

5. Immunologic messenger molecules: Cytokines, interferons, and chemokines

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Cytokines and chemokines are secreted proteins involved in numerous aspects of cell growth, differentiation, and activation. A prominent feature of these molecules is their effect on the immune system with regard to cell trafficking and development of immune tissue and organs. The nature of an immune response determines which cytokines are produced and ultimately whether the response is cytotoxic, humoral, cell mediated, or allergic. For this chapter, cytokines are grouped according to those that are predominantly antigen-presenting cell or T lymphocyte derived; that mediate cytotoxic, humoral, cell mediated, and allergic immunity; or that are immunosuppressive. A discussion of chemokine function and their role in cell trafficking and disease follows. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: Cytokine, chemokine, interferon, antigen-presenting cell, T lymphocyte

Cytokines are secreted proteins with growth, differentiation, and activation functions that regulate and determine the nature of immune responses. For this review, cytokines are grouped according to those that are predominantly antigen-presenting cell (APC) or T lymphocyte derived; that predominantly mediate cytotoxic (antiviral and anticancer), humoral, cell-mediated (T_H1 and T_H17), or allergic immunity (T_H2); or that are immunosuppressive (regulatory T [Treg]). This is followed by a discussion of the complementary family of secreted immune proteins, the chemokines. Cytokine families are summarized in Table I.

CYTOKINE PRODUCTION BY ANTIGEN-PRESENTING CELLS

Cytokines primarily derived from dendritic cells (DCs), mononuclear phagocytes, and other APCs are particularly effective in subserving the dual functions of generating a potent innate

Abbreviations used

ABPA: Allergic bronchopulmonary aspergillosis
 AHR: Airway hyperreactivity
 APC: Antigen-presenting cell
 APRIL: A proliferation-inducing signal
 BAFF: B-cell activation factor from the TNF family
 DC: Dendritic cell
 Foxp3: Forkhead box protein 3
 gp130: Glycoprotein 130
 ICAM: Intercellular adhesion molecule
 IFNGR: IFN- γ receptor
 IL-1ra: IL-1 receptor antagonist
 IL-2R: IL-2 receptor
 IL-4R: IL-4 receptor
 IL-5R: IL-5 receptor
 IL-6R: IL-6 receptor
 IL-10R: IL-10 receptor
 IL-12R: IL-12 receptor
 IL-13R: IL-13 receptor
 IL-17R: IL-17 receptor
 IL-20R: IL-20 receptor
 IL-22R: IL-22 receptor
 IRS: Insulin response element
 iTreg: Induced regulatory T
 JAK: Janus kinase
 MAPK: Mitogen-activated protein kinase
 MCP: Monocyte chemoattractant protein
 M-CSF: Macrophage colony-stimulating factor
 MIP: Macrophage inflammatory protein
 NK: Natural killer
 nTreg: Natural regulatory T
 ROR: Retinoic acid receptor–related orphan receptor
 SCF: Stem cell factor
 STAT: Signal transducer and activator of transcription
 TACI: Transmembrane activator and calcium modulator and cyclophilin ligand interactor
 T-bet: T-box expressed in T cells
 Treg: Regulatory T
 TSLP: Thymic stromal lymphopoietin
 VCAM: Vascular cell adhesion molecule

immune response and providing signals contributing to initiation and guidance of the nature of the adaptive immune response. The processing of antigens as they are taken up by APCs, metabolized, and presented to T_H lymphocytes provides one pathway for this class of cytokine production. Alternatively, APCs are potently triggered to produce cytokines through their pattern recognition receptors. The cytokines predominantly produced by APCs include TNF, IL-1, IL-6 (and other glycoprotein 130 [gp130]–utilizing factors), CXCL8 (IL-8), and other members of the chemokine family (discussed later), as well as IL-12, IL-15, IL-18, IL-23, IL-27, and IL-32.

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TABLE I. Cytokine families

Family	Members
Hematopoietic	
Common γ chain	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
Shared β chain (CD131)	IL-3, IL-5, GM-CSF
Shared	IL-2, IL-15
IL-2 β chain (CD122)	
Other hematopoietic	IFN- γ , IL-7, IL-13, IL-21, IL-31, TSLP
IL-1 family	IL-1 α , IL-1 β , IL-1ra, IL-18, IL-33
gp130-utilizing	IL-6, IL-11, IL-27, IL-31, ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), leukemia inhibitory factor (LIF), oncostatin M (OSM), osteopontin
IL-12	IL-12, IL-23, IL-35
IL-10 superfamily	IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, IL-29
IL-17	IL-17A-F, IL-25 (IL-17E)
Interferons	
Type I interferons	IFN- α , IFN- β , IFN- ω
Type II interferon	IFN- γ (also a hematopoietic cytokine)
Type III interferons	IFN- λ 1 (IL-29), IFN- λ 2 (IL-28A), IFN- λ 3 (IL-28B)
TNF superfamily	TNF- α , TNF- β , BAFF, APRIL

TNF

TNF represents 2 homologous proteins primarily derived from mononuclear phagocytes (TNF- α) and lymphocytes (TNF- β).¹ TNF- α is also produced by neutrophils, lymphocytes, natural killer (NK) cells, endothelium, and mast cells. TNF- α is processed as a membrane-bound protein from which the soluble active factor is cleaved by using the enzyme TNF- α converting enzyme.² TNF- β (also known as lymphotoxin α) can be synthesized and processed as a typical secreted protein but is usually linked to the cell surface by forming heterotrimers with a third membrane-associated member of this family, lymphotoxin β . TNF- α and TNF- β bind to the same 2 distinct cell-surface receptors, TNF receptor I (p75) and TNF receptor II (p55), with similar affinities and produce similar, although not identical, effects.³ Notably, the active form of both cytokines is a homotrimer. TNFs induce antitumor immunity through direct cytotoxic effects on cancerous cells and by stimulating antitumor immune responses. TNFs interact with endothelial cells to induce intercellular adhesion molecule (ICAM) 1, vascular cell adhesion molecule (VCAM) 1, and E-selectin, permitting the egress of granulocytes into inflammatory loci. TNFs are a potent activator of neutrophils, mediating adherence, chemotaxis, degranulation, and the respiratory burst. TNFs are responsible for the severe cachexia that occurs in chronic infections and cancer.¹ Furthermore, TNFs induce vascular leakage and have negative inotropic effects, and because the most potent inducer of TNF is endotoxin, it is the primary mediator of septic shock.⁴

IL-1

The IL-1 family represents 5 peptides (IL-1 α , IL-1 β , the IL-1 receptor antagonist [IL-1ra], IL-18, and IL-33).⁵ IL-1 α and IL-1 β have similar biologic activities and, along with IL-1ra, have similar affinities for the 2 IL-1 receptors. Type I receptors transduce the biologic effects attributed to IL-1.⁶ Type II receptors

have a minimal intracellular domain, and the capture and sequestration of IL-1 by these inactive receptors serves an anti-inflammatory function. The capacity of IL-1ra to bind IL-1 receptor without transducing activities is the basis for its antagonist function.⁷ IL-1ra is secreted in inflammatory processes in response to many cytokines, including IL-4, IL-6, IL-13, and TGF- β . Production of IL-1ra moderates the potentially deleterious effects of IL-1 in the natural course of inflammation.

IL-1 is primarily produced by cells of the mononuclear phagocytic lineage but is also produced by endothelial cells, keratinocytes, synovial cells, osteoblasts, neutrophils, glial cells, and numerous other cells. IL-1 production is stimulated by a variety of agents, including endotoxin, that stimulate molecular pattern receptors. Both IL-1 α and IL-1 β , as well as the related proteins IL-18 and IL-33 (discussed later), are synthesized as inactive precursors without a secretory sequence. The mechanism for their secretion depends on cleavage by a specific converting enzyme, termed IL-1 converting enzyme or caspase-1, contained within a specialized intracellular complex termed the inflammasome, which cleaves the procytokines into their active secreted forms.⁸

One of the most important biologic activities of IL-1 is its ability to activate T lymphocytes by enhancing the production of IL-2 and the expression of IL-2 receptors. In the absence of IL-1, a diminished immune response or tolerance develops. The production of IL-1 (and other APC-derived cytokines) during the immune response produces a spectrum of changes associated with being ill. IL-1 interacts with the central nervous system to produce fever, lethargy, sleep, and anorexia. An IL-1–hepatocyte interaction inhibits production of housekeeping proteins (eg, albumin) and stimulates the synthesis of acute-phase response peptides (eg, amyloid peptide, C-reactive peptide, and complement). IL-1 stimulates endothelial cell adherence of leukocytes through the upregulation of ICAM-1, VCAM-1, and E-selectin. IL-1 contributes to the hypotension of septic shock. TNF and IL-1 share numerous biologic activities, the major distinction being that TNF has no direct effect on lymphocyte proliferation.

IL-6

Mononuclear phagocytic cells are the most important source of IL-6⁹; however, IL-6 is also produced by T and B lymphocytes, fibroblasts, endothelial cells, keratinocytes, hepatocytes, and bone marrow cells. IL-6 signals through a ligand-binding IL-6 receptor (IL-6R) α chain (CD126) and the signal-transducing component gp130 (CD130). CD130 is the common signal transducer for several cytokines in the IL-6 family and is ubiquitously expressed. In contrast, the expression of IL-6R α is restricted. In addition to the membrane-bound receptor, a soluble form of IL-6R can capture circulating IL-6 and make it available to bind and activate gp130.¹⁰ In contrast, soluble gp130 functions as an anti-inflammatory decoy receptor. Other cytokines that signal through gp130-containing receptors are IL-11, IL-27, IL-31, ciliary neurotrophic factor, leukemia inhibitory factor, oncostatin M, and osteopontin. These cytokines are referred to as the IL-6–like or gp130-utilizing cytokines (Table II).¹¹

Under the influence of IL-6, B lymphocytes differentiate into mature plasma cells and secrete immunoglobulins. IL-6 mediates T-cell activation, growth, and differentiation. In addition to lymphocyte activation, IL-6 shares several activities with IL-1,

TABLE II. IL-6–like (gp130-utilizing) cytokines

IL-6–like cytokine	Characteristics
IL-31	Primarily expressed by T _H lymphocytes under T _H 2 conditions. Induces chemokines that recruit neutrophils, monocytes, T cells. Overexpression in mice leads to atopic dermatitis model. Increased IL-31 receptor levels in murine model of AHR.
IL-11	Increases production of acute-phase proteins. Induces lymphoid cell differentiation. Stimulatory factor for fibroblasts. Expression in severe asthma with remodeling.
Osteopontin	Induced by IFN- γ , IL-1 β , and TNF- α . Expression inhibited by IL-4 and IL-13. Upregulated in patients with chronic sinusitis, nasal polyps, and asthma.
Oncostatin	Synthesized by T cells and monocytes. Proinflammatory or anti-inflammatory functions. Roles in liver development, hematopoiesis, inflammation, and possibly CNS development. Signals through a shared type I receptor of gp130/LIFR- β and a specific type II receptor of gp130/OSMR β .
LIF	Induces terminal differentiation of myeloid leukemia cells. Influences bone metabolism, cachexia, neural development, embryogenesis, and inflammation. Binds to the specific LIF receptor (gp130/LIFR- α).

including the induction of pyrexia and the production of acute-phase proteins. IL-6 is the most important inducer of acute-phase proteins. As discussed below, IL-6 has a primary role in T_H17 immune deviation.

