IFN has been associated with the generation of autoimmunity. The autoimmune phenomena that manifest are quite diverse, ranging from the induction of autoantibodies to the development of autoimmune diseases including SLE, polymyositis, and rheumatoid arthritis (RA). [55]

Interestingly, the autoimmune symptoms that manifest can resolve after the cessation of treatment,[56] suggesting that, although type I IFNs can initiate symptoms of autoimmunity, additional factors are required for the initiation of a self-propagating loop. Additionally, low IFN levels are found in most patients in multiple sclerosis. [57]

It should be noted, that IFN-α and IFN-β are widely used in the clinical practice for treatment of hairy cell leukemia, malignant melanoma, AIDS-related Kaposi‘s sarcoma, hepatitis C infections, multiple sclerosis, genital warts, hepatitis C with HIV coinfection, hepatitis B, general viral infections, myelogenous leukemia, cutaneous T-cell lymphoma, follicular non-Hodgkin’s lymphoma, renal cell. [58, 59] Several drugs are registered, namely: Infergen (IFN--α-con-1), Alferon-N (IFN--α-n3 leukocyte derived), Roferon-A (Recombinant IFN-α-2a), Intron A (Recombinant IFN--α-2b), PEG Intron (PEG recombinant IFN--α-2b) and Avonex (IFN-β-1a). Additionally, they are tested in clinical trials for safety and potential treatment of lymphomas[60] and hepatocellular carcinoma, [61, 62]

Role in allergic disease

The importance of IFN-αβ-mediated suppression of allergic T cell subsets is underscored by studies demonstrating that pDCs from asthmatic patients secrete less IFN-αβ than healthy donor pDCs in response to viral infections and toll-like receptor (TLR) ligands.[63, 64] Similarly, impaired IFN-β levels, in response to rhinovirus infection, were found in epithelial cells from asthmatic children. [65] The cause of this deficiency is partially understood. Recently, Gielen *et al.* observed an upregulation of

supressor of cytokine signalling (SOCS), an inhibitor of IFN-I production, in bronchial epithelial cells of asthmatic patients.[66]

Likewise, Gill et al.[67] compared the induction of IFN-a by influenza virus in pDCs isolated from patients with asthma or healthy subjects and found that influenza virus infection promoted significantly less IFN-α secretion by pDCs from patients with asthma patients.

It has been suggested that the reduction in IFN-αβ secretion during upper respiratory viral infections may lead to exacerbated lung pathology in those with asthma because of the inability of innate secretion of IFN-αβ to control viral replication in the lungs.[63]

IgE cross-linking significantly reduced TLR9 expression, resulting in decreased IFN-α production in response to CpG DNA. These results are intriguing because they suggest that sensitization with allergens may block IFN-α secretion during viral infections. Moreover, Gill et al. [67] demonstrated that IgE, but not IgG, cross-linking significantly reduced IFN-α secretion from pDCs in response to both influenza A and B virus infection.

Type I IFNs elicit different mechanisms that may be protective from exaggerated Th2/IgE responses. IFN-αβ promotes IL-21 secretion, which is reported to negatively regulate both IgE production and allergic rhinitis.[68-70] These findings are supported by early studies demonstrating that IFN-αβ can suppress IgE class switching during B-cell priming.[71, 72]

Huber *et al.* found that type I IFNs block GATA-3 activation and, in turn, Th2 development. In the same manner, they inhibit cytokine secretion from committed Th2 cells. [73] An additional mechanism for dampening Th2 responses is IFNbeta-mediated upregulation of IL13R-alpha2 expression in primary fibroblasts with functional consequences in allergic reactions. Since this alternative IL-13 receptor does not induce the typical Th2 effects of this cytokine, stimulation of IFN-beta production by dsRNA was accompanied by a reduction of eotaxin expression.[74]

IFNAR-deficient mice and inactivated IFN-β gene mice

In the beginning of 1990s, mice models lacking the type I IFN-α/β receptor (A 129)[1], type II IFN-γ receptor (G 129)[75] or both types of IFN receptors (AG 129) were first developed.[76]

IFNAR-deficient mice are completely unresponsive to type I IFNs. These mice

show no overt anomalies but are unable to cope with viral infections[1] and they are more vulnerable to develop autoimmune disease of the central nervous system (CNS).[77]

Lena Erlandsson *et al.* generated a mouse strain with an inactivated IFN-β gene in 1998.[78] The mice produce neither IFN-β nor IFN-α upon Sendai virus infection. The heterologous sequences were grafted onto the IFN-β coding sequence, eliminating the region encoding the first 4 amino acids and no expression of the IFN-β protein was detected from the modified locus.

IFN-¥=

Discovery and structure

The unique member of the type II interferon family, IFN-γ, was first identified in the 1960s for its distinctive antiviral activity against the Sindbis virus in human leukocyte cultures. [79] Both human and mouse IFN-γ proteins are encoded by a single gene copy. The human *IFNG* gene is located on chromosome 12 and mouse gene on chromosome 10. [80-82] Interestingly, IL-22 is located in close vicinity of the *IFNG* gene into the same genomic locus both in human and mouse. Despite the fact that the genomic structure of the *IFNG* gene is highly conserved among vertebrates and consists of 4 exons and 3 introns, the interaction of IFN–γ and its receptor is species-specific and is restricted to the receptor extracellular domains. The human IFN-γ protein precursor contains 166 residues and includes a cleavable hydrophobic signal sequence of 23 amino acids. An active form of the IFN–γ protein is 34kDa homodimer that is formed by anti-parallel inter-locking of the two monomers, each consisting of a core of six α-helices and an extended unfolded sequence in the C-terminal region. [83-85]

Receptor and signaling

Active homodimer of IFN-γ interacts with heterodimeric receptor consisting of ligand-binding chains, designated as IFNGR1 or IFNGR α, and signal-transducing chains, known as IFNGR2 or IFNGR β, with a 1:2:2 stochiometry. [86, 87] The *IFNGR1* and *IFNGR2* genes are located on chromosome 6 and chromosome 21 in human and on chromosome 10 and 16 in mouse, respectively. [85, 86, 88] Both chains belong to the class II cytokine receptor family and IFNGR2 is usually the limiting factor in IFN–γ

responsiveness, since the IFNGR1 chain appears to be constitutively expressed. Due to the lack of intrinsic kinase or phosphatase activity, the IFNGR1 chain is persistently associated to JAK1 and the IFNGR2 chain to JAK2, in order to assure the signal transduction. IFN–γ signaling leads to the phosphorylation and homodimerization of the STAT1 protein, translocation of the homodimer into the nucleus, and its binding to the promoters containing a defined gamma activated site (GAS) to initiate the transcription. Interferon regulation factors (IRF) family members, including IRF-1, IRF-2, IRF-7 and IRF-9 are also involved in IFN–γ signaling.[89-92] In addition, coordination and cooperation of multiple distinct signaling pathways, including the mitogen-activated protein kinase p38 cascade, phosphatidylinositol 3-kinase (PI3K) cascade and ATF6-C/EBP-β signaling pathway are needed for generation of appropriate cellular response to IFN–γ.[93, 94] On the other hand, IFN–γ appears to suppress other signaling pathways, such as activation via IL-4, IL6 and TGF–β receptors and TLRs.[95]

A recent study has shown that IFN-γ signaling also primes promoter and enhancer regions genome wide via inducing histone acetylation. This effect is mediated through genome wide occupation of transcription factor binding regions by activated STAT1 and IRF-1. This priming of chromatin encompasses the key inflammatory cytokine genes *TNF, IL6* and *IL12B*, demonstrating an important role for IFN-γ signaling an epigenetic function for augmenting TLR responses.[96]

Cellular sources and regulation

In contrast to type I interferons, which can be expressed by all cells, the expression of IFN-γ is restricted to certain immune cells.[93] Number of cell population from both the innate (e.g. NK cells, NKT cells, macrophages, myelomonocytic cells) and adaptive immune systems (e.g. T_h1 cells, CTL and B cells) can secrete IFN-γ. Its production is controlled by APCs-secreted cytokines, mainly IL-12 and IL18. IL-12 promotes the secretion of IFN–γ in NK cells and the combination of IL-12 and IL-18 further increases IFN-γ production in macrophages, NK cells and T cells. The T_h2 inducing cytokine IL4, as well as IL-10, TGF-β and glucocorticoids, negatively regulate the production of IFN-γ.[97]

The expression of IFN-γ is tightly regulated. The promoter and introns of the *IFN-¥* gene contain binding sites for ATF-2, NF-κB, AP-1, YY1, NF-AT, STAT and T-box type transcription factors.[98] In T_h1 and NK cells, T-bet, a transcription factor

responsible for T_h1 commitment is important for production of IFN-γ.[98] However, T-bet also recruits Bcl-6 to the IFN-γ locus, which suppresses IFN-γ expression in late stages of T_h1 differentiation, possibly to prevent the overproduction of IFN-γ. [99] In CD8 T cells, T-bet apparently does not influence expression of IFN-γ. Instead, a transcription factor NFAT1 up-regulates IFN-γ production after activation via TCR. [100] However, another study demonstrates that T-bet and Runx3 transcription factors cooperatively regulate IFN-γ production $CD8^+$ T cells. [101] In NK cells, inhibitor of κB-ζ (IκBζ), a Toll-like receptor (TLR)/ interleukin-1 receptor (IL-1R) inducible transcription factor is a necessary factor that directly binds to IFN–γ promoter and regulates its production in response to stimulation by IL-12/IL-18. [102] As recently demonstrated in T-bet-ZsGreen reporter mouse strain, IL-12 induces transcription factor T-bet and STAT4 and this is critical for IFN-γ production and T_h1 responses in mice infected with Toxoplasma gondii. [103] Another negative regulator, Twist1, forms complex with Runx3 and abolishes Runx3 and T-bet binding at the *Ifng* locus and IFN-γ production. [104]

In addition, the *IFN-¥* gene locus in controlled by epigenetic modifications and IFN-γ production is regulated via post-transcriptional mechanisms. For instance, very recent study demonstrates that histone methylase SUV39H1, which participates in the trimethylation of histone H3 on lysine 9, a modification that leads to transcriptional silencing, is important for silencing of the *IFN-¥* gene and other T_h1 loci, ensuring T_h2 lineage stability. [105] Another study shows that IFN-γ mRNA is destabilized by RNA-binding protein Tristetraproline (TTP) and this results in reduced production of IFN-γ. [106] Recently; it has been also shown that miR-29 controls the level of IFN-γ by direct targeting of IFN–γ mRNA. [107]

Role in immune regulation and cellular networks

As a member of the interferon family, IFN-γ is one of the most potent cytokines for mobilizing antimicrobial effector functions against intracellular pathogens. IFN-γ exerts its antiviral effects mainly via the induction of key antiviral enzymes including the double stranded RNA activated protein kinase (PKR), 2'-5' oligoadenylate synthetase (2-5 synthetase) and the ds RNA specific adenosine deaminase (dsRAD). [108-110] In contrast to type I interferon response that is triggered directly by viral infection, IFN-γ rather acts as a secondary mediator and the immunomodulatory

activities of IFN-γ are also important during the development of adaptive immune response for the establishment of an antiviral state.

