

T_H17 and T_H22 cells: A confusion of antimicrobial response with tissue inflammation versus protection

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Activity Objectives

1. To identify the various CD4⁺ T_H cell subsets, including T_H1, T_H2, T_H9, T_H17, T_H22, and T follicular helper cells.
2. To review the differentiation and cytokine signatures of the T_H cell subsets.
3. To understand the role of the T_H cell subsets in disease.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: M. Akdis has received grants from the Swiss National Science Foundation and the European Union Commission. O. Palomares declares that he has no no relevant conflicts of interest. W. van de Veen has received grants from the Swiss National Science Foundation and the European Commission. M. van Splunter has received grants from CK-CARE. C. Akdis has received grants from Novartis, the European Union Commission, the Swiss National Science Foundation, the Global Allergy and Asthma European Network, and the Christine Kühne Center for Allergy Research and Education; has consulted for Actellion, Aventis, Stallergenes, and Allergopharma; is president of the European Academy of Allergy and Clinical Immunology; is a fellow and interest group member of the American Academy of Allergy, Asthma, & Immunology; is a former committee member of the Global Allergy and Asthma European Network; and is director of the Christine Kühne Center for Allergy Research and Education.

Substantial progress in understanding mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumors, organ transplantation, chronic infections, and pregnancy is in an exciting developmental phase that might lead to a variety

of targeted therapeutic approaches. Recent progress in the interaction between immune/inflammatory cell subsets through cytokines, particularly the extension of the knowledge on reciprocal regulation and counterbalance between subsets of T_H1, T_H2, T_H9, T_H17, T_H22, T follicular helper cells and different subsets of regulatory T cells, as well as corresponding and co-orchestrating B-cell, natural killer cell, dendritic cell, and innate lymphoid cell subsets, offers new possibilities for immune intervention. Studies on new subsets confirm the important role of T cells in the instruction of tissue cells and also demonstrate the important role of feedback regulation for the polarization toward distinct T-cell subsets. T_H17 and T_H22 cells are 2 emerging T_H cell subsets that link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both cytokines play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. This review focuses on current knowledge on T_H17 and T_H22 cells and their role in inflammation, with special focus on the mechanisms of their generation and driving and effector cytokines, as well as their role in host defense,

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The authors' laboratories are supported by Swiss National Foundation grants 320030-132899 and 320030-140772/1; the Christine Kühne-Center for Allergy Research and Education (CK-CARE); European 7th Framework projects MeDALL (Mechanisms of the Development of Allergy; no. 261357) and PREDICTA (Post-Infectious Immune Reprogramming and Its Association with Persistence and Chronicity of Respiratory Allergic Diseases; no. 260895). O.P. is a Ramon y Cajal Scholar funded by MINECO and the European Social Fund.

Received for publication April 18, 2012; revised May 2, 2012; accepted for publication May 2, 2012.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2012.05.003

Terms in boldface and italics are defined in the glossary on page 1439.

autoimmunity, and allergic diseases. (J Allergy Clin Immunol 2012;129:1438-49.)

Key words: *T cells, inflammation, T_H17, T_H22, epithelial cells, asthma, allergy*

The immune response of **memory T cells** is essential in the inflammation and immune regulation seen in patients with many diseases related to tissue inflammation, such as allergic rhinitis, asthma, and atopic dermatitis, as well as organ transplantation, tumors, autoimmunity, and infections. CD4⁺ **naive T cells** can differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, and T follicular helper cells depending on the vitamins and other substances in the micro-milieu, the adjuvanicity of the innate immune response stimulating substances coexposed with the antigen, the status that defines the responsiveness of T cells, the type and developmental stage of antigen-presenting cells, and the cytokines in the micro-environment. On the basis of their respective effector cytokine profiles and interactions with resident tissue cells, these T-cell subsets can promote different types of inflammatory responses (Fig 1). For the development of a certain type of immune response and to display their effector functions, these T cells, **dendritic cells** (DCs), innate lymphoid cells, and tissue cells in the environment develop a cytokine milieu that represents the type of immune response. During the development of allergic disease, effector T_H2 cells produce IL-4, IL-5, IL-9, and IL-13,^{1,2} and probably other recently identified interleukins are released from tissue cells and DCs, such as IL-25, IL-31, IL-33, which altogether contribute to T_H2 response and inflammation.³⁻⁵ These cytokines play roles in allergen-specific IgE production, eosinophilia, and mucus

Abbreviations used

CMC:	Chronic mucocutaneous candidiasis
DC:	Dendritic cell
FOXP3:	Forkhead box P3
γ _c :	γ-chain
IL-22BP:	IL-22 binding protein
NK:	Natural killer
ROR:	Retinoic acid receptor–related orphan receptor
RUNX:	Runt-related transcription factor
T-bet:	T-box transcription factor
Treg:	Regulatory T

production. T_H1 cells, with their prototype cytokine **IFN-γ**, play a role in defense against intracellular pathogens and activation-induced cell death of the skin and mucosal epithelium and T cells.^{6,7}

Most of the functions attributed to T_H1 cells are now better understood after the discovery of T_H17 cells. T_H17 cells are characterized by IL-17A, IL-17F, and IL-22 expression as major cytokines.^{8,9} IL-17A, initially called IL-17, is the founding member of a structurally distinct cytokine family. It binds as a homodimer or a heterodimer with IL-17F to its receptor, IL-17RA.¹⁰ IL-17A is expressed by activated CD4⁺ T_H17 cells,⁹ but its expression has also been detected in CD8⁺ T cells, **γδ T cells**, natural killer (NK) cells, and neutrophils.¹⁰ Consistent with the broad expression pattern of its receptor, IL-17A acts on a variety of cells, which respond by upregulating the expression of proinflammatory cytokines, chemokines, and metalloproteases.