IL-12, IL-18, and IL-23

IL-12 and IL-23 are heterodimers that share a larger (IL-12p40) subunit. Both are primarily derived from DCs.^{12,13} Their receptors are also heterodimers having distinct α chains and shared use of the IL-12 receptor (IL-12R) β 1 chain. These cytokines are involved in T-cell activation and immune deviation of T_H1 and T_H17 cells, respectively (discussed later).

IL-12 is derived most importantly from DCs but also from Langerhans cells, mononuclear phagocytic cells, B cells, PMNs, and mast cells. The biologically active form is a heterodimer. The larger subunit (IL-12p40) is homologous to the soluble receptor for IL-6, whereas the smaller subunit (IL-12p35) is homologous to IL-6. Homodimers of IL-12p40 are also functional (IL-12p80). IL-12 stimulates IFN- γ production and activates and induces proliferation, cytotoxicity, and cytokine production of NK cells. Other activities attributed to IL-12 include proliferation of T_H and cytotoxic lymphocytes.

IL-18, along with IL-12 and IL-23, is an inducer of IFN- γ .¹⁴ Similar to IL-1, IL-18 requires a specific converting enzyme (caspase-1) to permit secretion and activation. In contrast to most cytokines, IL-18 is constitutively expressed, and release of its active form is regulated through activation of this converting enzyme. IL-18 has an important role in cellular adhesion, being the final common pathway used by IL-1 and TNF that leads to ICAM-1 expression. IL-18 binds to a unique heterodimer receptor, the expression of which is upregulated by IL-12, and hence these 2 cytokines synergize to stimulate IFN- γ release.

Finally, as noted, IL-23 is a heterodimer consisting of a larger subunit shared with IL-12 (IL-12p40) and a unique subunit (IL-23p19). Its inflammatory response includes induction of remodeling through activation of matrix metalloproteinases, increased angiogenesis, and reduced CD8 T-cell infiltration. Its important synergistic role in T_H17 differentiation is discussed below.

IL-15

Mononuclear phagocytic cells are the main source of IL-15, whereas epithelium, fibroblasts, and placenta are additional sources. IL-15 is distinguished from IL-2 through its use of a unique α chain as part of its receptor signaling complex.¹⁵ Both receptors share the use of the IL-2 receptor (IL-2R) β and common γ chain (Table I). IL-15, similar to IL-2, is a T-cell growth factor and is chemotactic for T lymphocytes. The most important activity of IL-15 might be its activation of NK cells. IL-2 and IL-15 are contrasted in their roles in adaptive immune responses in which IL-2, but not IL-15, is involved in the generation and maintenance of Treg cells, whereas IL-15 is necessary for maintaining the survival of CD8 memory T cells. IL-15 is also active as an accessory mast cell growth factor.

IL-27

The cells responsible for most of the production of IL-27 are macrophages and DCs. IL-27 is a heterodimer composed of IL-27B (EBV-induced gene B) and IL-27p28 (also known as IL-30).¹⁶ IL-27 subserves important functions in T_H1 immunity, reflecting its ability to synergize with IL-12 to induce IFN- γ production from NK and T_H cells (T_H1 immune deviation). The effects of IL-27 are mediated through interaction with a receptor complex consisting of IL-27 receptor α and gp130.¹⁷

IL-32

IL-32 was discovered in a search for IL-18–inducible genes.¹⁸ Its biologic activities include induction of proinflammatory cytokines (eg, TNF- α) and chemokines from differentiated macrophages. The highest levels of expression are observed in NK and T cells; however, expression can also be observed in epithelial cells in response to IFN- γ and IL-1 β . IL-32 synergizes with nucleotide-binding oligomerization domain 1 and 2 ligands to stimulate IL-6 and IL-1 β release in a caspase-1–dependent manner.¹⁹

CYTOTOXIC IMMUNITY

Immune responses directed against virus-infected and neoplastic cells are primarily mediated by CD8⁺ cytotoxic lymphocytes and NK cells. As discussed elsewhere, numerous cytokines contribute to cytotoxic immunity, as well as IL-11 and the interferons.

IL-11

In addition to its functions in promoting cytotoxic antiviral immune responses, IL-11 was originally described as a stimulatory factor for hematopoietic cells, synergizing with other growth factors to produce erythrocytes and platelets. IL-11 increases the production of acute-phase proteins and induces lymphoid cell differentiation. It is an important stimulatory factor for connective

tissue cells, such as fibroblasts, that stimulate proliferation and collagen deposition. A role for IL-11 in asthma remodeling is suggested by studies demonstrating expression of IL-11 in patients with severe asthma.^{20,21}

Interferons

Interferons derive their name from their ability to interfere with viral growth. There are 3 major classes of interferons. Type I interferons (IFN- $\alpha/\beta/\omega$) are primarily derived from monocytes, macrophages, B lymphocytes, and NK cells. An important source of IFN- α is plasmacytoid DCs, reflecting their activation by viral RNA acting through Toll-like receptors 3 and 7. The antiviral activity of type I interferons is mediated through their ability to inhibit viral replication within virus-infected cells, protect uninfected cells from infection, and stimulate antiviral immunity by cytotoxic (CD8⁺) lymphocytes and NK cells. IFN- α has other important biologic actions, including upregulation of class I MHC antigens and mediation of antitumor activity. IFN- ω ²² displays a high degree of homology with various IFN- α species, including positions of the cysteine residues involved in disulfide bonds²³; however, sequence divergence allows classification as a unique protein family. IFN- ω binds to the same receptors as IFN- α and IFN- β .²⁴

A sole member makes up the class of type II interferons: IFN- γ . IFN- γ is a homodimer primarily made by T cells and NK cells and to a lesser degree by macrophages. The biologic activities of IFN- γ include only modest antiviral activity, and its derivation primarily from T lymphocytes suggests that it is more of an interleukin than an interferon. IFN- γ and its role in cellular immunity are discussed below.

The type III interferons consist of IFN- λ 1, IFN- λ 2, and IFN- λ 3, also called IL-29, IL-28A, and IL-28B, respectively. Type III interferons share with type I interferons the same Janus kinase (JAK) and signal transducer and activator of transcription (STAT) signaling pathways. IFN- λ s exhibit several other common features with type I interferons, including antiviral, antiproliferative, and antitumor activities. Despite amino acid homology with type I interferons, the intron-exon structure of the IFN- λ family more closely resembles that of IL-10.²⁵ Moreover, IFN- λ s act through a cell-surface heterodimer receptor, one chain being IFN- γ -specific (IFNLR1) and the second, IL-10 receptor (IL-10R) 2, being shared by IL-10, IL-22, and IL-26 (Table III). In addition to the full-length IFNLR1, 2 inhibitory splice variants have been identified, one variant deletes 29 amino acids in its intracytoplasmic portion, likely disabling its signaling capacity, and the second encodes a secreted (decoy) receptor.²⁵ Although IL-10R2 is ubiquitously expressed, IFNLR1 is more tightly regulated. IFN- λ subtypes are induced on infection by multiple viruses, which is consistent with their antiviral activities,^{25,26} and pretreating hepatocellular cells prevents viral infection.²⁵ One notable difference between IFN- λ and type I interferons is that IFN- λ shifts immature DCs toward a program characterized by the ability to produce forkhead box protein 3 (Foxp3)-expressing CD4⁺CD25⁺ Treg cells.²⁷

HUMORAL IMMUNITY

At least 2 cytokines contribute to B-lymphocyte maturation in the bone marrow: the lymphoid stem cell growth factors IL-7 and IL-11. IL-7 is critically important to the development of both B

and T lymphocytes through its production by stromal tissue of the bone marrow and thymus, from which it interacts with lymphoid precursors. In addition, IL-7 stimulates the proliferation and differentiation of cytotoxic T and NK cells and stimulates the tumoricidal activity of monocytes and macrophages. The central importance of IL-7 to lymphoid maturation is reflected in severe combined immune deficiency resulting from the absence of either IL-7 or functional IL-7 receptors (IL-7 receptor α [CD127] or common γ chain).

IL-21

IL-21 is increasingly recognized as being central to B-cell proliferation, survival, and differentiation into immunoglobulin-producing plasma cells.²⁸ Its induction of activation-induced cytidine deaminase contributes to class-switch recombination. IL-21 receptors are expressed on activated B, T, and NK cells. It shares numerous biologic activities with IL-2 and IL-15, with which it is homologous, including the capacity to activate NK cells and promote the proliferation of B and T lymphocytes.²⁹ Its receptor shares the common γ chain with IL-2, IL-4, IL-7, IL-9, and IL-15. Among T cells, it is preferentially expressed by T_H17 cells and is involved in T_H17 differentiation (discussed below).

B-cell activation factor from the TNF family and a proliferation-inducing ligand

Two other TNF family cytokines, B-cell activation factor from the TNF family (BAFF) and a proliferation-inducing ligand (APRIL), enhance the maturation and survival of transitional and mature B cells. BAFF and APRIL are expressed in bone marrow nonlymphoid cells, with low levels also in developing B cells. BAFF overexpression leads to an expanded B-cell compartment, and increased amounts of BAFF have been found in autoimmune patients. BAFF knockout mice have a severe block in B-cell development in the spleen, although not in bone marrow. Three receptors from the TNF receptor family bind to BAFF and APRIL: transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), B-cell maturation antigen, and BAFF-R.^{30,31} BAFF-R binds specifically to BAFF, whereas TACI and BMCA bind primarily to APRIL. Similar to BAFF-deficient mice, BAFF-R-null mice show defective splenic B-cell maturation. Mutations in TACI have been identified as an important factor in common variable immunodeficiency.^{32,33}

After B cells egress from the bone marrow, isotype switching, the activation of mature B cells into immunoglobulin-secreting B cells, and their final differentiation into plasma cells are processes that are under T-cell control.³⁴ Cytokines that trigger isotype switching include IL-4 and IL-13, which induces the IgE isotype TGF- β , which triggers IgA, and IL-10, which contributes to the generation of IgG4.

CELLULAR IMMUNITY IL-2

Stimulation of T cells by antigen (signal 1) in the presence of accessory signals provided by the cognate interaction of the B7 molecules (CD80 or CD86) with CD28 (signal 2) and the cytokines IL-1 and IL-6 (signal 3) induces the simultaneous secretion of IL-2 and the expression of high-affinity IL-2R by effector T cells. Subsequently, the binding of secreted IL-2 to

TABLE III. IL-10 superfamily

Interleukin	1° Cell source	Receptor	Activated signal transducer	Biologic effect	Clinical association
IL-10	Monocytes, B cells, Treg cells	IL-10R1/IL-10R2	JAK1, TYK2, STAT1, STAT3	Immune suppression, anti-inflammatory	Burkitt lymphoma, malignant B-cell lymphomas
IL-19	Monocytes	IL-20R1/IL-20R2	STAT1, STAT3	Skin development, immunoregulatory	Psoriasis, asthma
IL-20	Monocytes, skin keratinocytes	IL-20R1/IL-20R2, IL-22R1/IL-10R2	JAK/STAT	Skin development, innate immunity, hematopoiesis	Psoriasis, atherosclerosis, angiogenesis
IL-22	Activated T cells, activated NK cells, T _H 17 cells	IL-22R1/IL-10R2	STAT3	Acute-phase response, innate immunity	Crohn disease, interstitial lung disease, rheumatoid arthritis, psoriasis
IL-24	Melanocytes, monocytes, T _H 2 cells	IL-20R1/IL-20R2, IL-22R1/IL-20R2 (skin only)	STAT3	Proapoptosis, epidermal functions, inflammatory cascade	Melanoma, psoriasis, inflammation
IL-26	Monocytes, memory T cells	IL-20R1/IL-10R2	STAT1, STAT3	Mucosal and cutaneous immunity	T-cell transformation
IL-28, IL-29	DCs	IFNLR1/IL-10R2	JAK1, STAT1, STAT2, STAT3, and STAT5	Antiviral immunity	Hepatitis B/C infections

these IL-2R-expressing T cells induces clonal T-cell proliferation. The requirement for both IL-2 production and IL-2R expression for T-cell proliferation ensures that only effector T cells specific for the antigen inciting the immune response become activated. This is in contrast to Treg cells, which constitutively express IL-2R and can thereby be spontaneously activated in the presence of IL-2. IL-2 is also necessary during Treg cell development in the thymus.³⁵ IL-2 signals through a receptor complex consisting of IL-2-specific IL-2R α (CD25), IL-2R β (CD122), and the common γ chain. In addition to its role as an effector and Treg cell growth factor, IL-2 is also involved in activation of NK cells, B cells, cytotoxic T cells, and macrophages. Many of the immunosuppressive drugs used in the treatment of autoimmune diseases, such as corticosteroids, cyclosporine, and tacrolimus, work, in part, by inhibiting the production of IL-2 by antigen-activated T cells, whereas others (eg, rapamycin) block IL-2R signaling.