IFN-γ coordinates a broad range of biological functions. As the major product of fully differentiated T_h1 cells, IFN-γ promotes cytotoxic activity by both direct and indirect mechanisms. Directly, together with IL-12 and IL-27, IFN-γ participates in the events taking place during the commitment of naïve $CD4^+$ T cells towards a T_h1 phenotype.[111] Indirectly, IFN-γ can regulate antigen processing, and via its ability to inhibit cell growth, IFN-γ can reduce the T_h2 cell population, and thus, contribute to the T_h1 cell differentiation.

Another important physiological role of IFN-γ is its capability to up-regulate MHC class I and II proteins and the related factors, which is compulsory for the recognition of infected cells by the immune system. Within the class I antigen-presentation pathway, IFN-γ induces expression of new proteasome subunits, LMP2, MECL-1 and LMP7, to form an inducible proteasome. This is a mechanism by which IFN-γ can increase the quantity, the quality and the repertoire of peptides for class I MHC loading. [111] IFN-γ also induces the proteasome regulator PA28, which associates with the proteasome and alters proteolytic cleavage preference and allows more efficient generation of TAP- and MHC- compatible peptides to increase the overall efficiency of class I MHC peptide delivery. [112] In addition to inducing TAP transporter that is vital for the transport of the peptide from the cytosol to the ER lumen, IFN-γ also up-regulated class I MHC complex. [113]

IFN-γ can also promote activation of CD4+T cells via up-regulation of class II antigen-presenting pathway in professional and non-professional APCs. By inducing the expression of several key proteins, IFN-γ up-regulates the quantity of peptide:MHC class II complexes on the surface of the cell. Among these, there is the constituents of the MHC complex itself, lysosomal proteases cathepsins B, H and L that are implicated in peptide production, DMA and DMB that function to remove CLIP from the peptide binding cleft to render it available to peptide loading, and a key transcription factor for the regulation of expression of genes involved in the MHC II complex, class II transactivator (CIITA). [114-116]

Other important features of IFN-γ are the inhibition of cell growth and capability to induce cell death. IFNs inhibit proliferation primarily by increasing protein levels of cyclin-dependent kinase inhibitors (CKI) of the Cip/Kip family. IFN-γ induces the CKI

p21 and p27 that inhibits the activity of CDK2 and CDK4, respectively, causing the cell cycle to arrest at the G1/S checkpoint.[117-120] IFN-γ treatment of cells bearing high levels of IFNGR can induce apoptosis in an IRF-1 dependent manner via activation of IL-1β-converting enzyme caspase-1.[121] IFN-γ also induces a number of other pro-apoptotic proteins, including the antiviral enzyme PKR, the death associated DAP factors and cathepsin D. IFN-γ may enhance cell sensitivity to apoptosis by increasing the surface expression of Fas/Fas ligand and of the TNF-α receptor. [122-124] Concordantly, IFN-γ is capable of modulating the immune responses by controlling activation-induced cell death (AICD) of $CD4^+$ T cells through signaling via the death receptor Fas. [125] $CD4^+$ T-cells that lack IFN-γ or STAT1 are resistant to AICD and IFN-γ was proposed to increase $CD4^+$ T-cells apoptosis through a mitochondrial pathway, which requires the production of caspases.[126] Retrovirus-mediated expression of caspase-8 could restore the sensitivity of Stat1-deficient T-cells to AICD.[125] However, a recent study challenged this mechanism of action of IFN-γ by showing a function for IFN-γ in controlling $CD4^+$ T cell death in ways that do not seem to involve Fas or its ligand and neither to require the production of caspases.[127] This study suggests that mycobacterial infection-induced $CD4^+$ T cell death occurs due to autophagy and that Irgm1, also called LRG47, is an interferon-inducible GTPase that seems to suppress IFN-γ-induced autophagy in $CD4^+$ T cells. The expression of several members of the family of the anti-apoptotic protein Bcl-2 was not affected by either IFN-γ or the absence of Irgm1, which suggests a lack of involvement of the mitochondrial cell death pathway.

Production of IFN-γ by activated monocytes also significantly upregulates TRAIL receptors of NK cells, increasing the cytotoxicity of tumour localized NK cells against TRAIL-sensitive tumour cells; such as breast cancer or prostate cancer. [128] IFN-γ can also contribute to cancer pathogenesis by affecting cell proliferation. A recent study has shown that IFN-γ secreted by cytotoxic T cells contributes significantly to the proliferation of chronic myeloid leukemia stem cells (LSCs). Additionally, inhibitory molecules PD-L1 and PD-L2 are upregulated on LSCs in response to IFN-γ signaling; contributing to the immune escape capabilities of LSCs. [129] IFN-γ stimulation also results in PD-L1 upregulation on neutrophils, which allows PD-L1 mediated suppression of lymphocyte proliferation by neutrophils during bacterial

infections. This is the first *in vitro* study documenting an immunosuppressive capability of IFN-γ. [130]

In addition to its role in the development of a T_h1-type response, IFN-γ plays a role in the regulation of local leukocyte-endothelial interactions. IFN-γ regulates this process by up-regulating expression of numerous chemoattractant (e.g., IP-10, MCP-1, MIG, MIP-1a/b and RANTES) and adhesion molecules (e.g., ICAM-1 and VCAM-1). [131-135] Moreover, IFN-γ causes major changes in gene expression program in epithelial cells influencing the expression of up to several thousands of genes. For instance, 3530 genes were reported to be differentially expressed in human IFN-γ treated keratinocytes compared to non-treated cells, whereas more than 800 genes were induced more than 2-fold. [136]

IFN-γ was originally called ‘macrophage activated factor’, and enhanced microbial killing ability is observed in IFN-γ treated macrophages. IFN-γ induces the anti-microbial function of macrophages and neutrophiles by induction of the NADPH-dependent phagocyte oxidase (NADPH oxidase) system (called "respiratory burst"), production of NO intermediates, tryptophan depletion, and up-regulation of lysosomal enzymes. [137, 138] IFN-γ can effectively prime macrophages to respond to LPS and other TLR agonists since TLR4 transcription and subsequent surface expression are increased by IFN-γ. LPS-dependent signaling is enhanced by IFN-γ via the induction of MD-2 accessory molecule, MyD88 adaptor, and IRAK expression. [139, 140] IFN-γ was recently identified as a modulator of the cooperation between TLR and Notch pathways. By inhibiting Notch2 signaling and downstream transcription, IFN-γ abrogates Notch-dependent TLR-inducible genes, which represents another means how IFN-γ can modulate effector functions in macrophages. [141]

Functions as demonstrated in transgenic mice

Despite the important functions of IFN-γ in the immune system, both *Ifn-γ* $^{-/-}$ and *Ifngr*$^{-/-}$ mice showed no obvious developmental defects and their immune system appeared to develop normally. [75] However, these mice show deficiencies in natural resistance to several bacterial, parasitic, and viral infections. *Ifn-¥*$^{-/-}$ mice are characterized by suppressed splenic NK cells activity, uncontrolled splenocyte proliferation, reduced expression of the MHCII proteins and antimicrobial factors in macrophages. *Ifngr*$^{-/-}$ mice show a deficiency in IgG2a production, increased susceptibility to vaccinia virus, *Listeria monocytogenes*, pseudorabies virus,

Mycobacterium bovis and increased resistance to endotoxic shock. [142-146] Localized site inflammation, lymphocyte infiltration and severe tissue destruction has been observed in transgenic mice overproducing IFN-γ, such as *Socs1*$^{-/-}$ and *miR-146a*$^{-/-}$ mice. [147, 148] By using the sanroque mouse model of lupus, it has been shown that decreased *Ifng* mRNA decay caused excessive IFN–γ signaling in T cells and led to accumulation of follicular T cells, spontaneous autoantibody formation, and nephritis. [69]

Role of IFN-¥ in human diseases

Because IFN-g is a multipotent cytokine that plays an important role in both the innate and the adaptive immune response, it is not surprising that its deficiency is associated with the pathogenesis of several diseases. Therefore, use of bioengineered IFN-γ (Actimmune) is common clinical strategy for treatment of chronic granulomatous disease[149] and osteopetrosis.[150] Moreover it has been shown to be effective in atopic dermatitis treatment[151] and is tested in clinical trials for Friedreich's Ataxia, [152, 153] Pulmonary Fibrosis,[154-156] among others. On the other hand, IFN-γ neutralization by using humanized mAbs (Fontolizumab) is a clinical strategy for treatment of Crohn's disease [157]. Additionally, Fontolizumab was tested in phase 2 clinical trials for potential use in rheumatoid artritis, however the study was terminated.[62]

Low levels of IFN-γ correlate with an increased susceptibility to intracellular pathogen infection with subsequent tissue destruction, as well as tumour development. Patients with acquired IFN-γ deficiency; which is caused by serum auto-antibodies that specifically neutralized the biological activity of IFN-γ, show defects in the T_h1-cytokine pathway together with disseminated tuberculosis and non tuberculous mycobacterial infections. [158-161] On the other hand, early IFN-γ production in response to live parasite stimulation correlates with a protective immunity to symptomatic malaria in Papua New Guinean children. [162]

IFN-γ may also play an important role in the pathogenesis of type 1 diabetes as suggested by the decreased levels of IFN-γ were observed in newly diagnosed diabetic patients.[163] The cellular arm of the immune system is implicated in the pathogenesis of the disease and diabetes can be induced by the transfer of T_h1 $CD4^+$ T-cells expressing cytokine in a non-obese mouse model of autoimmune diabetes

(NOD). Decreased apoptosis of activated T-cells in NOD mice is a feature or the outcome of the loss of IFN-γ-mediated immune suppression. [164]

Depending on cellular environment, IFN-γ can either induce or restrict the development of autoimmunity. For instance, arthritis onset and severity are reduced under conditions, where IFN-γ is neutralized or in mice deficient in IFN-γ, suggesting a role of IFN-γ in the initiation of the disease. [165] In another model of autoimmune disease, in experimental autoimmune encephalomyelitis (EAE), the disease is enhanced in IFN-γ-deficient mice. [166, 167] IFN-γ can also inhibit the inflammatory process at a later stage of the disease and it was proposed that this was due to the ability of IFN-γ to suppress IL-17 secretion. However, it seems that IL-17 production is dispensable for the exacerbation of the disease and that IFN-γ mediates this inhibition via its anti-proliferative and pro-apoptotic effects on activated T-cells. [166, 168]

Since the biological effects of IFN-γ are widespread, the polymorphisms in the *IFN-¥* or *IFNGR* genes have been shown to be associated with susceptibility to several diseases, including pulmonary tuberculosis, multiple sclerosis, myasthenia gravis and arthritis manifestation. In addition, mutation in the IFN-γ gene has been shown to lower the body's ability to resist mycobacterial infection. [169]

Complete *IFNGR1* deficiency is due to homozygous recessive mutations or to heterozygous mutations affecting the extracellular domain of the IFNGR1 protein and preventing the expression of the receptor at the cell surface.[170] In the patients with mutations in *IFNGR2*, the cell surface expression of IFNGR1 is normal, but functional response to IFN-γ is lacking. [171, 172] Individuals with mutations in the human *IFNGR1* or *IFNGR2* genes that lead to defective expression or function of the IFN-γ receptor, show severe susceptibility to poorly virulent mycobacteria and often acquire a bacillus Callmette-Guerin infection. [173]

Development of allergic diseases and atopic state have been associated with poor function of IFN-γ or the receptors. Gene variants of *IFN-¥* and *IFNGR1* have been shown to be associated with atopic dermatitis complicated by Eczema Herpeticum. [174] Concordantly, DCs from patients with atopic dermatitis have reduced IFN-γ receptor expression and attenuated IFN-γ response. [175] It has been proposed that T_h2 dominance in atopic patients is caused by selective activation-induced cell death of high IFN-γ-secreting T_h1 cells in peripheral blood that skews the immune response

towards surviving T_h2 cells. [176] In asthma, IFN-γ expression in airways was found to be a strong distinguishing factor for aspirin-tolerant asthma and aspirin-exacerbated respiratory disease (AERD). AERD is characterized by a high expression of IFN-γ in comparison to aspirin-tolerant asthma, alongside a T_h2 cytokine profile. Immunohistochemistry staining showed that the main source of IFN-γ in AERD to be eosinophils. [177] The expression of IFN-γ in airways contributes significantly to upregulation of CysLT production by eosinophils infiltrating airway tissue in AERD patients and leads to increased severity of its inflammatory features.[177] Pro-inflammatory effects of IFN-γ in asthmatic lung are counter balanced by IL-22; and IL-22 is capable of decreasing IFN-γ-induced CCL5/RANTES, as well as MHC I, MHCII and ICAM-1 in asthmatic lung epithelial cells. [178]

Similarly to autoimmunity related chronic tissue inflammation, enhanced level of IFN-γ appears to influence inflammatory processes in the epithelial cells in the chronic phase of allergic inflammation, whereas IFN-γ most probably is the main cytokine responsible for eczema formation in atopic dermatitis causing apoptosis of keratinocytes. [179-183] IFN-γ also plays role in chronic epithelial inflammation related to asthma and chronic sinusitis. [184]

TNFα

Discovery and structure

The history of tumor necrosis factor α (TNF-α) begins at the end of the 19th century, when Dr. William B. Coley used a bacterial extract of heat-killed *Streptococcus pyogenes* and *Serratia marcescens* to induce tumor necrosis in sarcoma patients.[185, 186] Variations of this formula, later known as Coley's toxins and representing one of the first forms of immunotherapy, were in use for treatment of various types of cancer until mid-20th century with more or less success. In accordance with previous observations in patients with spontaneously regressing tumors, the regression of tumors in patients receiving Coley's toxins was accompanied by a severe systemic inflammatory reaction. Today we know that one of the key inflammatory molecules causing this reaction was TNF-α. Identified in 1975, this cytokine was first described as TNF, a protein factor in the serum of mice infected with bacillus Calmette-Guérin (BCG) and treated with LPS that caused hemorrhagic necrosis of different transplanted tumors *in vivo* and cytolysis of a

mouse fibrosarcoma cell line *in vitro.*[187] Several years later the protein inducing wasting (cachexia) and septic shock in mice was purified from the supernatant of endotoxin-treated macrophages.[188-190] This protein, at the time named cachectin, was soon revealed to be identical to TNF-α.[191]

In 1985 human TNF-α gene was cloned and expressed.[192-195] It is located in region 6p21.3 of chromosome 6 as a single copy 3-kb gene consisting of 4 exons. Its promoter region contains several binding sites for the transcription factor nuclear factor kappa B (NF-κB). TNF-α exists as two protein forms associating into homotrimers[196]: the 26-kd membrane-bound form (mTNF-α), a type II integral membrane protein, and the 17-kd soluble form (sTNF-α).[197] sTNF-α is generated by proteolytic cleavage of mTNF-α mainly by TNF-α converting enzyme (TACE, ADAM17)[198] at the cell surface. If not emphasized otherwise, TNF-α usually refers to the soluble form of this cytokine.

Cloning of lymphotoxin (LT) and TNF cDNAs revealed structural and functional homology between the two proteins. This led to the renaming of TNF to TNF-α and LT to TNF-β. Along the same line, LT-β was renamed to TNF-C. Today these alternative names for LTs are not frequently used and there are opinions that TNF-α should again be called by its original name TNF.

Receptor and signaling

TNF-α binds specifically to two cell-surface receptors: TNFR1 (p55/60, CD120a) and TNFR2 (p75/80, CD120b), two structurally related, but functionally somewhat distinct receptors. They are single transmembrane glycoproteins with elongated extracellular domains containing four cysteine-rich repeat motifs. Each of the two receptors binds both mTNF-α and sTNF-α. However, TNFR1 can be fully activated by both mTNF-α and sTNF-α, while TNFR2 can only be efficiently activated by mTNF-α. Upon interaction with their ligands, both TNFR1 and TNFR2 form a homotrimer, which initiates subsequent signaling pathways. Intracellular regions of TNFR1 and TNFR2 differ significantly, suggesting that the two TNFRs signal through distinct molecular interactions.

Signaling through TNFR1 is mainly associated with pro-inflammatory, cytotoxic and apoptotic responses and plays a critical role in host defense against microbes and their pathogenic factors. Upon receptor-ligand binding the death domain of TNFR1 interacts with TNF receptor-associated death domain (TRADD) adapter protein. Following TRADD activation, three pathways can be initiated[199-201]: apoptotic,

NF-κB or MAPK/AP-1 pathway. In case of programmed cell death pathway initiation, TRADD recruits downstream Fas-associated death domain (FADD) adapter protein and initiates the signaling pathway leading to recruitment and activation of proteins of the caspase cascade (caspase 8, caspase 10 and effector caspases). However, apoptosis induced by TNF-α plays only a minor role in the repertoire span of TNFR1, especially compared to the strong inflammatory response it can trigger, and is often masked by anti-apoptotic effects of NF-κB activation. When initiating a pro-inflammatory cascade, TRADD recruits two types of adapter molecules, the receptor interacting protein (RIP) and the TNF receptor-associated factors (TRAFs), which initiate the signaling cascade leading to the activation of gene transcription via transcription factors NF-κB and AP-1. Some of the genes whose transcription is activated include molecules important for cell survival, proliferation and differentiation, pro-inflammatory cytokines and chemokines, growth factors and TNF-α itself. There is an extensive cross-talk between these two opposite pathways, one of them leading to programmed cell death and the other to cell activation and potent inflammatory response. For instance, NF-κB enhances the transcription of inhibitory proteins that interfere with the apoptotic pathway and on the other hand, activated caspases cleave several components of the NF-κB pathway. The fine balance between the two pathways can be shifted towards one or the other by many factors, such as cell type, cytokine stimulation etc. Further, recent studies have shown that there is another programmed death pathway, necroptosis, depending on activity of TGF-β–activated kinase 1 (TAK1) and RIP kinase 3 (RIPK3).[202-204] The result of such finely tuned cross-connection between the two complex signaling pathways is the appropriate response of various cell types and conditions harboring diverse functions upon TNF-α release in inflammation.