IFN- γ

The most important cytokine responsible for cell-mediated immunity is IFN- γ .³⁶ It is the signature cytokine produced by T_H1 cells but is also derived from cytotoxic T cells and NK cells. IFN- γ mediates increased MHC class I and II expression and stimulates antigen presentation and cytokine production by APCs. IFN- γ stimulates mononuclear phagocytic functions, including adherence, phagocytosis, secretion, respiratory burst, and nitric oxide production. The net result is the accumulation of macrophages at the site of cellular immune responses, with their activation into macrophages capable of killing intracellular pathogens. In addition to its effects on mononuclear phagocytes, IFN- γ stimulates killing by NK cells and neutrophils. It stimulates adherence of granulocytes to endothelial cells through the induction of ICAM-1, an activity shared with IL-1 and TNF. As with other interferons, IFN- γ inhibits viral replication. IFN- γ is critical for many aspects of innate and adaptive immunity, but its singular importance in the immune response to intracellular pathogens is shown by the enhanced susceptibility to tuberculosis observed in patients with

mutations that result in defects in its synthesis or responsiveness.³⁷ IFN- γ is an inhibitor of T_H2-mediated allergic inflammatory responses through its capacity to suppress many IL-4-mediated effects.

Cellular responses to IFN- γ are activated through its interaction with a heterodimer receptor consisting of IFN- γ receptor (IFNGR) 1 and IFNGR2. Binding of IFN- γ to the receptor activates the JAK-STAT pathway. JAK1 and JAK2 constitutively associate with IFNGR1 and IFNGR2, respectively, and binding ultimately leads to phosphorylation of 2 STAT1 molecules, as discussed in greater detail below.³⁸

IL-16

IL-16 is a T cell-derived product that is chemotactic for CD4⁺ lymphocytes, eosinophils, and monocytes and uses the CD4 molecule as its receptor.³⁹ The product of this gene undergoes proteolytic processing by caspase-3 and yields 2 functional proteins. The cytokine function is exclusively attributed to the secreted C-terminal peptide, whereas the N-terminal product might play a role in cell-cycle control.⁴⁰

IL-17

Whereas IFN- γ is important in orchestrating the cellular immune response to intracellular pathogens, IL-17 generates T cell-mediated immune responses to extracellular pathogens. It is produced by a unique family of T_H lymphocytes, termed T_H17 cells. IL-17 comprises a structurally related family of 6 proteins (IL-17A through IL-17F) having no sequence similarity to any other cytokine.⁴¹ Because of its unique spectrum of activities, IL-17E is now termed IL-25 and is discussed separately. IL-17A (generally referred to as IL-17) is mainly expressed in CD4⁺ T_H (T_H17) cells and, to a lesser extent, neutrophils, eosinophils, and CD8 T cells. Similar to IL-17A, its most closely structurally related family member, IL-17F, is expressed by T_H17 cells but also activated basophils and mast cells.⁴¹ The primary cellular sources for IL-17B and IL-17C

have not been determined. IL-17D is expressed in resting CD4 T and B cells.

IL-17 induces expression of a variety of cytokines and chemokines from stromal cells, fibroblasts, endothelium, and epithelium, including IL-6, IL-11, granulocyte colony-stimulating factor, GM-CSF, CXCL8, CXCL10 (IFN-inducible protein 10), and TGF- β , cytokines important to both fibroblast activation and neutrophil recruitment. Activation of fibroblasts by IL-17 might contribute to fibrotic autoimmune diseases, and a role for IL-17 has been proposed in inflammatory bowel disease and multiple sclerosis. IL-17 family members are also expressed in patients with asthma.⁴² The tendency to induce neutrophil, but not eosinophil, migration makes it plausible that IL-17 plays a role in severe persistent asthma, in which accumulation of neutrophils is a hallmark. Both IL-17 and IL-17F induce goblet cell hyperplasia and mucus hypersecretion and activate epithelial innate immune responses. IL-17 could therefore plausibly contribute to the development of airway hyperreactivity (AHR), remodeling, neutrophilic infiltration, and subepithelial fibrosis.

Induction of cytokines responsible for PMN recruitment and activation is central to its role in driving cellular immune responses to extracellular pathogens, as suggested by increased susceptibility to infection by *Staphylococcus aureus* and *Citrobacter* and *Klebsiella* species in IL-17-deficient mice.⁴³ In human subjects hyper-IgE syndrome has been characterized by a genetic deficiency in T_H17 cell differentiation.^{44,45} Increased susceptibility of these patients to infections with *Candida* species and *S aureus* is consistent with T_H17 cells' role in immunity against these pathogens.⁴⁶

The IL-17 receptor (IL-17R) family consists of 5 broadly distributed receptors that have individual ligand specificities. IL-17RA is the best described and binds both IL-17A and IL-17F. IL-17RB binds both IL-17B and IL-17E, whereas the less well-described IL-17RC and IL-17RD might undergo alternate splicing to produce soluble (decoy) forms.⁴¹ The least described of these receptors, IL-17RE, is expressed in the pancreas, brain, and prostate.

IL-34

IL-34 is a newly discovered interleukin also having no homology to other cytokines.⁴⁷ It is expressed in numerous tissues but is most abundant in the spleen. The receptor for IL-34 is colony-stimulating factor 1 receptor (CD115), a receptor also used by macrophage colony-stimulating factor (M-CSF), and like M-CSF, IL-34 stimulates monocyte proliferation and function.

ALLERGIC IMMUNITY

An additional outcome of proinflammatory T-cell activation is the development of allergic (and presumably antiparasitic) immunity. Several features specifically associated with the allergic state are regulated by cytokines, including the regulation of IgE, eosinophilia, and mast cell proliferation, and these will be discussed separately.

Regulation of IgE

The inappropriate production of IgE in response to allergen defines atopy and is primarily mediated by IL-4 and IL-13.

IL-4. In addition to T_H2 lymphocytes, IL-4⁴⁸ is derived from basophils, NK T cells, eosinophils, and mast cells. In both eosinophils

and basophils, IL-4 exists as a preformed, granule-associated peptide that can be rapidly released in allergic inflammatory responses. IL-4 stimulates MHC class II, B7 (CD80/CD86), CD40, surface IgM, and low-affinity IgE receptor (CD23) expression by B cells, thereby enhancing the antigen-presenting capacity of B cells. IL-4 induces the immunoglobulin isotype switch from IgM to IgE.^{49,50} IL-4 can be identified in the sera, bronchoalveolar lavage fluid, and lung tissue of asthmatic subjects and in nasal polyp tissue and nasal mucosa of subjects with allergic rhinitis.

In addition to these effects on B cells, IL-4 has important influences on T lymphocytes. As will be discussed later, IL-4 contributes to the differentiation of naive T_H0 lymphocytes toward a T_H2 phenotype. IL-4 is also important in maintaining allergic immune responses by preventing apoptosis of T_H2 lymphocytes.^{51,52} IL-4 renders T_H2 cells refractory to the anti-inflammatory influences of corticosteroids.

Another important activity of IL-4 in allergic inflammation is its ability to induce expression of VCAM-1. This produces enhanced adhesiveness of endothelium for T cells, eosinophils, basophils, and monocytes, but not neutrophils, as is characteristic of T_H2-mediated allergic reactions.⁵³ IL-4 interacts with mast cells to stimulate IgE receptor expression and regulates expression of leukotriene C₄ synthase, thereby determining their capacity to produce cysteinyl leukotrienes.⁵⁴ IL-4 contributes to the excessive mucous production in the asthmatic airway. Functional IL-4 receptors are heterodimers consisting of the IL-4 receptor (IL-4R) α chain interacting with either the shared γ chain or the IL-13 receptor (IL-13R) α 1 chain.⁵⁵ This shared use of the IL-4R α chain by IL-13 and IL-4 explains many of the common biologic activities of these cytokines.

In contrast to these proinflammatory effects, IL-4 downregulates antibody-dependent cellular cytotoxicity by mononuclear phagocytes, inhibits their expression of Fc γ receptors and differentiation into macrophages, and downregulates production of nitric oxide, IL-1, IL-6, and TNF- α while stimulating production of IL-1ra and IL-10.⁵⁶

IL-13. IL-13 shares much of IL-4's biologic activities on mononuclear phagocytic cells, endothelial cells, epithelial cells, and B cells. Thus IL-13 induces the IgE isotype switch and VCAM-1 expression.⁵⁷ Functional IL-13 receptors are heterodimers containing the IL-4R α chain and a unique IL-13R α chain. The 2 IL-13R α chains include the active form (IL-13R α 1) and a decoy (IL-13R α 2), which lacks the motif required for initiating intracellular signaling cascades.⁵⁸ IL-13R α 1 expression is more limited than IL-4 receptors and includes endothelial cells, B cells, mononuclear phagocytes, and basophils but not mast cells or T cells. This more limited distribution of IL-13R α 1 explains the unique ability of IL-4 to induce T_H2 lymphocyte differentiation and mast cell activation. However, IL-13 is more widely produced than IL-4 and is more readily identified in allergic inflammatory tissue.⁵⁹ In murine studies IL-13 has a singularly important role in causing mucus hypersecretion and nonspecific AHR, and its expression results in the characteristic airway metaplasia of asthma with the replacement of epithelial cells with goblet cells.⁵⁹

Eosinophilia

Another characteristic feature of allergic diseases is the presence of increased numbers of activated eosinophils.