For a long time the importance of TNFR2 signaling was rather neglected in favor of TNFR1, but recently its role is ever more acknowledged. It is now known that although it plays a role in both, TNF-α-induced cell activation and TNF-α-induced apoptosis, it is still mainly associated with cellular activation, proliferation and migration. Because it requires mTNF-α binding for activation, it plays an important role in TNF-α signaling in cell-to-cell contact, a fact which was very often neglected because of routine use of sTNF-α as cell culture stimulus in lab conditions. Since it has no death domain, TNFR2 typically engages TRAFs directly, which then leads to

the activation of NF-κB and AP-1. In mediating apoptosis it also does it directly through interaction with RIP leading to the activation of caspase cascade.

As a mechanism to keep inflammation under control, extracellular portions of TNFRs can be released from the cell surface upon cell activation or injury. The soluble TNFRs, which retain the property of binding TNF-α, can then dampen the TNF-α activity by competing for TNF-α binding with the TNFRs associated to the cell membrane and thus neutralizing excess TNF-α.

Cellular sources and targets

Many potentially harmful stimuli of physical, chemical, or immunologic nature have the potential to induce rapid TNF-α expression. The most common inducers of TNF-α expression are LPS and other substances of microbial origin, detected by innate immune receptors such as TLRs. TNF-α is mainly produced by activated macrophages, but can also be produced by other immune cell types, such as monocytes, $CD4^+$ T-lymphocytes, B-lymphocytes, neutrophils, NK cells and mast cells. It can also be produced by non-immune cells, such as fibroblasts, astrocytes, microglial cells, endothelial cells, smooth muscle cells, adipocytes, intrinsic renal cells and others.

Differential effects of TNF-α on specific cell types are probably mediated by differential expression of TNFRs, TNFR-associated proteins and other members of signaling cascades. TNF-α targets cells that express TNFR1 - all somatic cell types with the exception of erythrocytes, and cells that express TNFR2 - mainly lymphocytes and endoepithelial cells.

Role in immune regulation and cellular networks

TNF-α is an important pleiotropic cytokine involved in host defense, regulation of immune responses, inflammation and apoptosis. Regulating immune responses it plays a double role as a pro-inflammatory mediator, initiating a strong inflammatory response, and an immunosupressive mediator, inhibiting the development of autoimmune diseases and tumorigenesis and exhibiting a vital role in maintenance of immune homeostasis by limiting the extent and duration of inflammatory processes.

TNF-α is one of the most important pro-inflammatory cytokines, mediating systemic inflammation, either by direct action or by stimulation of IL-1 and IL-6 secretion. It is a potent endogenous pyrogen, causing fever and other symptoms associated with bacterial infections, including septic shock, muscle ache, lethargy, headache, nausea and inflammation. In addition to being an important mediator of

innate inflammation, TNF-α also plays a role in the regulation of adaptive immunity, making it indispensable in mounting appropriate inflammatory response serving optimal host defense. TNF-α affect various organs and organ systems, generally together with IL-1 and IL-6. Among others, it stimulates the acute phase response in the liver, leading to an increase in C-reactive protein concentration and a number of other mediators. It induces the infiltration of inflammatory cells to the inflamed site by up-regulating the expression of adhesion molecules and increasing relevant cytokine production. TNF-α induces the synthesis of a number of chemoattractant cytokines, including IP-10, JE, KC, in a cell-type and tissue-specific manner. One of its primary targets is neutrophils. It plays an important role in neutrophil migration acting as chemoattractant and promoting the expression of adhesion molecules on endothelial cells. TNF-α also acts as neutrophil activator, enhancing their phagocytotic and cytotoxic properties and modulating the expression of Fos, Myc, IL-1, IL-6 and many other inflammation-related proteins. TNF-α also targets components of the monocyte-macrophage system, acting chemotactically on monocytes and activating macrophages. In resting macrophages it induces synthesis of IL-1, different intracellular oxidants and superoxide dismutase, inflammatory lipid prostaglandin E_2 (PGE_2), TNF-α itself etc. It also stimulates phagocytosis in already activated macrophages. In progenitors of leukocytes and lymphocytes TNF-α stimulates the expression of class I and II MHC molecules and differentiation antigens, as well as the production of IL-1, CSFs and IFN-γ. TNF-α enhances the proliferation of T-lymphocytes induced by various stimuli in the absence of IL-2. It also promotes the proliferation and differentiation of B-lymphocytes in the presence of IL-2. TNF-α is essential for the development of secondary lymphoid organ structures and follicular dendritic cells.

When it comes to its immune-regulatory properties, TNF-α can mediate autoimmunity suppression (probably through TNFR1 activation), and promote organ-specific injury (potentially through TNFR2 activation). It can especially function as an immunosuppressive mediator in chronic inflammatory and autoimmune diseases, probably acting through several cellular mechanisms. Chronic TNF-α exposure attenuates TCR signaling and down-modulates T-lymphocyte proliferation and cytokine release *in vitro* and *in vivo*, which probably prevents the development of autoreactive T-lymphocytes at sites of TNF-α-induced inflammation. TNF-α-mediated apoptosis is involved in the controlled removal of cells involved in certain types of

autoimmunity and the activation-induced apoptotic cell death of $CD8^+$ T cells, providing a potent mechanism of terminating T-cell responses. TNF-α-induced apoptosis of parenchymal cells contributes substantially to organ-specific damage, as reported in some acute non-immune nephropathies. TNF-α may also stimulate regulatory T-cell responses that induce tolerance and suppress autoimmunity. For instance, it stimulates the production of IL-10 in monocytes by up-regulation of their PD-1 levels and causes a subsequent IL-10-dependent inhibition of $CD4^+$ T-lymphocyte expansion and function[205].

Role in host defense, autoimmunity and other diseases

TNF-α plays an important role in host defense against viral, bacterial, fungal, and parasitic pathogens, in particular against intracellular bacterial infections, such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*. It is a key cytokine in induction of innate and adaptive immune responses and a crucial mediator of both acute and chronic systemic inflammatory reactions. It induces its own secretion, and stimulates the production of other inflammatory cytokines and chemokines. Grand increase in systemic TNF-α level can lead to septic shock. Local increase in TNF-α concentration causes the five cardinal signs of inflammation: heat, swelling, redness, pain and loss of function. It causes fever by acting through hypothalamus, and stimulates the synthesis of acute phase proteins in the liver. Numerous pro-inflammatory functions of TNF-α in innate and adaptive immunity include cell activation, proliferation and migration. It induces the expression of endothelial adhesion molecules and chemokines, facilitating local accumulation and subsequent activation of immune effector cells. It stimulates proteolytic enzyme synthesis and enhances microbicidal activity (including oxidative radical production) within various cell types. It also induces: angiogenesis; activation of thrombocytes and leukocytes; expression of MHC I and II molecules; increase in the affinity of adhesion receptors; maturation and migration of dendritic cells into secondary lymphoid organs; leukocyte positioning and germinal center reaction in secondary lymphoid organs; proliferation of fibroblasts and mesangial cells; up-regulation of matrix metalloproteinases; production of prostaglandins, leukotrienes, nitric oxide, and reactive oxygen species; etc.

Although pivotal for immune system development, normal immune response and homeostasis, dysregulation in TNF-α synthesis or signaling can have severe pathological consequences. Systemic or local increase in TNF-α concentration can

exert deleterious effects on the organism by inducing genes involved in acute and chronic inflammatory responses. In addition to its crucial role in the development of septic shock and systemic inflammatory response syndrome (SIRS), TNF-α has been implicated in etiology of a variety of diseases, including chronic inflammatory and autoimmune disorders (psoriasis, psoriatic arthritis, rheumatoid arthritis [RA], juvenile arthritis, ankylosing spondylitis, inflammatory bowel disease [IBD] including Crohn's disease and ulcerative colitis, systemic sclerosis, systemic lupus erythematosus [SLE]), pulmonary diseases (idiopathic pulmonary fibrosis, emphysema, sarcoidosis, acute lung injury, bacterial pneumonia), allergic diseases (asthma, allergic rhinitis, atopic dermatitis), insulin resistance, depression and cancer (including cachexia, cancer-associated chronic inflammation and tumor lysis syndrome), vascular diseases (venous thromboses, arteriosclerosis, vasculitis, disseminated intravasal coagulation), neurological diseases (multiple sclerosis, Alzheimer's disease, astrogliosis), dermathological diseases (hidradenitis suppurativa) etc.

Role in allergic disease

TNF-α activity has been extensively studied in terms of its pro-inflammatory effects, but the exact role of TNF-α in adaptive immune diseases and disorders have traditionally been less explored. However the relationship between allergic inflammation and TNF-α is now becoming more accepted. TNF-α is involved in the development of allergic diseases, particularly asthma, via production of Th2 cytokines and the migration of Th2 cells to the sites of allergic inflammation. It mediates the upregulation of endothelial cell adhesion molecules, migration and activation of mast cells, macrophages, neutrophils and eosinophils, epithelial barrier disruption and increase in airway hyperreactivity (AHR).[206]

TNF-α has been implicated in the pathogenesis of a number of inflammatory conditions in the lung, including allergic inflammation. Some reports show that Th2 inflammation can be induced by recombinant TNF-α administration and attenuated by inhibition of TNF-α signaling.[207, 208] Contrary to the before established opinion that allergic diseases are caused by strictly Th2-type immune response, it is now known that as asthma progresses and becomes more severe it adopts some characteristics of Th1 response, such as neutrophilia and TNF-α secretion. TNF-α is therefore an important pro-inflammatory mediator in airway allergic inflammation and asthma pathogenesis[209, 210], and newer studies suggest that TNF-α participates in further

polarization of Th2 cells.[211] Observations that TNF-α is released via the IgE-dependent activation of mast cells[212, 213] or sensitized human lung also suggest that TNF-α contributes to allergen-induced inflammatory responses. Increased TNF-α levels can be found in the sputum, serum, airways and BALF of asthmatic patients[214, 215], usually accompanied by increased levels of sTNFRs and IL-1RA in the serum[216] and high levels of intracellular TNF-α mRNA and protein in mast cells, eosinophils, T-lymphocytes and macrophages. Leukocytes and monocytes isolated from BALF obtained from asthmatic patients are characterized by ability to secrete higher levels of TNF-α than cells from control subjects[210]. Increased concentration of TNF-α has also been found in the BALF of sensitized and subsequently antigen-challenged animals.[217-219] Compared with patients with mild-to-moderate asthma and controls, patients suffering from refractory asthma show an up-regulation of the TNF-α axis, as evidenced by an increased expression of mTNF-α, TNFR1 and TACE by peripheral blood monocytes.[207] Moreover, the level of TNF-α in the airways of asthmatic patients increases proportionally with disease severity, making TNF-α a new promising therapeutic target in severe asthma.

TNF-α administration induces AHR in animals and humans. In healthy subjects TNF-α inhalation resulted in higher neutrophil levels in the sputum and increased AHR to metacholine.[220] TNF-α inhalation in rat model of lung inflammation also caused an increase in AHR[221] and upregulation of adhesion molecules ICAM-1 and VCAM-1.[222]

Work undertaken on mice and other animals in order to study the early effects of TNF-α in allergic inflammation shows that acute TNF-α inhibition after OVA sensitization attenuates the allergic response in a single-challenge model of allergic inflammation.[217-219] On the contrary, in the multiple-challenge OVA model chronic neutralization of TNF-α or TNFR deletion result in a comparable or even accentuated allergic response.[223, 224] These results suggest that the importance of TNF-α varies at different stages of allergic inflammation development. This was confirmed in the murine model of asthma, characterized by a biphasic late AHR. In this model, pre-challenge inhibition of TNF-α in sensitized animals resulted in abrogation of the first-phase late AHR.[225]

TNF-α and other pro-inflammatory cytokines can be detected in nasal secretions and mucosa of allergic rhinitis patients. TNF-α has also proven to be necessary for antigen-specific IgE production and the induction of Th2 cytokines and chemokines in

murine model of OVA-induced allergic rhinitis.[226] Inhibition of TNF-α in a similar model resulted in reduced local and systemic Th2 cytokine production, total and allergen-specific IgE levels, expression of adhesion molecules and eosinophil infiltration into the nasal mucosa.[227]

Increased TNF-α levels can be found in plasma[228] and epidermis[229] of atopic dermatitis patients. TNF-α secreted by epidermal resident cells (keratinocytes, mast cells and dendritic cells) plays a role in the development of skin lesions by activation of vascular endothelial cells.[230]

Functions as demonstrated in TNF-α- and receptor-deficient mice and human mutations

As expected, TNF-α- or TNFR-deficient mice show impaired defense against bacterial and viral infections. They also show an inability to control latent tuberculosis infection[231], as well as an impaired lymph node follicle and germinal center formation and absence of follicular dendritic cells.[232] Surprisingly, TNF-α knock-out mice do not seem to be more susceptible to spontaneous tumor development. Studies on TNFRs knock-out mice have demonstrated that TNF-α toxicity as well as the tumoricidal effect is in great part mediated through the TNFR1. Mice deficient in TNFR1 but still expressing TNFR2 are resistant to lethal dosages of LPS or enterotoxins but succumb readily to infections with *L. monocytogenes.*[233] At the same time they do not seem to show a shift towards an autoimmune phenotype, since the development of thymocyte and lymphocyte populations are unaltered and the clonal deletion of potentially self-reactive T-lymphocytes is not impaired.

Transgenic mice over-expressing human TNFR2 spontaneously develop SIRS, providing proof for a pro-inflammatory role of TNFR2. Knock-in mice expressing a mutated non-sheddable TNFR1 show enhanced susceptibility to inflammatory diseases. They develop spontaneous hepatitis, exacerbated TNF-α-dependent arthritis, and autoimmune encephalomyelitis. In humans, structural mutations in TNFR1 that impair its release from the cell surface result in TNFR-associated periodic syndrome, characterized by febrile episodes caused by overstimulation of TNF-TNFR signaling.

In mouse models of asthma, TNF-α-deficiency or TNFR-deficiency results in the attenuation of antigen-induced AHR and eosinophilic airway inflammation. More precisely, TNF-α deficient mice exhibit an abrogation of the first-phase late AHR in allergic asthma model[225]. TNFR-deficient mice, and TNFR1-deficient mice show a

reduced eosinophil recruitment after allergen challenge in mouse model of pulmonary eosinophilic inflammation.[234] TNFR-deficient mice also display a reduced airway remodeling in chronic OVA-induced airway remodeling model.[235] Contrary to expectations, TNFR-deficient mice in the multiple-challenge OVA model of allergic inflammation had comparable of even greater immune responses (including airway response after metacholine challenge, BAL fluid leukocyte and eosinophil numbers, serum and BAL fluid IgE, lung IL-2, IL-4 and IL-5 levels, and lung histological scores) among multiple end points compared with wild-type mice.[224] It is speculated that the accentuated allergic response in TNFR-deficient mice in this model may be a result of the loss of TNF-mediated T-lymphocyte regulation. This is supported by the study showing that the increase in AHR, eosinophil infiltration and IL-5 level in BALF is not affected by γδ T-lymphocyte depletion in TNF-α deficient mice in contrast to control mice.[236]

Studies examining genetic associations have linked several polymorphisms in the TNF gene cluster with TNF-α production and potential increased risk of allergic diseases. Among them is the TNF-α-308 promoter single nucleotide polymorphism, possibly associated with asthma and its severity[237] and allergic rhinitis.[238]

In OVA allergic rhinitis model TNF-α deficient mice showed severely impaired production of specific IgE, Th2 cytokines and chemokines, endothelial adhesion molecules, leading to an inhibition of disease induction[226] and demonstrating an indispensable role of TNF-α in the development of allergic rhinitis.

Both TNFRs appear to be mediators for the immunosuppressive function of TNF-α. TNFR1 deficiency in B6/lpr mice, which develop a mild lupus-like syndrome, resulted in a greatly accelerated autoimmune disease with increased TNF-α levels, high mortality, severe lymphadenopathy, and lupus nephritis. In another study, using experimental autoimmune encephalomyelitis as a mouse model of multiple sclerosis, TNF-α deficiency prolonged the expansion of myelin-specific autoreactive T cells, leading to disease exacerbation. This effect did not require TNFR1 activation. In contrast, TNFR1 was responsible for TNF-α-dependent priming of autoreactive T-lymphocytes and local cerebral injury during the acute phase of the disease. Because suppression of autoimmune reactivity was also present in TNFR2-deficient mice, but not in double-deficient TNFR1 and TNFR2 mice, both receptors apparently can relay the immunosuppressive effects of TNF-α.

Studies in TNF-α- or TNFR-deficient mice have also revealed that TNF-α plays an important role in hepatotoxicity, regulation of embryo development and the sleep-wake cycle.

Clinical use of TNF-α and anti-TNF-α treatment

Despite TNF-α being originally identified by its capacity to induce necrosis in murine tumors, its severe side effects (shock, cachexia) and sometimes TNF-α resistance prevented its development into a routine antineoplastic drug. The results of studies with experimental fibrosarcoma metastasis model show that TNF-α induces a significant increase in the number of lung metastases, suggesting that TNF-α administration may enhance the metastatic potential of circulating tumor cells. Usage of TNF-α as an anti-cancer drug therefore still remains controversial. Nevertheless, isolated tasonermin (recombinant human TNF-α) perfusion and intratumoral TNF-α application have been used for the treatment of localized tumors, such as melanoma and soft tissue sarcoma. A high dose of regional TNF-α is shown to cause necrosis and the subsequent destruction of tumor cells and blood vessels. When compared to chemotherapeutic drugs TNF-α has an important advantage in its specificity against malignant cells. Used therapeutically it also exhibits a broad range of immunomodulatory effects on diverse immune effector cells, such as neutrophils, macrophages, and T cells. TNF-α seems to have a protective role against irradiation and cytotoxic agents in hematopoietic progenitor cells, suggesting its potential therapeutic applications in chemotherapy- or bone marrow transplantation-induced aplasia. Although TNF-α inhibits the growth of endothelial cells *in vitro* it is a potent promoter of angiogenesis *in vivo*. The angiogenic activity of TNF-α is significantly inhibited by IFN-γ. There are therefore opinions that the use of agents with cytotoxic or immune modulatory properties, in particular IFN-γ and possibly IL-2, in addition to TNF-α, may be appropriate for the treatment of some tumor types.

In the field of TNF-α inhibition there has been a great therapeutic success. Although the anti-TNF-α strategy has not proven to be successful in the treatment of septic shock, it can ameliorate the severe consequences of systemic inflammatory response syndrome. Anti-TNF-α therapy has also shown high clinical efficacy in the management of many chronic inflammatory, cancer and cancer-related diseases, including RA, IBD, ankylosing spondylitis, psoriasis, psoriatic arthritis, hidradenitis suppurativa, uveitis, refractory asthma, cancer-related cachexia, leukemia, ovarian cancer etc. [239] Although anti-TNF-α therapy has proved effective in asthma

(particularly severe asthma), the results of some clinical trials are still conflicting. [207, 240-243] The strategies developed to neutralize TNF-α utilize either anti-TNF-α monoclonal antibodies: infliximab (mouse-human chimeric Ab), adalimumab (fully human mAb), golimumab (fully human mAb), certolizumab (PEGylated humanized Fab fragment); or soluble TNFR2 etanercept (human dimeric fusion protein of IgG1-Fc and extracellular domains of TNFR2). In general, anti-TNF-α therapy has proven to be very successful in alleviating the symptoms of autoimmune disorders, including Crohn's disease, ulcerative colitis,[244] ankylosing spondylitis [245], rheumatoid arthritis,[246] Behçet's disease,[247] and moderate to severe chronic psoriasis[248] However, a certain risk of its possible side effects has to be taken into account. This includes unexpected toxicity, immune activation, enhanced risk of viral, bacterial and fungal infections or infection reactivation (especially tuberculosis) autoimmune symptoms (development of autoantibodies, lupus-like syndrome, immune-complex glomerulonephritis), exacerbation of pre-existing multiple sclerosis and increased risk of developing asthma and various types of cancer.