IL-5. IL-5 is the most important eosinophilopoietin.⁶⁰ In addition to stimulating eosinophil production and release from the

bone marrow,⁶¹ IL-5 is chemotactic for eosinophils and activates mature eosinophils, inducing eosinophil secretion and enhanced cytotoxicity. Another mechanism by which IL-5 promotes accumulation of eosinophils is through its ability to upregulate chemokine receptors and $\alpha\text{D}\beta 2$ integrins, thereby promoting their adherence to VCAM-1–expressing endothelial cells. IL-5 prolongs eosinophil survival by blocking apoptosis.⁶² Administration of IL-5 causes mucosal eosinophilia and an increase in bronchial hyperreactivity. IL-5–dependent activation of eosinophils is now thought to be less central to the pathophysiology of asthma as a result of the disappointing results in trials using IL-5 antagonists, perhaps because of redundant cytokine profiles involving GM-CSF and heterogeneous presentations of asthma that are less dependent on eosinophils. Thus in asthmatic patients screened for sputum eosinophils, anti-IL-5 does have increased therapeutic benefit.^{63,64} Other activities of IL-5 include basophil differentiation. In addition to $\text{T}_\text{H}2$ -like lymphocytes, other sources for IL-5 include mast cells, NK T cells, and eosinophils themselves. IL-5 interacts with specific IL-5 receptors (IL-5Rs) that consist of a heterodimer containing IL-5R α and a β chain (CD131) shared with GM-CSF receptor and IL-3 receptor (Table 1).⁶⁵

IL-3 and GM-CSF. In addition to IL-5, IL-3⁶⁶ and GM-CSF⁶⁷ also strongly contribute to the activity of eosinophils in allergic inflammation through their capacities to prolong eosinophil survival and to generate activated eosinophils. IL-3 is an important factor that supports the growth of precursors for a variety of hematopoietic cells, including DCs, erythrocytes, granulocytes (especially basophils), macrophages, mast cells, and lymphoid cells. The major source of IL-3 is T lymphocytes, but in patients with allergic inflammation, it is also derived from eosinophils and mast cells.

GM-CSF supports the maturation of DCs, neutrophils, and macrophages. GM-CSF synergizes with other colony-stimulating factors to support the production of platelets and erythrocytes. GM-CSF is an activating factor for mature granulocytes and mononuclear phagocytic cells. In the lungs GM-CSF is uniquely important in the maturation of alveolar macrophages, including their expression of matrix metalloproteinases and reactive oxygen species and their processing of surfactant proteins.^{68,69} The role of GM-CSF in allergic immunity is derived from its shared ability with IL-3 and IL-5 to inhibit apoptosis of eosinophils and thereby prolong the survival of eosinophils at sites of allergic inflammation. GM-CSF is particularly important in the allergic airway because mature activated eosinophils lose their expression of IL-5Rs and responsiveness to IL-5 but instead upregulate GM-CSF receptors. Thus GM-CSF, and not IL-5, might be responsible for the persistent survival and function of eosinophils in the asthmatic airway. These observations provide one explanation for the failure of IL-5 antagonism in asthma trials. GM-CSF activates mature eosinophils, increasing their degranulation, cytotoxicity, and response to chemoattractants.

Mast cell proliferation and activation

Increased numbers of mast cells characterize allergic diseases, and this is a T cell–dependent process. The most important cytokine responsible for mast cell growth and proliferation from hematopoietic precursors is stem cell factor (SCF; or c-kit ligand).⁷⁰ SCF is derived from bone marrow stromal cells, endothelial cells, and fibroblasts. SCF induces histamine release from mast cells but inconsistently from basophils and remains the only cytokine with this property. In addition to being essential for mast

cell differentiation, SCF interacts with other hematopoietic growth factors to stimulate myeloid, lymphoid, and erythroid progenitor cells. Several cytokines, including and especially IL-3, IL-5, IL-6, IL-9, IL-10, IL-11, and nerve growth factor, also contribute to mast cell proliferation.^{71–75} In addition to the factors that stimulate mast cell proliferation, several cytokines induce histamine release from basophils, including several members of the chemokine family (discussed later).

Other $\text{T}_\text{H}2$ cell–derived cytokines involved in allergic inflammation: IL-9, IL-25, and IL-31

IL-9 was originally described as a mast cell growth factor⁷⁶ and contributes to mast cell–mediated allergic responses through its ability to stimulate production of mast cell proteases. In addition, IL-9 increases expression of the IgE high-affinity receptor on mast cells. IL-9 synergizes with IL-4 to enhance the production of IgE and IL-5 to enhance the production of eosinophils. IL-9 supports the growth and survival of T lymphocytes. IL-9 has other important activities in allergic inflammation, including inducing expression of CCL11 (eotaxin-1), IL-5 receptors, and chemokine receptor 4. IL-9 is derived from eosinophils and $\text{T}_\text{H}2$ -like lymphocytes. Its selective production by $\text{T}_\text{H}2$ cells supports a role in allergic inflammation. It appears to be primarily produced by a unique subfamily of $\text{T}_\text{H}2$ cells termed $\text{T}_\text{H}9$ lymphocytes (discussed below).^{77,78}

IL-25 was originally described as a member of the IL-17 family (IL-17E) but has now been given its distinct nomenclature because of its unique spectrum of activities. Similar to IL-4, IL-5, IL-9, and IL-13, it is derived in part from $\text{T}_\text{H}2$ -like lymphocytes. It stimulates release of IL-4, IL-5, and IL-13 from nonlymphoid cells and from T_H lymphocytes themselves, contributing to $\text{T}_\text{H}2$ immune deviation. IL-25 enhances IgE secretion through its ability to stimulate IL-4 and IL-13 production.⁷⁹ IL-25 stimulation of IL-5 production promotes eosinophilopoiesis. IL-25 increases expression of CCL5 (RANTES) and CCL11, which further contribute to the homing of eosinophils to the lungs.⁴¹

IL-31 is a member of the subfamily of hematopoietin cytokines that also includes IL-3, IL-5, and GM-CSF. It is primarily expressed by $\text{T}_\text{H}2$ lymphocytes. Its activities include induction of chemokines that are involved in recruitment of neutrophils, monocytes, and T cells. Overexpression of IL-31 in mice produces an inflammatory infiltrate suggestive of atopic dermatitis.^{80–82} Similarly, the murine model of AHR demonstrates increased expression of the IL-31 receptor.

ANTI-INFLAMMATORY CYTOKINES

In addition to cytokines that stimulate cytotoxic, cellular, humoral, and allergic inflammation, several cytokines have predominantly anti-inflammatory effects, including, as previously discussed, IL-1ra, but also TGF- β and members of the IL-10 family.

TGF- β

TGF- β represents a family of peptides that are arguably the most pleiotropic of the cytokines, including having both stimulatory and inhibitory effects on numerous cell types.⁸³ TGF- β is synthesized as an inactive precursor that requires cleavage for activation. It is produced by numerous cell types, including

eosinophils, monocytes, and T cells. TGF- β is an important stimulant of fibrosis, inducing formation of the extracellular matrix and promoting wound healing and scar formation. In immunity it is largely inhibitory for B cells and T_H/cytotoxic lymphocytes. In general, it inhibits proliferation and induces apoptosis. The production of TGF- β by apoptotic cells creates an immunosuppressive milieu and is one explanation for the absence of inflammation and autoimmunity as a consequence of apoptotic cell death.⁸⁴ It inhibits cytotoxicity of mononuclear phagocytes and NK cells. The primary TGF- β -producing T_H lymphocytes are Treg cells (discussed below), and the expression of membrane-bound TGF- β mediates much of their suppressive activity. TGF- β production by mucosal (T_H3) cells supports the α isotype switch and secretory IgA production by B cells⁸⁵ and is also critical for the maintenance of immune nonresponsiveness to otherwise benign gut pathogens and food allergens. TGF- β is constitutively produced in the healthy lung and helps promote B- and T-cell nonresponsiveness and lessens allergic inflammation through inhibition of IgE synthesis and mast cell proliferation. In established allergic inflammation, eosinophils comprise the most important source of TGF- β ,⁸⁶ and their expression of TGF- β is a cause of the fibrosis observed in patients with asthma.

In contrast to these largely anti-inflammatory influences, TGF- β is central to the differentiation of T_H17 and IL-9-producing T_H2 (T_H9) lymphocytes. These conflicting proinflammatory and anti-inflammatory effects reflect the distinctive actions of TGF- β as a function of which cells are producing it, the stage of the immune response during which it is acting, different signaling pathways it engages, and other divergent influences.

IL-10 family

IL-10 is an important immunoregulatory cytokine with multiple biologic effects on different cell types. Although the primary T-cell source for IL-10 is regulatory T lymphocytes, monocytes and B cells are the major sources of IL-10 in human subjects.⁸⁷ IL-10 forms a homodimer and exerts its biologic function through IL-10R1 and IL-10R2 receptor complex. IL-10 inhibits production of IFN- γ by T_H1 lymphocytes; IL-4 and IL-5 by T_H2 lymphocytes; IL-1 β , IL-6, CXCL8, IL-12, and TNF- α by mononuclear phagocytes; and IFN- γ and TNF- α by NK cells. MHC class II expression by APCs is inhibited by IL-10, as is CD23 (low-affinity IgE receptor [Fc ϵ RII]) and ICAM-1. IL-10 inhibition of expression of the costimulatory molecules CD80 and CD86 by DCs and other APCs eliminates the ability of the APC to provide the accessory signals necessary for T_H cell activation,⁸⁸ which is primarily responsible for the inhibition of cytokine production. However, IL-10 also functions directly on T cells to inhibit their cytokine production by suppressing expression of CD28 and inducible T-cell costimulator.⁸⁹ Constitutive expression of IL-10 in the respiratory tract of healthy subjects has a role in the maintenance of tolerance to allergens, whereas asthma and allergic rhinitis are associated with diminished IL-10 expression.⁹⁰ This diminished IL-10 expression contributes to the development of an inflammatory milieu, reflecting in part the presence of mature DCs.

Other members of the IL-10 family: IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29

These newer members of the IL-10 family cytokines and their receptors loosely share homologies with interferons/interferon

receptors, and many display antiviral activity.⁹¹ In contrast to IL-10, none of these cytokines significantly inhibit cytokine synthesis, an activity that remains unique for IL-10. Features of the IL-10 superfamily are summarized in Table III.

IL-19 shares 21% amino acid identity with IL-10, but as with other members of the IL-10 superfamily, it is the exon-intron structure that primarily defines their homology. Within the immune system, IL-19 is primarily produced by monocytes, and its expression can be induced by LPS, IL-4, and GM-CSF. IL-19 signals through a receptor complex composed of the IL-20 receptor (IL-20R) 1 and IL-20R2 chains and activates monocytes to release IL-6, TNF- α , and reactive oxygen species. IL-19 contributes to T_H2 immune deviation, as well as the development of airway inflammation, in murine models, and its increased expression has been observed in asthmatic patients.⁹²

Similar to IL-19, IL-20⁹³ signals through the IL-20R1/IL-20R2 heterodimer; however, IL-20 also binds to the receptor complex composed of IL-22 receptor (IL-22R) 1/IL-20R2. IL-20 is predominantly expressed by monocytes and skin keratinocytes, and it is overexpressed in patients with psoriasis. It induces keratinocyte proliferation, and overexpression in mice is lethal, secondary to defective skin formation.

IL-22 is derived from T lymphocytes, mast cells, and, at lower levels, activated NK cells.⁹⁴ Among T-lymphocyte subsets, IL-22 is preferentially expressed by T_H17 cells. Notably, patients with psoriasis, Crohn disease, interstitial lung diseases, and rheumatoid arthritis all have evidence of increased levels of IL-22 that correlate with disease severity.⁹⁵⁻⁹⁷ The IL-22 receptor complex is a heterodimer consisting of IL-22R1/IL-10R2 chains. Neither resting nor stimulated immune cells express IL-22R1, and therefore despite its structural similarity to IL-10, immune cells are not the target cells of IL-22. The predominant biologic activity described for IL-22 is induction of acute-phase proteins by hepatocytes, including serum amyloid A protein, and it likely provides a protective role in liver injury. In addition, IL-22 leads to the production of antimicrobial peptides, and consistent with its expression by T_H17 cells, it is presumed to play an important role in defense against extracellular pathogens.