Newer non-antibody anti-TNF-α proteins include progranulin and its derivative antagonist of TNF-TNFR signaling via targeting to TNFR (Atsttrin) that inhibit the interaction of TNF-α with its receptors by binding competitively to TNFRs ligand-binding interface; and soluble preligand-binding assembly domain (PLAD), expressed within cysteine-rich domain 1 (CRD1) of TNFR1 extracellular portion and mediating receptor trimerization upon ligand binding by stabilizing and propagating ligand-receptor contacts. Therapeutic administration of progranulin/Attstrin or soluble TNFR1 PLAD in mouse models of relevant diseases yielded beneficial results, opening the door to future investigation.

Small molecules shown to inhibit TNF-α signaling in addition to other effects and used for various indications include xanthine derivatives, thalidomide, burpropion, p38 MAPK inhibitors, glucocorticosteroids, 5-HT_{2A} agonists and others.

TGFβ

The TGFβ superfamily is conserved through out evolution and can be found in every multicellular organism. In humans the TGFβ superfamily consists of more than 30 members including the TGFβ isoforms, activins and inhibins, bone morphogenic

proteins (BMP), growth and differentiation factors (GDF), nodal and anti-müllerian hormone (AMH).[249]

Discovery and structure

There are three highly homologuos isoforms of TGFβ in humans: TGFβ 1-3. They use the same receptor complexes and have similar signaling pathways, but their expression levels vary in different tissues and show distinct functions.[250] TGFβ 1 was first cloned out of placenta in 1985.[251] It consists of a 390 aa long precursor and is located on chromosome 19q13.2 in humans and on chromosome 7 in mice. TGFβ 2, which shows 71.4% homology to TGFβ 1, was discovered 1987.[252] It forms a 412 aa long precursor and is located on human chromosome 1q41 and also on mouse chromosome 1. TGFβ 3, which shows 80% homology to TGFβ 1 and 2 in the C-terminal active peptide, was discovered the following year, 1988.[253] It consists of a 412 aa long precursor as well and is located on chromosome 14q24.3 and mouse chromosome 12.

All isoforms show the same composition: a 20-30 amino acid long secretory signal peptide is followed by the proregion and the mature TGFβ is formed by the 112-114 aa long C-terminus. Two peptides dimerize to form the active TGFβ. A motif of nine cyteine residues is conserved between the isoforms. The eighth form a tight cyteine knot while the ninth is crucial for homodimerization. In the crystal structure, the dimer forms a ring-like structure, where the three and a half alpha-helix of one subunit packs against the concave surface of the β-strands of the other monomer and the propeptide is shielding the TGFβ from being recognized by its receptors.[254, 255] The propeptide is also called latency-associated peptide (LAP) and forms together with TGFβ and the latent TGFβ-binding protein the large latent complex (LLC), which is only secreted as a whole complex and associates then with the extracellular matrix, for example fibrillin.

For activation TGFβ needs to be released from the LLC by different mechanisms. MMP2 and MMP9 are known to cleave latent TGFβ. alphaV integrins can release TGFβ after mechanical stress by binding to LAP.[255, 256] TGFβ can also be released by cleavage with other proteinases like thrombospondin, pH drop and ROS.[257] CD36 can bind TGFβ over its ligand thrombospondin-1 to the surface where it can be activated by plasmin in an inflammatory environment and directly signal to the macrophages.[258]

Receptor and signaling

TGFβ binds to a heterotetrameric receptor complex consisting out of each two TGFβ type I and type II receptors (TR-I and Tβ-II).[259, 260] Initially, TGFβ binds to the TβR-II and then they recruit TβR-I into the complex, which binds to both TGFβ and TβR-II.[261, 262] The two receptors are structurally similar to each other with homologuos ectodomains, single-spanning transmembrane domains and cytoplasmic serine-threonine kinase domains.[263] Intracellular signaling is activated by the phosphorylation and activation of TβR-I kinase through the TβR-II.[264] SMAD2 and SMAD3 (R-SMAD or receptor SMAD) are recruited to the activated receptor complex and phosphorylated.[265] They form heterotrimers with the co-SMAD SMAD4 (2 R-SMADs, 1 co-SMAD). After translocation to the nucleus they interact with other transcription factors to regulate target gene transcription. They inversely regulate TGFβ autoinduction in *Clostridium butyricum*-activated DCs.[266] Recently, members of the early growth response (Egr)-3 are potently induced by TGFβ via SMAD3.[267] The inhibitory SMAD, SMAD7 can block heterotrimer formation and nuclear translocation.[268, 269] Besides the canonical SMAD pathway, TGFβ signals through the p38-JNK MAP kinase pathway, the phosphoinositol 3-kinase-Akt-mTOR axis, and the small GTPases: Rho, Rac, Cdc42 and the Ras-ERK MAP kinase pathway. On the other hand, a variety of other signaling pathways, especially the Ras and calcium-calmodulin dependent protein kinase II as well as the Hedgehog, Notch, Wnt, Interferon and TNF pathways can influence the TGFβ signaling pathway.[270] This tightly regulated crosstalk leads to a highly differential outcome of the TGFβ signaling largely dependent on the cell type involved and the microenvironment the cell is located in.[271]

TGFβ signaling crosstalk is not limited to other transcription factors. microRNAs strongly control the expression of components of the TGFβ pathway, especially the receptor subunits and the SMAD proteins. In return, activated R-SMAD proteins are directly recruited to pri-miRNAs together with the RNA helicase p68 where they interact with Drosha and increase the processing of pre-miRNAs in a transcriptional independent manner.[272, 273]

Cellular sources and targets

TGFβ is constitutively expressed in most tissues, but overexpressed in many disease states like cancer, fibrosis and inflammation.[274] A large variety of cells are able to express TGFβ including structural cells like epithelial cells, fibroblasts as well as immune cells like eosinophils, macrophages and regulatory T cells. For regulatory

T cells, TGFβ is one of the major cytokines, by which it suppresses immune responses.[275]

Most cell types express TGFβ receptors and respond to TGFβ signaling. Theses cells include, epithelial and endothelial, mesenchymal as well as immune cells. For example TGFβ receptors can be found on almost all immune cells including CD8 T cells, CD4 T cells, NK cells, monocytes, macrophages, neutrophils and eosinophils.[276]

Role in cellular networks and immune regulation

TGFβ plays a role in a large variety of physiological and pathological mechanisms starting early in life with the embryonic development. At bone resorption sites, TGFβ induces the migration of bone mesenchymal stem cells and is thus responsible for a proper bone formation.[277] It also coordinates the proper development of the cardiac system, especially the heart valves.[278]

The ability of TGFβ to induce epithelial and endothelial to mesenchymal transition (EMT) is necessary during development and wound healing but it is also the basis for several pathophysiological effects of TGFβ. Epithelial or endothelial cells loose their cell-cell contacts, show increased migration and invasiveness, display fibroblast or stem cell-like properties and can finally differentiate towards myofibroblasts.[279] This can lead to an increased tumor invasiveness and dedifferentiation of tumor cells as well as decreased drug delivery in cancer pathology.[280] Epithelial and endothelial to mesenchymal transition also exacerbates among others pulmonary, cardiac and renal fibrosis by an increase in mesenchymal cells.[281, 282]

Extracellular matrix (ECM) deposition and fibrosis are also more directly regulated by TGFβ, which can increase the proliferation of fibroblasts and increase the synthesis and deposition of several ECM proteins. This is also a negative feedback loop since TGFβ binds to ECM proteins in the large latency complex and is inactivated this way.[283] The importance of this can be seen in Marfan Syndrome, where patients carry a mutation in the fibrillin gene. Several symptoms including the cardiovascular problems are thought to originate from a decreased binding of TGFβ to the ECM and thus an overactive TGFβ signaling.[284, 285] Also in Duchenne muscular dystrophy, TGFβ is thought to be critical in the early stages of muscular fibrosis.[286] The increase in EMT and ECM deposition has not only pathological effects but is essential in the process of wound healing, where TGFβ attracts macrophages during inflammation phase. During proliferation phase it increases ECM production,

angiogenesis and epithelialization and increases myofibroblast contraction in the maturational phase.[287, 288, 289] One of the most prominent effects of TGFβ is the blockage of cell proliferation in epithelial cells, endothelial cells, haematopoietic cells and immune system cells.[290] TGFβ induces the transcription of cycline-dependent kinase inhibitors $p21^{cip1}$ and $p15^{INK4B}$, which leads to cell cycle arrest.[291] Furthermore, TGFβ represses myc expression, which activates cell proliferation and growth.[292] Strong TGFβ signaling cannot only induce cell cycle arrest but also apoptosis in epithelial cells. In addition, TGFβ signaling is transiently activated in hematopoietic stem cells during hematopoietic regeneration and restores hematopoietic homeostasis.[293] In carcinogenesis many tumor cells still respond to the pro-tumorigenic effects of TGFβ, but evolve to be inert to the growth-inhibitory effects downstream of TGFβ.[294]