IL-24 is produced by both monocytes and T_H2 lymphocytes in an IL-4-inducible fashion. Originally identified as a tumor-suppressor molecule (melanoma differentiation-associated gene 7) that was expressed in healthy melanocytes but not metastatic melanoma cells, it was subsequently discovered to share structural homology with IL-10 and to be located within the same locus on chromosome 1. IL-24 signals through a heterodimer consisting of IL-20R1/IL-20R2. Its potential role as a cancer therapeutic is derived from evidence that IL-24 induces antitumor immune responses with significant independent "bystander" antitumor effects.^{98,99} Given the apparently ubiquitous apoptotic effect on malignant cells, the lack of an effect on normal cells, and the absence of significant side effects (eg, cytokine storm), IL-24 is a potential cancer therapeutic.

IL-26 is located in a chromosomal cluster with IL-22 and IFN- γ in an area thought to contribute to allergic and autoimmune diseases; in contrast, IL-10, IL-19, IL-20, and IL-24 cluster separately. IL-26 is primarily generated by monocytes and T memory cells. IL-26 has a unique receptor consisting of a heterodimer of IL-20R1/IL-10R2.¹⁰⁰ Binding of the IL-26 receptor leads to induction of CXCL8, IL-10, and ICAM-1.

As previously discussed, the type III interferons IL-28 and IL-29 are closely related to the type I interferons, but their genomic

organization and receptor use is more similar to that of members of the IL-10 family.

IL-35

IL-35 is a dimer composed of IL-12p35 and IL-27p28 (IL-30) chains. It is primarily secreted by Treg cells and suppresses inflammatory responses by causing proliferation of Treg cells while reducing the activity of T_H17 cells.¹⁰¹ Studies using a murine model show that the absence of either IL-35 chain from Treg cells reduces their ability to suppress inflammation.¹⁰²

T_H LYMPHOCYTE FAMILIES

T_H1, T_H2, and T_H17 lymphocytes

Subclasses of T_H lymphocytes can be identified based on their repertoire of cytokines (Table IV).¹⁰³ Naive T_H0 cells produce primarily IL-2 but might also synthesize cytokines characteristic of effector T lymphocytes. In contrast to murine studies, categorically distinct T_H cytokine profiles are seldom apparent in human cells, although there remains an inverse relationship between the tendency of T lymphocytes to produce IFN- γ as opposed to IL-4/IL-5 or IL-17. In human subjects T_H1 cells primarily produce IFN- γ and TNF- β but not IL-4 and IL-5. T_H2 cells more prominently produce IL-4, IL-5, IL-9, and IL-13 but not IFN- γ . T_H1 lymphocytes promote cell-mediated immune responses and are important in antibody-dependent immunity. T_H17 cells are more important in the T cell-mediated immune response to extracellular pathogens and likely contribute to autoimmune diseases. T_H2 lymphocytes produce IL-4, IL-5, and IL-13, which induce antiparasitic and allergic immune responses. A subclass of T_H2 cells characterized by prominent IL-9 production has recently been described (T_H9 cells).^{77,78}

Cytokines involved in T_H1 differentiation

One of the more important questions in understanding the cause of immune disorders is to determine the basis for effector T-cell differentiation in response to antigen. The most critical element in determining T_H differentiation is the cytokine milieu in which the T lymphocyte is activated (Table IV). T_H1 differentiation is induced and maintained through the influences of IL-12, IL-18, and IL-27, with IL-12 providing the most important role.¹⁰⁴ IL-12 interacts with naive T_H lymphocytes to activate STAT4, leading to expression of the transcription factor T-bet expressed in T cells (T-bet). T-bet is a nuclear transcription factor that is the master regulator responsible for the differentiation of T_H1 cells. Actions of T-bet include production of IFN- γ and IL-12R. Simultaneously, it blocks alternative T_H differentiation pathways by suppressing expression of T_H2 cytokines, such as IL-4, and acting as a negative regulator of T_H17 differentiation. Similar to IL-12, IL-27 also activates STAT4, leading to increased expression of T-bet and IFN- γ . Addition of recombinant IL-27 to naive T cells in culture under T_H2-polarizing conditions results in decreased expression of GATA-3, the transcription factor that is the master regulator for T_H2 development, along with a decrease in production of IL-4 and other T_H2 cytokines.¹⁰⁵ Once T_H1 cells become differentiated, newly synthesized IFN- γ , acting through STAT-1, also increases expression of T-bet and functions as a negative regulator of T_H17 and T_H2 differentiation. IL-18 upregulates IL-12R expression and is a growth factor for T_H1

cells. IL-12-producing DCs are the most important mediator of T_H1-like immune deviation. In addition, insofar as mononuclear phagocytes are an additional source of IL-12, this suggests a mechanism whereby antigens likely to be processed by macrophages, including obligate intracellular bacteria (eg, mycobacteria), produce T_H1 responses.

Cytokines involved in T_H2 differentiation: IL-4, IL-19, IL-25, IL-33, and thymic stromal lymphopoietin

One determinant of T_H2 differentiation is IL-4 itself.¹⁰⁶ IL-4 activates STAT6, which in turn promotes expression of GATA-3, the master regulator of T_H2 cells, and suppresses expression of T-bet. GATA-3 potentiates IL-4 expression and suppresses expression of T_H1 differentiation and cytokine (IFN- γ) production. IL-4 and GATA-3 similarly inhibit differentiation of T_H17 lymphocytes. Other transcription factors, including especially MAF and NFAT, contribute to IL-4 and other T_H2 signature cytokine production once T_H2 differentiation is established. The original source of the IL-4 responsible for T_H2 differentiation can be the naive T_H0 lymphocytes themselves. Basophils, NK T cells, and mast cells are also capable of robust IL-4 secretion.^{107,108} Whatever the source is for the IL-4, the end result is that in a milieu in which allergic inflammation is present (eg, bronchial lymphatic tissue), more and more extensive allergenic responses against bystander antigens develop.

IL-19, a member of the IL-10 family, is primarily produced by mononuclear phagocytic cells, and its expression is upregulated by IL-4 and downregulated by IFN- γ . IL-19 promotes T_H2 immune deviation.¹⁰⁹ IL-19 expression is important to the development of airway inflammation in murine models, and its increased expression has been observed in asthmatic patients.⁹²

As discussed, IL-25 induces expression of T_H2 signature cytokines from numerous cell types but also specifically contributes to T_H2 immune deviation.¹¹⁰ Its production by T_H2 lymphocytes suggests a positive feedback cascade.

Currently, the 2 most important cytokines responsible for T_H2 immune deviation are considered to be IL-33 and thymic stromal lymphopoietin (TSLP). Similar to IL-18, IL-33¹¹¹ is an IL-1–like cytokine that signals through an IL-1 receptor–related protein.¹¹² As with IL-1 and IL-18, IL-33 is produced as an inactive precursor, and its secretion and activation are dependent on cleavage by caspase-1. IL-33 is expressed by bronchial epithelial cells, fibroblasts, smooth muscle cells, keratinocytes, macrophages, and DCs. IL-33 receptors are expressed on T cells (specifically nascent and mature T_H2 cells), macrophages, hematopoietic stem cells, mast cells, and fibroblasts. Administration of IL-33 induces T_H2 immune deviation and cytokine production, causes increased IgE levels, and generates profound mucosal eosinophilic inflammation in the lung and gastrointestinal tract.^{111,113} Administration of an IL-33 receptor antagonist reduces production of T_H2 cytokines and airway inflammation in murine asthma models.^{112,114} Its primary production by epithelial cells suggests a mechanism whereby the respiratory tract can generate a “danger signal” that will drive a subsequent T_H2 immune response, arguably the initial trigger of asthma.

The cytokine TSLP has also been suggested as a primary instigator of T_H2 immune deviation.¹¹⁵ TSLP is expressed by epithelial cells of the skin, gut, and lung and activates DCs in such a way as to promote T_H2 cytokine production by their subsequently engaged effector T cells. The expression of TSLP in the lungs of

TABLE IV. T_H lymphocyte families

Family	Cytokine repertoire	Cytokines involved in differentiation	Transcription factors involved in differentiation
T _H 1	IFN- γ , TNF- α , TNF- β , GM-CSF, IL-2, IL-3	IL-12 : activates STAT4, leading to expression of T-bet; induces IL-18R expression IL-18 : upregulates IL-12R, further induces IFN- γ expression IL-27 : activates STAT4, leading to increased expression of T-bet and IFN- γ IFN-γ : increases expression of T-bet by increasing expression of STAT1; negative regulator of T _H 17 and T _H 2	T-bet : master regulator of T _H 1 cells; potentiates production of IFN- γ and IL-12R β 2; suppresses T _H 2 and T _H 17 differentiation STAT4 : produced in response to IL-12 and potentiates production of IFN- γ STAT1 : increases expression of T-bet; negative regulator of T _H 17
T _H 2	IL-2, IL-3, IL-4, IL-5, IL-9, IL-13, IL-24, IL-25, IL-31, TNF- α , GM-CSF	IL-4 : activates STAT6, leading to expression of GATA-3; negative regulator of T _H 17, IL-19, IL-25, IL-33 TSLP : promote differentiation and survival of T _H 2-like cells	GATA-3 : master regulator of T _H 2 cells; potentiates IL-4 expression; suppresses expression of T _H 1 differentiation and cytokines expression (IFN- γ) MAF : contributes to IL-4 production once a T _H 2 program is established; inhibition of T _H 17 differentiation STAT6 : promotes T _H 2 cell differentiation; negative regulator of T-bet expression and T _H 1 differentiation NFAT : increases transcription of IL-4
T _H 9	IL-4, IL-9	TGF-β : induces the high IL-9 phenotype of T _H 2-like lymphocytes	
T _H 17	IL-17 (IL-17A), IL-17F, IL-21, IL-22	IL-6 : differentiation factor for the generation of T _H 17 cells TGF- β , IL-21 IL-23 : support the differentiation and function of T _H 17 cells in the additional presence of IL-6	ROR-γt (retinoic acid-related orphan nuclear receptor) is the master regulator of T _H 17 cell differentiation STAT3 : activated by IL-6 and essential for T _H 17 differentiation
nTreg/iTreg	IL-10	TGF-β : differentiation factor for the generation of nTreg cells IL-10 : important for differentiation of peripheral iTreg cells, role in nTreg development uncertain IL-2 : promotes survival, proliferation, and survival of nTreg cells through their constitutive expression of CD25	FOXP3 : master regulator of thymus-derived nTreg cells
T _H 3	TGF- β , IL-10		

mice produces severe AHR,^{116,117} and similarly, expression in the skin produces skin inflammation suggestive of atopic dermatitis.¹¹⁸ TSLP is highly expressed in the keratinocytes of patients with atopic dermatitis and the lungs of asthmatic patients.¹¹⁹ The TSLP receptor is a heterodimer composed of a unique TSLP-specific receptor and the IL-7 receptor α chain (CD127). TSLP receptors are primarily expressed by DCs, but their expression by mast cells also promotes secretion of T_H2 signature cytokines. As with IL-33, its prominent expression by epithelium suggests an initial triggering event plausibly central to the development of allergic diseases of the skin and airways.

T_H9 lymphocytes are a recently described proposed subfamily of T_H2 cells characterized by prominent production of IL-9 and relatively less IL-4. They result from the differentiation of T_H2 cells in the concomitant presence of TGF- β .^{77,78}

T_H17 lymphocytes

The selective production of IL-17 by clonal T_H lymphocytes has led to the recognition of the T_H17 cell as a distinct lymphocyte subset.¹²⁰ The presence of distinct pathways involved in differentiation of IL-17-producing T lymphocytes (Table IV) and that counterregulate development of the alternative T_H1- and T_H2-like pathways further supports the concept that these T_H17-producing T_H lymphocytes comprise a distinct lineage. The mechanisms underlying T_H17 differentiation in human subjects are not fully

established. In mice IL-6 acting in the additional presence of TGF- β is the most important cytokine responsible for differentiation of T_H17 cells.¹²¹ IL-21 and IL-23 further contribute to T_H17 differentiation and expansion of established T_H17 cells.¹²² Only in the absence of IL-6 does TGF- β promote differentiation into Treg cell pathways, as previously described. The highly pleiotropic cytokine TGF- β is therefore involved in the differentiation of Treg cells or, in the additional presence of IL-6 or IL-4, can be switched to induced T_H17 or T_H9 cells, respectively.¹²³ The action of IL-6 in inducing T_H17 is mediated through its activation of STAT3. The net result is activation of retinoic acid receptor-related orphan receptor (ROR) γ t, the master regulating transcription factor for T_H17 cells. Heterozygous mutations in STAT3 produce the hyper-IgE syndrome,^{124,125} a condition characterized by deficient T_H17 lymphocytes.^{44,46}

TREG LYMPHOCYTE FAMILIES: NATURAL TREG, INDUCED TREG, AND T_H3 CELLS

In addition to traditional T_H subclasses, much progress has been made in the past several years in identifying and clarifying the characteristics of several families of regulatory T lymphocytes (Table V).¹²⁶ These include peripherally differentiated (induced) IL-10-producing lymphocytes, termed induced Treg (iTreg) cells; thymic-derived CD25⁺ natural Treg (nTreg) cells; and

TABLE V. CD4⁺ T cells with regulatory activity

Treg cell subtype	Characteristics
nTreg (natural Treg cells)	CD25 ⁺ Foxp3 ⁺ thymus derived. Not dependent on IL-10 for their biologic activity. Mediate self-tolerance/prevent autoimmune disease. Not likely to be relevant to acquired tolerance to allergens.
T _H 3	Characterized by TGF-β (± IL-10) production. Mediate mucosal tolerance/antigen-specific IgA production. Not relevant to inhalant allergy or immunotherapy.
iTreg (induced Treg cells)	Peripheral-derived Treg cells. IL-10 responsible for their biologic activity (± TGF-β). Thought to be derived from T _H 1/T _H 2-like effector lymphocytes ± CD25 expression (reflecting their effector function/activation) ± FOXP3 expression. Induced in contact-dependent fashion by membrane TGF-β. Proposed mechanism of immunotherapy

TGF-β-producing T_H3 cells. Thymus-derived nTreg cells are characterized by their constitutive expression of IL-2Rα chains (CD25) and the transcription factor FOXP3. Similar to the role assumed by T-bet in T_H1, GATA-3 in T_H2, and RORγt in T_H17 differentiation, FOXP3 serves as a master regulator of nTreg cells (Table IV). Although they secrete IL-10, membrane TGF-β appears to be primarily responsible for mediating their immune suppression, which is contact dependent. nTreg cells are produced in response to expression in the thymus of self-antigens and are thereby important for the prevention of autoimmunity. These nTreg cells are unlikely to be involved in tolerance to antigens not presented in the thymus (eg, in either tolerance to allergens in healthy subjects or in the immune benefits associated with allergen immunotherapy). T_H3 cells are primarily gut derived and generate mucosal tolerance. Reflecting their prominent production of TGF-β, in addition to tolerance, they are relevant to secretory IgA production. In contrast to thymus-derived nTreg cells, an additional, less well-characterized class of adaptive Treg cells has been described that can develop in the periphery. These iTreg cells differentiate from pre-existing effector T lymphocytes or possibly circulating naive T_H0 cells and are characterized by their prominent production of IL-10. iTreg expression of FOXP3 and CD25 is controversial but does occur. For example, it is unclear whether CD25 expression reflects the constitutive expression of this component of IL-2R, the signature characteristic of nTreg cells, or the derivation of iTreg cells from activated effector T cells that are transiently expressing CD25. The induction of IL-10-producing iTreg cells plays a key role in reducing allergen-specific T-cell responsiveness after immunotherapy.^{127,128}

SIGNAL TRANSDUCTION BY CYTOKINE RECEPTORS

Two key events are required to initiate the intracellular signaling pathways activated by cytokines. First, binding of a cytokine to its receptor mediates the transduction of signals from the extracellular environment into the cytoplasm. Second, activation of tyrosine kinases results in phosphorylation of the receptor and signaling molecules, events that ultimately lead to

delivery of intracellular signals. With the notable exceptions of the receptors for SCF (c-kit or CD117) and M-CSF (colony-stimulating factor 1 receptor [also used by IL-34]), cytokine receptors generally do not have cytoplasmic domains with intrinsic tyrosine kinase activity; however, cytokine receptors do activate cytoplasmic tyrosine kinases.

Although numerous biochemical cascades are involved in cytokine signaling, this discussion will primarily focus on 2 families of protein tyrosine kinases, termed JAKs and STATs, which uniquely function in cytokine signaling (Fig 1, A).^{129,130} The role for JAK family members in the pathway to gene activation was largely deduced from studies of signal transduction by the interferon receptors. The 2 chains of the IFN-α receptor bind JAK1 and TYK2, respectively, whereas the 2 chains of the IFN-γ receptor bind JAK1 and JAK2. The receptors and the JAKs themselves become phosphorylated, and this phosphorylated complex becomes the catalyst for the phosphorylation of cytoplasmic substrates. There are 4 JAKs, JAK1, JAK2, JAK3, and TYK2, and as such, receptor signaling is mediated by a surprisingly limited number of highly redundant tyrosine kinases. For example, JAK2 is involved in GM-CSF, granulocyte colony-stimulating factor, IL-6, and IL-3 signaling.

JAK1 and JAK3 are tyrosine phosphorylated in response to IL-2, IL-4, and all the other cytokines whose receptors are members of the shared γ chain family. This use of JAK3 by the shared γ chain is consistent with JAK3 deficiency sharing the severe combined immunodeficiency syndrome phenotype with γ chain deficiency. Once engagement of a cytokine receptor has led to tyrosine phosphorylation of the receptor and of receptor-associated JAKs, the next step in signal transduction involves the tyrosine phosphorylation of the STATs (Table VI).^{129,130} After their activation, these proteins migrate to the nucleus, where they bind to specific regulatory sequences in the promoters of cytokine-responsive genes, thereby initiating gene transcription. As with the JAKs, the function of STATs was originally characterized with studies involving the biochemical events of interferon-induced gene transcription. Ligand binding of IFN-α/β induces the formation of a trimer composed of STAT1, STAT2, and a non-STAT protein, interferon regulatory factor protein p48. Evidence suggests that STAT2 is the crucial STAT in establishing type I interferon activity because it is specifically recruited to DNA sequences comprising interferon-stimulated response elements present in the promoters of type I interferon-responsive genes.¹³¹ In contrast, the stimulation of cells with IFN-γ results in the tyrosine phosphorylation of STAT1 by JAK1 and JAK2 but not of STAT2. These homodimers of STAT2 recognize IFN-γ activation site DNA sequences in the promoters of IFN-γ-responsive genes. Similar to type I interferons, IL-28 and IL-29 (IFN-λs) induce the activation of the JAK/STAT signaling pathways.^{26,132,133} JAK1 in particular is critical in mediating IFN-λ-induced STAT phosphorylation.¹³² IFN-λ induces homodimers of STAT2 capable of recognizing both interferon-stimulated response element and IFN-γ activation site sequences. It is therefore not surprising that many genes whose expression is classically induced by both type I interferons and IFN-γ are also induced by IFN-λs.

There are 5 additional members of the STAT family. STAT3, STAT4, and STAT6 were identified as IL-6-, IL-12-, and IL-4-inducible peptides, respectively. Although important in cytokine signaling, STAT5 (consisting of 2 homologous genes, STAT5A and STAT5B) was originally defined as a prolactin-activated

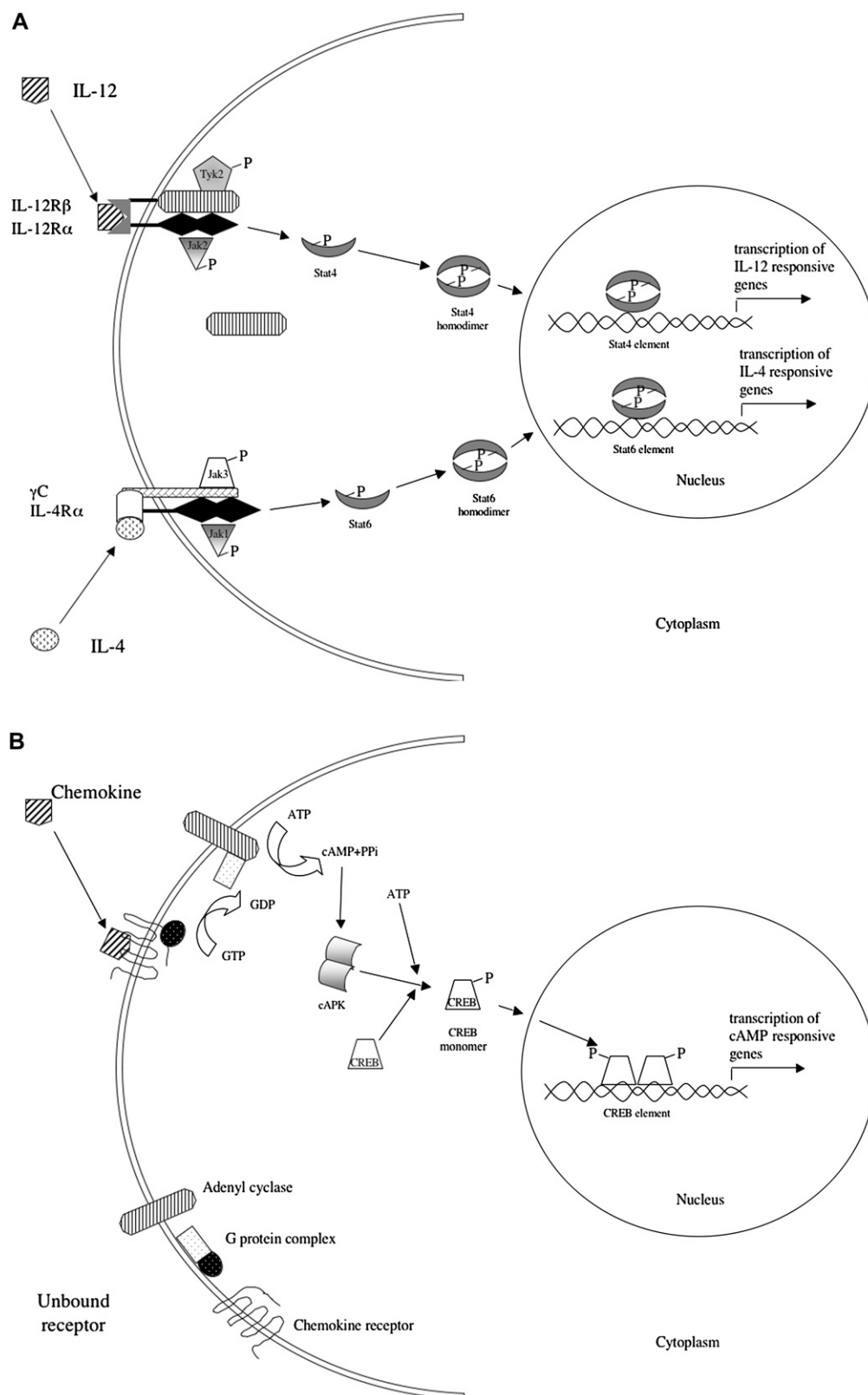


FIG 1. Comparison of cytokine and chemokine signaling. **A**, Generalized cytokine signaling: a model of intracellular signaling pathways leading to transcription modulation by IL-4 and IL-12 (see text for details). **B**, Generalized chemokine signaling: a model of chemokine binding and activation of G proteins leading to induction of transcription factors and gene expression (see text for details). *cAPK*, cAMP-dependent protein kinase; *CREB*, cAMP response element binding protein.