In the regulation of the immune system, TGFβ has a central and balancing role with both, pro- and anti-inflammatory effects. TGFβ can decrease the cellular growth of almost all immune cell precursors esp. B and T cells. It is also a potent suppressor of mature T cell proliferation by both, cell cycle arrest and suppression of IL-2 secretion.[295] Besides IL-2, TGFβ also suppresses pro-inflammatory cytokine release from different $CD4^+$ T cell subsets as well as the cytolytic function of $CD8^+$ T cells and thus suppresses the effector function of T cells.[296, 297]

TGFβ regulates the differentiation of several T helper cell subsets. It induces regulatory T cells, of which TGFβ is also one of the major effector cytokines. Regulatory T cells prevent an overreaction of the immune system and take part in immune response resolution.[298,299] Foxp3 is the key transcription factor of regulatory T cells. TGFβ can regulate Foxp3 expression directly by SMAD binding[300, 301] or indirectly by increasing the binding of E2A, a SMAD-controlled transcription factor, and by relieving GATA-3-mediated transcriptional repression of Foxp3. Absence of signaling into $CD4^+$ cells via C3aR and C5aR is important for TGFβ signaling and induction of $Foxp3^+$ regulatory T cells.[302] Id3 is induced by TGFβ and competes with GATA3 for the same promoter binding sites.[303] In the presence of the inflammatory cytokine IL-6, TGFβ is not inducing regulatory T cells, but the pro-inflammatory Th17 cells further adding to the proinflammatory response.[304-306] Recently, however, the necessity of TGFβ during Th17 commitment has been challenged and the actual significance of TGFβ for Th17 cells needs further clarification.[307, 308] TGFβ can induce another pro-inflammatory T cell subset in the presence of IL-4. Th9 cell differentiate

out of Th2 cells after stimulation with IL-4 and TGFβ. [309, 310] In B cells TGFβ can induce apoptosis via the Bim pathway.[311] B cells are not susceptible to apoptosis switch towards IgA secretion under the influence of TGFβ. Other factors can also induce IgA switch but TGFβ seems to be necessary for specific IgA.[312] Certain regulatory B cell subtypes are also able to secret TGFβ, but their definite role still needs to be clarified.[313] For leukocytes, TGFβ has again both a pro- and anti-inflammatory effect. Early in inflammation it is a chemoattractant for several leukocytes.[314] TGFβ plays also a role in DC subset development, e.g. the development of Langerhans cells in the skin[315, 316] and it can control antigen presentation by DCs *in vitro.*[317] In addition, TGFβ enhance DC migration and immune responses to contact sensitizers.[318] In cancer environment, however, TGFβ blocks the DC differentiation and reduces their chemotactic migration.[319, 320] Furthermore, a tolerogenic phenotype of DCs is initiated by TGFβ and the consecutive induction of Indoleamine-pyrrole 2,3-dioxygenase (IDO).[321] TGFβ has a direct suppressive effect on NK cells and their IFNγ secretion by SMAD3 effects on the NK cell promoter, further adding to the immuno suppressive function of TGFβ also in the innate immune system.[322] Even though macrophages are important source of TGFβ, TGFβ inhibits macrophage activation and turns both macrophages and neutrophils from a type I to a type II phenotype. Type I cells show high productive activity, while type II exhibit reduced effector ability but produce high amounts of pro-inflammatory cytokines.[323, 324] Taken together, TGFβ is balancing the immune response. TGFβ exhibits strong influence on both pro- and anti-inflammatory immune responses and the outcome depends largely on the microenvironment.

Role in autoimmune and other diseases

The most striking data for the involvement of TGFβ in autoimmune diseases are TGFβ 1 knockout mice. They show 50% embryonical lethality, the others succumb due to multiorgan autoimmunity.[325, 326] The pathological phenotype shows increased T cells activity and cytokine secretion in these mice, but they also show increased apoptosis, which is more pronounced for $CD8^+$ T cells in comparison to $CD4^+$ T cells. Regulatory T cell number and their suppressive function are decreased in the periphery, and autoreactive T cells are increased. The antibody profile is changed to more IgM, IgE and IgG with low levels of IgA. Since there is no constitutive expression of TGFβ, there is an inflammatory response to apoptotic cells. In accordance with this phenotype, the blocking of TGFβ in several models of

autoimmune diseases leads to an abrogation of the protective effect of Tregs and an increase in disease severity.[327] TGFβ is essential for the survival of naïve T cells in periphery, but also for maintaining peripheral tolerance. It inhibits proliferation and differentiation of self-reactive T cells and signals on DCs to keep the tolerance.[328] Due to the protective role of regulatory T cells and its major effector cytokine TGFβ in autoimmune diseases, several phase I and II clinical trials are going on right now, trying to supplement the patients with autologous Tregs or increasing their number with self-antigen specific immunotherapy (SIT) or IL-2 complex treatment.[329, 330]

TGFβ cannot only control extra cellular matrix protein deposition, but also pathological protein deposition. In healthy brains, TGFβ is involved in neuronal differentiation and synaptic plasticity. In Alzheimer disease TGFβ signaling is impaired and associated with β-amyloid deposition and neufibrillary tangle formation as well as neurodegeneration. Therapeutic usage of TGFβ in early phases of Alzheimer disease is being considered right now.[331, 332]

In the vascular system, TGFβ can induce cell proliferation and migration, arteriogenesis, angiogenesis, and is involved in several cardiovascular pathologies. However, these effects are complex and sometimes contradictory.[333, 334] Both, TGFβ signaling up-and down-regulation was observed together with alternative receptor usage, crosstalk with BMPs and contrasting effects on different vascular cells.[335] For example, TGFβ has a protective role in atherosclerosis,[336] while it is also a key factor in cardiac remodeling in heart disease[337] and in induction of endothelial to mesenchymal transition in cardiac fibrosis,[338] and liver fibrosis.[339] In cancer pathology, TGFβ has a biphasic role. Early on, TGFβ displays mainly tumor-suppressing characteristics, while it has tumor-promoting functions later in the course of the pathology. Mutations and loss of heterozygosity of components of the TGFβ signaling pathway can be found in many tumors and several germline mutations in the TGFβ signaling pathway have been implicated with increased cancer risk.[340, 341] As discussed earlier, TGFβ can suppress proliferation and initiate apoptosis in several cell types like epithelial, hematopoetic and neuronal cells, of which many tumors originate from. Furtheremore, TGFβ can indirectly block tumor progression by suppressing pro-cancerogenic factor release from stromal cells, like the suppression of HGF release from fibroblasts, which was verificated in a mouse model of prostate and invasive squamous cell carcinoma of the forestomach.[*342*] In aggressive tumors anyhow, many mutations in the TGFβ signaling pathway were not found in its core

components, so that the cells, while circumventing the tumor-suppressing functions of TGFβ, still could profit from the pro-cancerogenic effects like EMT, increased tumor invasion, metastatic dissemination and immune evasion.[294] EMT leads to loss of polarity and cell-cell contacts, and fibroblast-like properties, which makes the cells highly motile and invasive. Hallmarks of EMT was found histologically at the invasive front of human tumors, verifying the results from a variety of mouse models.[343] Besides increasing the invasiveness and motility, the cells undergoing EMT also seem to obtain stem cell-like properties.[344] Recent findings suggest that silencing of peptidyl arginine deiminase 4 (PAD4) leads to a striking reduction of nuclear GSK3β protein levels, increased TGF-β signaling, and induction of EMT.[345]

The influence of TGFβ on metastatic dissemination is largely context and tumor dependent. For example, TGFβ is necessary for the establishment of lung metastasis of breast cancer.[346] The effects are also dependent on the duration and location of TGFβ. For some tumors it is beneficial to have TGFβ present at the primary tumor for dissemination, but for extravasation and metastasis establishment TGFβ levels should be low.[347] Thus, TGFβ can increase early invasion and intravasation or extravasation and colony formation depending on the tumor and the metastatic site.[294] For example, TGF-β1 induces upregulation of CXCR4 in tumor cells by phosphorylation of ERK1/2-ETS-1 pathway and enhances tumor cell invasion and angiogenesis.[348] TGFβ does not only have direct effects on tumor cells, but can also prevent the recognition of the cancer cells by the immune system and help the immune evasion of tumors. Mice with a dominant negative TβRII on T cells show a reduced growth of melanoma and lymphoma cell lines due to better recognition by the immune system.[349] TGFβ in the tumor microenvironment not only suppresses T cells but also prevents tumor cell killing by NK cells[350] by downregulating important NK cell receptors like NKG2D.[351]

Role in allergic disease

In asthmatic individuals eosinophils and macrophages are the main producers of TGFβ in the asthmatic lung, while also other cells like lymphocytes and structural cells can express it.[352-354] TGFβ levels are increased in BAL fluid and are further increased after allergen challenge.[355] This TGFβ might be proinflammatory by serving as a potent chemoattractant since blocking TGFβ lead to decreased monocyte and macrophage recruitment and decreased numbers of lymphocytes and eosinophils in the BAL.[356] A TGFβ polymorphism that might be associated with

asthma severity, airway inflammation, and remodeling,[357, 358] associates as well with increased levels of TGFβ, decreased FEV_1 and less eosinophils in sputum.[359, 360] In contrast, in mouse models where an increase in TGFβ was induced in the lungs, airway inflammation was reduced[361-363] and in certain models the asthma phenotype was exaggerated after reduction of TGFβ in the lung.[364, 365] One of the anti-inflammatory effects of TGFβ in airway inflammation is the induction of regulatory T cells.[366] Regulatory T cells are able to suppress asthmatic airway inflammation in mice on multiple levels, like the suppression of Th2 and Th1 cells. They have also suppressive function on many other cell interactions in asthma[367, 368] and need among others TGFβ to exert their suppressive function.[363, 369] Induction of TGFβ and regulatory T cells is one of the major hallmarks in efficient specific immunotherapy leading to induced allergen tolerance.[370] Besides the differentiation of Tregs, TGFβ also drives the differentiation of Th17 and Th9 cells that can add to inflammatory response in asthma like the recruitment and activation of mast cells by Th9 cells.[371]