TABLE VI. STAT family

STAT protein	Cytokine
STAT1	IFN- α / β * IFN- γ * Epidermal growth factor, platelet-derived growth factor, M-CSF, IL-6, IL-11
STAT2	IFN- α / β * IFN- λ
STAT3	IL-6 (IL-6 family cytokines, including IL-6, oncostatin M, and LIF) trigger STAT3 through the gp130 receptor IL-5, IL-10, epidermal growth factor, human growth factor
STAT4	IL-12 (essential endogenous mediator of T _H 1 differentiation)
STAT5A and STAT5B†	Prolactin IL-2, IL-3, IL-7, GM-CSF, erythropoietin, thrombopoietin
STAT6	IL-4 (essential endogenous mediator of T _H 2 differentiation)

*IFN- α / β signaling complex (interferon-stimulated gene factor 3) consists of trimers of STAT1 (alternatively spliced α [p91] or β [p84] peptides), STAT2, and the non-STAT protein p48. IFN- γ signaling complex consists of dimers of STAT1.

†Two distinct genes that are 90% identical.

peptide. Engagement of the IL-4 receptor leads to the activation of JAK1, which in turn phosphorylates STAT6. STAT6 is necessary for IL-4-dependent expression of IL-4 receptor (IL-4R) α , the ϵ heavy chain, MHC class II, CD23, and mucin.¹³⁴ An endogenous inhibitor of STAT6 is referred to as the suppressor of cytokine signaling 1.¹³⁵ Suppressor of cytokine signaling 1 inhibits IL-4-induced activation of JAK1 and STAT6 and thereby effectively inhibits IL-4 signaling.

Compared with the number of cytokines, relatively few STATs exist, and therefore the signaling pathways of numerous distinct cytokines share common STAT proteins. For example, epidermal growth factor, platelet-derived growth factor, M-CSF, IL-6, IL-11, and the interferons all activate STAT1 α . Mechanisms must exist that lead to the distinct responses to different cytokines. In part these reflect the activities of other signaling pathways stimulated by cytokine receptors. For example, the Ras-dependent pathway is also activated by members of the cytokine receptor families. In this cascade Ras, Raf-1, Map/Erk kinase kinase, and mitogen-activated protein kinases (MAPKs) are sequentially phosphorylated and activated. The MAPK pathway is associated with induction of several transcription factors, such as c-myc, c-fos, and nuclear factor-IL-6. This ras pathway is activated by several growth factors, as well as by the cytokines IL-2, IL-3, IL-5, and erythropoietin. An example of another complementary distinct pathway used for cytokine signaling is provided by IL-4, which activates the signaling protein insulin response substrate (IRS) 1 and its homologue, IRS-2. IRS-1 and IRS-2 regulate cellular proliferation and protection from apoptosis.

CHEMOKINES

Chemokines are a group of small (8–12 kd) proteins that possess the ability to induce cell migration or chemotaxis in numerous cell types, including neutrophils, monocytes, lymphocytes, eosinophils, fibroblasts, and keratinocytes. Activity is regulated through binding to members of the 7-transmembrane, G protein-coupled receptor superfamily. This section uses the systematic nomenclature with the common names listed in parentheses the first time the chemokine is described. To date, 52 chemokines and

20 chemokine receptors have been described, which are listed in Table VII^{136,137} along with the known chromosomal location and physiologic properties of each. Many of the chemokine receptors can bind more than 1 ligand, allowing extensive overlap and redundancy of chemokine function.

Originally, chemokines were described as inflammatory mediators produced at sites of infection or injury or in response to proinflammatory stimuli. Inflammatory chemokines recruit and activate leukocytes to mount an immune response and initiate wound healing. Although chemotaxis stands as the cardinal feature of chemokines, their physiologic role is more complex than originally described, with many having additional homeostatic or housekeeping functions. These functions range from trafficking of lymphocytes during hematopoiesis, antigen sampling in secondary lymphoid tissue, immune surveillance, and organ development.¹³⁶ In general, homeostatic chemokines are expressed in specific tissues or organs, whereas inflammatory chemokines are produced by many cell types in multiple locations.

Classification

Chemokines are characterized by the presence of 3 to 4 conserved cysteine residues and can be subdivided into 4 families based on the positioning of the N-terminal cysteine residues (Table VII). Within a subfamily, there exists 30% to 90% amino acid identity between members; however, across subfamilies, the amino acid identity decreases to less than 30%. The C-X-C subfamily is characterized by the separation of the first 2 cysteines by a variable amino acid. The CXC chemokines can be broken into 2 general subgroups: ELR and non-ELR containing. ELR is a conserved amino acid motif (Glu-Leu-Arg) immediately preceding the first cysteine residue. The ELR chemokines (CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, and CXCL8) are angiogenic and act mainly through the CXCR2 receptor. In contrast, the non-ELR chemokines (CXCL4, CXCL9, CXCL10, CXCL11 and CXCL17) are angiostatic and act mainly through the CXCR3B receptor. This non-ELR group of chemokines can be induced by a variety of interferons. The exception to this is CXCL12, which is a non-ELR chemokine but is angiostatic and binds to the CXCR4 on endothelial cells. In the C-C subfamily the cysteine residues are adjacent to each other. The majority of the known chemokines are contained in these 2 families. Additionally, these groups can be distinguished by their primary target cell, with the C-X-C subfamily targeting neutrophils and the C-C family targeting eosinophils, monocytes, and T cells. A third family of chemokines, referred to as the C subfamily, lacks the first and third cysteines, containing only a single cysteine residue in the conserved position. This subfamily includes the lymphocyte-specific chemotactic peptide XCL1 (lymphotactin).¹³⁸ A fourth subfamily (CX3C) has the 2 N-terminal cysteine residues separated by 3 variable amino acids.¹³⁹ In human subjects this family only has 1 member, CX3CL1 (fractalkine), and it is unique in that it has a mucin-like glycosylated stalk that allows it to exist as a soluble or membrane-bound chemokine.

Receptors and signal transduction

Receptor number on the cell surface varies from 3000 per cell on monocytes and lymphocytes for CCR1 and CCR2 to 40,000 to 50,000 per cell on eosinophils for CCR3.^{140–142} Receptor numbers can be altered depending on the environmental milieu and the

TABLE VII. CC, C, CXC, and CX3C chemokine/receptor families

Systematic name	Human chromosome	Common name	Receptor	Physiologic features
CC chemokine/receptor family				
CCL1	17q11.2	I-309	CCR8, R11	Inflammation
CCL2	17q11.2	MCP-1, MCAF	CCR2	Inflammation
CCL3	17q11-q21	MIP-1 α /LD78 α	CCR1, R5	Inflammation, homeostasis
CCL3L1	17q21.1	LD78 β	CCR5	Inflammation
CCL4	17q11.2	MIP-1 β	CCR5	Inflammation
CCL4L1	17q12	None	CCR5	Inflammation
CCL4L2	17q12	None	CCR5	Inflammation
CCL5	17q11.2	RANTES	CCR1, R3, R4, R5	Inflammation
CCL6	(mouse)	C-10	CCR1, R2, R3	Unknown
CCL7	17q11.2	MCP-3	CCR1, R2, R3	Inflammation
CCL8	17q11.2	MCP-2	CCR1, R2, R5, R11	Inflammation
CCL9	(mouse)	MRP-2/MIP-1 γ	CCR1	Unknown
CCL10	(mouse)	MRP-2/MIP-1 γ	CCR1	Unknown
CCL11	17q11.2	Eotaxin	CCR3	Inflammation, homeostasis
CCL12	(mouse)	MCP-5	CCR2	Unknown
CCL13	17q11.2	MCP-4	CCR1, R2, R3, R11	Inflammation
CCL14	17q11.2	HCC-1	CCR1	Inflammation
CCL15	17q11.2	HCC-2, Lkn-1	CCR1, R3	Inflammation
CCL16	17q11.2	HCC-4, LEC	CCR1	Inflammation
CCL17	16q13	TARC	CCR4	Inflammation, homeostasis
CCL18	17q11.2	DC-CK1, PARC	Unknown	Homeostasis
CCL19	9p13	MIP-3 β , ELC	CCR7, R11	Homeostasis
CCL20	2q33-q37	MIP-3 α , LARC	CCR6	Inflammation, homeostasis
CCL21	9p13	6Ckine, SLC	CCR7, R11	Homeostasis
CCL22	16q13	MDC, STCP-1	CCR4	Inflammation, homeostasis
CCL23	17q11.2	MPIF-1	CCR1	Inflammation
CCL24	7q11.23	MPIF-2, Eotaxin-2	CCR3	Inflammation
CCL25	19p13.2	TECK	CCR9, R11	Homeostasis
CCL26	7q11.23	Eotaxin-3	CCR3	Inflammation
CCL27	9p13	CTACK, ILC	CCR2, R3, R10	Homeostasis
CCL28	5p12	MEC	CCR3, R10	Inflammation, homeostasis
C chemokine/receptor family				
XCL1	1q23	Lymphotactin	XCR1	Inflammation
XCL2	1q23	SCM1-b	XCR1	Inflammation
CXC chemokine/receptor family				
CXCL1 (ELR)	4q12-q13	GRO α , MGSA- α	CXCR2>R1	Inflammation, homeostasis
CXCL2 (ELR)	4q12-q13	GRO β , MGSA- β	CXCR2	Inflammation
CXCL4 (non-ELR)	4q12-q13	GRO γ , MGSA- γ	CXCR2	Inflammation
CXCL4L1 (non-ELR)	4q12-q21	PF4	CRCR3	Inflammation
CXCL5 (ELR)	4q12-q13	ENA-78	CXCR1, R2	Inflammation
CXCL6 (ELR)	4q12-q13	GCP-2	CXCR1, R2	Inflammation
CXCL7 (ELR)	4q12-q13	NAP-2	CXCR2	Inflammation
CXCL8 (ELR)	4q12-q13	IL-8	CXCR1, R2	Inflammation
CXCL9 (non-ELR)	4q21.21	Mig	CXCR3	Inflammation
CXCL10 (non-ELR)	4q21.21	IP-10	CXCR3	Inflammation
CXCL11 (non-ELR)	4q21.21	I-TAC	CXCR3	Inflammation
CXCL12 (non-ELR)	10q11.1	SDF-1 α / β	CXCR4, R7	Inflammation, homeostasis

(Continued)

Table VII. (Continued)

Systematic name	Human chromosome	Common name	Receptor	Physiologic features
CXCL13 (non-ELR)	4q21	BLC, BCA-1	CXCR3, R5	Inflammation, homeostasis
CXCL14 (non-ELR)	5q31	BRAK, bolekin	Unknown	Homeostasis
CXCL15 (ELR)	(mouse)		Unknown	Unknown
CXCL16 (non-ELR)	17p13	SR-PSOX	CXCR6	Inflammation
CXCL17 (non-ELR)	19q13.2	VCC1, DMC	Unknown	Inflammation, homeostasis
CX3C chemokine/ receptor family				
CXCCL1	16q13	Fractalkine	CR3CR1	Inflammation

This table is an adaptation of the tables presented by Zlotnik and Yoshie¹³⁷ and Moser and Loetscher.¹³⁶ The terms *inflammation* and *homeostasis* under the “Physiologic features” heading refer to inflammatory chemokines and homeostatic chemokines, respectively. The most common names for the human ligands are listed but are not all inclusive of ligand names found in the literature. ELR is a conserved amino acid motif (Glu-Leu-Arg) immediately preceding the first cysteine amino acid in the CXCL chemokine family.

signals a cell receives. A given cell can express multiple chemokine receptors, each of which can induce specific signals, suggesting that each receptor can signal through different pathways. Additional complexities of receptor use are emerging through the recent demonstration that CXCR4 and CCR5 can heterodimerize and transmit a compound signal when stimulated with their respective ligands.¹⁴³ The ability to signal through different pathways is due in part to the heptahelical transmembrane property of the receptors. A large surface area, allowing interactions with the α and $\beta\gamma$ subunits of the heterotrimeric G proteins and other effector molecules, is created by looping of the receptor along the inner plasma membrane and the lateral orientation of the carboxy terminus.¹⁴⁴

Signaling is initiated after binding of the chemokine to the receptor, which activates guanine exchange factors, allowing replacement of guanine diphosphate with guanine triphosphate on the $G\alpha$ subunit (Fig 1, B). The result is dissociation of the heterotrimeric G protein complex from the receptor and separation of the $G\alpha$ and $G\beta\gamma$ subunits. The $G\alpha$ subunit is able to directly activate the Src family kinases, leading to activation of the MAPKs and protein kinase B.¹⁴⁵ Signaling through the $G\beta\gamma$ subunit is more complex, involving at least 3 separate pathways. $G\beta\gamma$ can activate protein kinase B and the MAPKs through phosphatidylinositol 3-kinase γ and PKC through phospholipase C and Pyk-2.¹⁴⁶⁻¹⁴⁸ Activation of phospholipase C increases the intracellular calcium ion concentration. Calcium influx activates many cellular processes, including degranulation of neutrophils, eosinophils, and basophils. Other pathways activated by chemokines include phospholipases A₂ and D, protein tyrosine kinases, low-molecular-weight guanine triphosphatases, Rho, and Rac. Several other reviews cover chemokine signaling in more extensive detail.^{144,149} Signaling through the G proteins ends when a phosphate group is removed from the guanine triphosphate bound to the $G\alpha$ subunit reforming guanine diphosphate. This allows the $G\alpha$ and $G\beta\gamma$ subunits to rejoin and terminate downstream signaling events. Chemokines can also activate signaling pathways, such as MAPK and protein tyrosine kinase, through G protein-independent mechanisms. Signaling through chemokine receptors can be dampened through several processes, including homologous and heterologous desensitization.

Homologous desensitization occurs when G protein-coupled receptor kinases selectively phosphorylate chemokine-occupied receptors, leading to endocytic uptake of chemokine receptor complexes. Heterologous desensitization occurs when non-G

protein-coupled receptor kinases phosphorylate ligand-free (non-engaged) chemokine receptors, preventing future G protein coupling and receptor activation.

In addition to the receptors that activate cellular responses to chemokines, 3 other receptors bind chemokines: duffy antigen receptor for chemokines, D6, and CCX-CKR. These receptors bind chemokines but do not signal, leading to their designation as decoy receptors. Decoy receptors bind ligand and prevent the ligand from being able to act. In terms of chemokine action, decoy receptors play a role in dampening the immune response, leading to resolution of inflammation. Recently, this concept has been challenged by the finding that duffy antigen receptor for chemokines can mediate chemokine transcytosis, leading to apical retention of the chemokine and enhanced leukocyte migration across monolayers.¹⁵⁰

Chemokine function

The original description of chemokines focused on their primary role in directing lymphocytes to sites of inflammation. A detailed examination of cell migration and recruitment is beyond the scope of this review and is covered elsewhere.¹⁵¹ Briefly, in a process known as rolling, lymphocytes interact transiently with the vascular endothelium, searching for activating signals from chemokines. On binding of a chemokine to its receptor, integrins are expressed, which mediate high-affinity interactions and lead to firm arrest of the leukocytes. This has been demonstrated for the chemokines CCL19 (ELC), CCL21 (SLC), and CXCL12 (SDF-1), which rapidly induce a high-affinity state for the β_2 -integrin lymphocyte function-associated antigen 1.¹⁵² Once the cell has ceased rolling, it can cross the endothelium and will continue this process as it migrates along a concentration gradient and crosses the endothelial layer to the source of the generated chemokine. It is the expression of particular chemokines, receptors, and adhesion molecules that contribute to the selective migration and tissue specificity of leukocytes.

Chemokines perform a variety of functions aside from chemotaxis. Chemokines can have direct effects on T-cell differentiation through ligand-receptor interactions on the developing cell or indirectly by altering APC trafficking or cytokine secretion. Functioning through the CCR5 receptor, CCL3 (macrophage inflammatory protein [MIP] 1 α), CCL4 (MIP-1 β), and CCL5 can directly promote development of IFN- γ T_H1 cells or indirectly by increasing IL-12 production from APCs. In contrast, CCL2

(monocyte chemoattractant protein [MCP] 1), CCL7 (MCP-3), CCL8 (MCP-2), and CCL13 (MCP-4) can inhibit IL-12 production from APCs and enhance IL-4 production from activated T cells, leading to a T_H2 phenotype.¹⁵³ Chemokine receptor expression can serve as a marker for maturation and differentiation of lymphocytes. When monocytes and immature DCs exit blood in tissues and begin immune surveillance, they express the CCR1, CCR2, CCR5, CCR6, and CXCR2 receptors, which are classified as inflammatory receptors. As antigen is encountered and the DCs mature, the inflammatory receptors are downregulated and replaced by expression of CCR7. CCR7 expression allows the DCs to accumulate in the draining lymphatics and T-cell areas of the lymph nodes.¹⁵⁴ Expression of CXCR5 has been demonstrated on a distinct memory T-cell subset that displays B helper cell function. These cells respond to CXCL13 (BLC) and are directed to the B-cell follicle to help support production of antibodies.^{155,156} Release of mature neutrophils from the bone marrow is regulated by binding of CXCL12 with its receptor, CXCR4.¹⁵⁷ Other examples include a role for CXCL1, CXCL12, and CCL3 in brain development; a role for CCL2 and CXCL8 in wound healing; and a role for CXCL12 in organogenesis.

Clinical relevance

Aberrant regulation of chemokine expression has been implicated in many diseases (Table VIII); however, the focus of this section will be on the role that chemokines play in allergic disorders. Many studies have demonstrated increased chemokine levels in asthmatic patients compared with control subjects, as measured in bronchoalveolar lavage and biopsy samples.^{158,159} These include CCL2, CCL3, CCL5, CCL7, CCL11, CCL13, CCL24, CXCL8, and CXCL10. Investigators have used murine models of asthma to understand the role that chemokines play in inducing AHR. CCL2, CCL5, CCL11, CXCL10, and CXCL12 all contribute to AHR and cellular emigration in these models of airway inflammation.¹⁶⁰⁻¹⁶²

The C-C chemokine family has been extensively studied in allergic diseases because of its members' ability to recruit eosinophils, T cells, and monocytes to regions of inflammation. CCL5 and CCL11 are the most important eosinophil chemoattractants in allergic inflammation.¹⁶³ This has been demonstrated in mice, in which instillation of CCL5 or CCL11 into the lungs results in an eosinophilic and mononuclear cell infiltrate in the absence of neutrophils.¹⁶⁴ Aside from production by eosinophils, macrophages, mast cells, and T cells, CCL5 and CCL11 are produced by structural cells of the airway, including airway smooth muscle and fibroblasts. In addition to lymphoid tissue, nasal epithelial cells express CCL17 (TARC), and expression of this chemokine and its receptor, CCR4, was higher in patients with allergic rhinitis compared with that seen in nonallergic control subjects. Both IL-4 and IL-13 promote CCL17 expression, leading to a T_H2 response.¹⁶⁵ This is relevant in allergic bronchopulmonary aspergillosis (ABPA), in which increased serum levels of CCL17 predict ABPA exacerbations better than IgE levels.¹⁶⁵ CCL17 levels might serve as a marker of ABPA in patients with cystic fibrosis.¹⁶⁶

CXCL8 is derived primarily from mononuclear phagocytes and endothelial and epithelial cells but also from T cells, eosinophils, neutrophils, fibroblasts, keratinocytes, hepatocytes, and chondrocytes. CXCL8 synthesis can be induced by LPS, IL-1, TNF, or

TABLE VIII. Chemokine/chemokine receptor involvement in human disease

Chemokine/chemokine receptor	Disease
CCR5, CCL3L1, CCL4L1, CXCR4	HIV/AIDS
CXCR4	WHIM syndrome
CX3CR1, CX3CL1, CXCL1, CXCL8, CXCR2, CCL2	Atherosclerosis
CCL2, CCL5, CCL7, CCL11, CXCL8	Asthma, allergic diseases
CXCR4, CXCL1, CXCL12	Cancer metastases
CXCL4	Heparin-induced thrombocytopenia
CCL26	Eosinophilic esophagitis
CCR5	Rheumatoid arthritis
CCR5	Renal allograft rejection
CCR5	West Nile virus infection
Duffy antigen receptor for chemokines	Malaria (<i>Plasmodium vivax</i> infection)

WHIM, Warts, hypogammaglobulinemia, infection, and myelokathexis.

viral infection.^{167,168} On a molar basis, CXCL8 is one of the most potent chemoattractants for neutrophils in addition to stimulating the neutrophil respiratory burst and adherence to endothelial cells through CXCR1.¹⁶⁹ CXCL10 and CXCL13 are induced at different times after allergen exposure. CXCL10 is produced in the early phases after allergen exposure, whereas CXCL13 is only induced after secondary and subsequent allergen exposures.¹⁷⁰ This might have to do with the cellular sources of these cytokines. Airway epithelial cells produce CXCL10, and contact with allergen might induce expression and thus explain the high levels early after allergen exposure. CXCL13 is produced by T_H17, but not T_H1 or T_H2, cells. It is tempting to speculate that T_H17 cells might play a role in asthma in later exposures after the allergic phenotype has already been established.

T-cell subsets that might have regulatory activity are being identified, and chemokines and their receptors appear to have important roles in mediating activity and migration of these cells. Among CD4⁺CD25⁺Foxp3⁺ nTreg cells, there appears to be at least 2 subgroups that can be distinguished based on CCR6 expression. Those that are high in CCR6 seem to have regulatory activity, whereas those low in CCR6 secrete T_H2 cytokines on stimulation with bacterial superantigen.¹⁷¹ Another group has demonstrated low levels of XCR1 on the surface of CD4⁺CD25^{hi}CD127^{low} T cells isolated from allergic asthmatic subjects compared with those from healthy control subjects.¹⁷² Although in the early stages, this emerging field of chemokine response and expression by Treg cells will hopefully clarify many of the questions about how these cells work.

CONCLUSIONS

It has been almost 25 years since the cloning of the first cytokine was described. Since that time, more than 300 cytokines, chemokines, and growth factors have been described, with varying functions on not just the immune system but on every organ system in the body. Despite the large number of articles

concerning the role of these proteins, we are still in our infancy in understanding how these factors alone and in concert with other factors influence homeostatic and inflammatory events. Abnormal production of these factors can lead to diseases such as asthma and atopy, and continued research is needed to piece together how these can be balanced to eliminate disease processes without compromising the individual to other deleterious outcomes.

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