TGFβ does not only influence the immune response in asthma, but is also a key factor in asthma-associated airway remodeling. Instillation of TGFβ into the lung leads to airway fibrosis.[372] In OVA-induced airway inflammation, mice showed reduced pulmonary fibrosis, reduced collagen deposition, decreased smooth muscle cell proliferation and goblet cell mucus production in $SMAD3^{-/-}$ mice or after blockage of TGFβ,[373-375] while in a HDM model $SMAD3^{-/-}$ mice had comparable remodeling to wt mice.[376] Patients treated for 2 months with anti-IL-5 had not only reduced tissue eosinophilia but also reduced TGFβ levels and ECM deposition.[377] IL-5 knockout mice showed a comparable phenotype.[378] Airway remodeling by TGFβ seems to be insensitive to corticosteroid treatment.[379] TGFβ induces a big variety of changes leading to airway remodeling. It induces epithelial apoptosis and in presence of the cell stress in the lungs leads to detachment of epithelial cells. Epithelial cells in asthmatics further undergo EMT under the influence of TGFβ. Subcellular fibrosis is orchestrated by TGFβ by increased ECM deposition and increased fibroblast proliferation, increased myofibroblast differentiation and increased factor secretion from fibroblasts further accelerating fibrosis. TGFβ also increases smooth muscle cell proliferation and migration, increases mucus secretion by goblet cells and increases angiogenesis by the enhanced release of pro-angiogenic factors like VEGF.[380]

Due to the controversial role of TGFβ in asthma Yang et al. proposed a two-step model where an early deficiency in Tregs and possibly TGFβ lead to a Th2 driven

airway inflammation, eosinophilic infiltration and following to that an increase in TGFβ. A continued deficiency of Tregs and their effector function, possibly by inefficient suppression of Th2 immune responses,[381, 382] results in airway remodeling by TGFβ while it still can not suppress the immune response. The paradoxical effect of TGFβ on the pathogenesis of asthma by inducing airway remodeling and fibrosis as well as T-cell tolerance at the same time is an interesting phenomenon and requires further research.[383] In atopic dermatitis (AD) there was no difference of TGFβ levels found in between lesional and non-lesional skin[384] In association studies however there was a link between a low TGFβ producing polymorphism and AD.[385] SMAD3$^{-/-}$ mice show a decreased skin inflammation in a mouse model of AD, but an increase in mast cells together with an increase in specific IgE[386] and TGFβ application can suppress AD like skin lesions in a mouse model.[387] TGFβ was also implicated in ECM deposition and skin remodeling in AD.[388] Initially, there was an absence of Foxp3^{+} Tregs described in AD lesions while Tr1 cells were present. None of the both Treg subsets was able to suppress cytokine induced apoptosis *in vitro*.[389] But other groups described the presence of Foxp3^{+} Tregs.[390, 391] Similar to the findings in skin, results in peripheral blood are controversial. While some studies found an increase in Tregs, which correlated with disease activity, others could not observe any differences.[392-394] The observed differences might be explained by differences in disease stage and treatment of the patients.

TGFβ plays also a role in allergic rhinitis. Although there was no difference in TGFβ, observable levels of TGFβ receptors were increased in allergic rhinitis.[395] A polymorphism in TGFβ 1 was also associated with the risk of developing allergic rhinitis.[396] Serum TGFβ levels were found to be increased during pollen season and even higher after specific immunotherapy.[397] The increased levels of TGFβ might increase the chemotaxis of mast cells to the site of allergic inflammation.[398] Chronic rhinosinusitis is associated with allergy development and TGFβ plays a major role in its development, and has been extensively reviewed lately.[399] In eosinophilic esophagitis, phospholamban is regulated by TGFβ1, and it might provide a novel therapeutic target to improve esophageal dysmotility and clinical dysphagia.[400]

TGFβ is essential in maintaining food tolerance directly and by controlling Treg induction and being part of Treg function[401] and thus control immune response and IgA production in the gastrointestinal tract. CD5^{+}CD19^{+}CX3CR1^{+} tolerogenic B cells are capable of inducing Tregs in the intestine and suppress food allergy-related Th2

pattern inflammation in mice.[402] Orally administered TGFβ is active and can suppress allergic immune response and induce tolerance.[403, 404] TGFβ is contained in breast milk and might this way be important in the allergen tolerance during early life.[405]

Functions as demonstrated in TGFβ-deleted mice, receptor-deficient mice, human mutations and therapeutic applications

TGFβ knockout mice show isotype specific phenotypes. 50% of the TGFβ 1 knockout mice die in utero and it is postnatally lethal for the other newborns. The mice die from multiorgan autoimmunity.[325, 326] The deficiency in immune response containment is mainly due to a missing TGFβ signaling to T cells, resulting in autoimmunity, CD4 T cell activation, especially Th1 cells, decreased $CD8^+$ cytotoxic lymphocyte differentiation and lack of NKT cells.[406, 407] Thrombospondin deficient mice exhibit a similar phenotype to TGFβ 1 knockout mice due a deficiency in activating TGFβ.[408]

The TGFβ 2 knockout is perinatally lethal. These mice show no signs of autoimmunity, so they have no overlapping phenotype with TGFβ 1. TGFβ 2 deficient mice have defects in heart and skeletal development, the eye and inner ear, the urogenital tract, and are not viable after birth.[409] TGFβ 3 knockout mice do neither show an autoimmune phenotype, but a failure of closing of the palate shelves leaving a palatal cleft without further craniofacial abnormalities. The mice have also a consistent delay in pulmonary development, and they die within 1 day after birth.[410, 411] Knockout of the Tβ-II in mesenchymal stem cell lead to less development of osteoarthritis, suggesting that TGFβ1 in subchondral bone seem to initiate the pathological changes of osteoarthritis.[412]

For humans there is no description of TGFβ isoform mutations with a complete loss of function. Regarding the results from the knockout mice these mutations might not be viable. Several different mutations in TGFβ 1 lead to an increase in TGFβ activity. This autosomal dominant syndrome, called Camurati-Engelmann disease, displays a progressive diaphyseal dysplasia characterized by hyperostosis and sclerosis of the long bones.[413, 414] Patients with a haploinsufficient for TGFβ 2 suffer from the autosomal dominant Loeys-Dietz syndrome type 4. They develop aortic aneurysm, aortic dissection, intracranial aneurysm and subarachnoidal hemorrhage.[415, 416] In addition, patients with Loeys-Dietz syndrome are strongly predisposed to develop allergic diseases, including asthma, food allergy, eczema, allergic rhinitis, and eosinophilic gastrointestinal disease.[417] T cells from patients with

this syndrome has increased phosphorylation of SMAD2 and SMAD3 in response to TGFβ, which suggests that TGFβ receptor signaling is enhanced, rather than repressed, in these individuals.[417] Mice with a haploinsufficiency of TGFβ 2 display similar defects like human patients.[415] Mutations in the 5-prime or 3-prime UTR of TGFβ 3 causing an increase in activity of TGFβ 3 lead to arrhytmogenic right ventricular dysplasia type 1, an autosomal dominant disease with reduced penetrance. Usually the arrhytmias are well tolerated, but they are also one of the major genetic causes of sudden juvenile death.[418, 419]

Haploinsufficiency caused by mutations in the receptor genes TGFBR1 and TGFBR2 lead to Loeys-Dietz syndrome type 1A and 2A, respectively type 1B and 2B. As described for TGFβ 2, it is an aortic aneurysm syndrome here accompanied with arterial tortuosity, and bifid uvula. Type 1 patients have craniofacial involvements like cleft palate, craniosynostosis and hypertelorism, why only some type 2 patients have a bifid uvula. Patients with this syndrome show a high rate of pregnancy related complications.[420] In addition to the Loeys-Dietz syndrome, germline and somatic missense mutations in TGFBR2 can result in hereditary nonpolyposis colorectal cancer-6.[421]

Due to its involvement in many diseases, TGFβ is targeted for therapeutic use in many clinical trials. The TGFβ blocker target almost every step in the TGFβ pathway: expression, activation, receptor binding and signaling. Different approaches to target TGFβ are used, including antisense nucleotides, ligand competitive peptides, small molecular inhibitors against the receptor kinase and antibodies against ligands, receptors or associated proteins. The main disease groups targeted are cancer therapy, fibrosis, scleroderma, restenosis following artery bypass and angioplastic, and postoperative scaring in ocular conditions.[276] Since TGFβ has multiple functions in cancer pathology targeting TGFβ can also have several beneficial effects. For example, blocking TGFβ during radiation therapy of breast cancer can increase immune response and decrease cancer progression and metastasis. At the same time it can diminish therapy induced fibrosis.[422] Marfan syndrome is accompanied by elevated levels of TGFβ due to the decreased binding of TGFβ to the ECM. Vascular symptoms in Marfan syndrome might be alleviated by blocking of TGFβ [284, 285] and there are clinical trials now in phase II. [276] The perinatal blocking might also relief the distal airspace enlargement in lungs by preventing apoptosis in the developing lung. [285] Concomitantly, TGFβ blocking might further improve muscle function and repair in

both Marfan syndrome and Duchenne muscular dystrophy. [423]

In total there are so far 106 SNPs and 11 other variations described for TGFβ 1 and it's downstream signaling, with ethnical differences.[424] TGFβ 2 and TGFβ 3 display additional. It's not difficult to imagine that these variations are associated with different susceptibilities to a large variety of diseases.

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