GLOSSARY

AUTOSOMAL DOMINANT HYPER-IgE SYNDROME: A condition that results from mutations in the signal transducer and activator of transcription 3 (*STAT3*) gene. *STAT3* is a transcription factor.

ANTIMICROBIAL PEPTIDES (AMPs): Components of the innate immune system that are capable of inserting into bacterial phospholipids to slow microbial growth. AMP levels are decreased in the skin of patients with atopic dermatitis.

CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD): T cells from a hematopoietic stem cell transplant react against the recipient's antigens. Chronic GVHD is defined as the persistence or appearance of symptoms from 100 days after transplantation. Risk factors for chronic GVHD include a history of acute GVHD, older age of the recipient at the time of transplantation, transplantation from a multiparous female donor into a male recipient (with reactivity to Y chromosome–associated antigens), and incompatibility at minor histocompatibility loci.

DENDRITIC CELLS: Hematopoietic cells that function as antigen-presenting cells for naive lymphocytes. Their name is derived from their multiple, thin membranous projections.

DIGOXIN: A cardiac glycoside used for atrial fibrillation, heart failure, and supraventricular tachycardia. Digoxin inhibits the Na⁺/K⁺ ATPase pump in myocardial cells, causing increased intracellular Na⁺, which in turns results in increased Ca⁺⁺ influx through the Na⁺/Ca⁺⁺ exchange pump. The result is enhanced cardiac contractility. Digoxin also directly suppresses the atrioventricular node.

γδ T CELL: A subpopulation of T cells located at epithelial barriers and sites of inflammation. γδ T cells are capable of binding to antigens directly without MHC presentation. They can also react to MHC molecules without an associated peptide. In addition to playing a role in

defense against multiple different types of bacteria, they can accumulate at inflammatory sites in patients with autoimmune disease.

IFN-γ: A cytokine with a multitude of effects in addition to promoting CD4⁺ T-cell differentiation into T_H1 cells. Other actions of IFN-γ include activation of macrophages, upregulation of MHC class II expression, maturation of CD8⁺ T cells into cytotoxic T cells, activation of endothelial cells and neutrophils, and promotion of antiviral defenses.

KERATINOCYTE: An epidermal cell that produces keratins, sulfur-containing fibrous proteins that form the basis of epidermal tissues, such as hair or nails.

MEMORY T CELL: A subset of CD4⁺ and CD8⁺ cells characterized by the cell-surface marker CD45RO. They are capable of surviving for long periods of time without antigenic stimulation. Memory B cells have been demonstrated to survive into the tenth decade of life.

NAIVE T CELL: CD4 and CD8 T cells emigrate from the thymus as naive T cells. Naive T cells produce IL-2 but only low levels of other cytokines. They are not strong helpers to B cells. They can survive without antigen but require the presence of MHC molecules. Naive T cells circulate from the blood to the spleen and lymph nodes.

PLASMACYTOID DENDRITIC CELLS: A type of dendritic cell with a distinct histologic morphology that can produce high levels of type I interferon and are thought to play special roles in antiviral host defense and autoimmunity.

POLYMORPHISM: The existence of a gene in several allelic forms.

TOLL-LIKE RECEPTOR 6: A Toll-like receptor that binds to lipoproteins and lipoteichoic acid found on pathogens, such as gram-positive bacteria and *Mycoplasma* species.

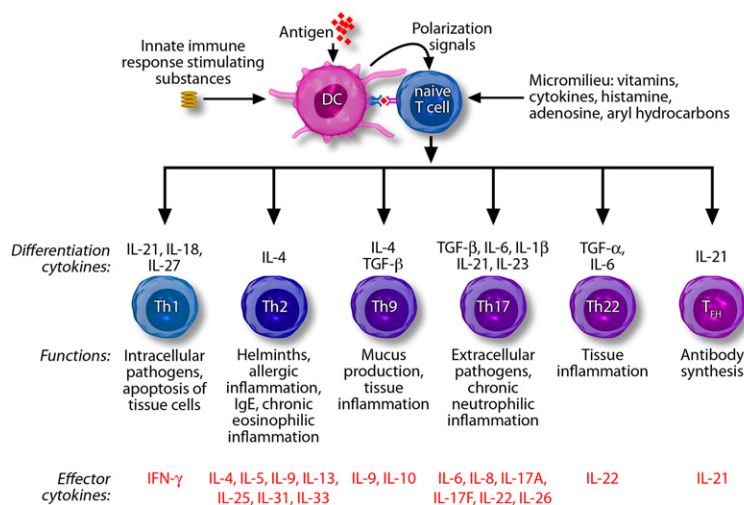


FIG 1. Differentiation pathways of CD4⁺ T_H cell subsets. Depending on the adjuvant effects of the substances coexposed with the antigen and on the status of the cells and cytokines in the microenvironment, naive CD4⁺ T cells can differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, or follicular helper T cells (T_{FH}). These T-cell subsets can promote different types of inflammatory responses based on their respective cytokine profiles, responses to chemokines, and interactions with other cells.

In contrast to the homolog IL-17A, IL-17B and its receptor, IL-17RB, are not expressed in immune cells but instead in the spinal cord, testis, small intestine, pancreas, stomach, prostate, ovary, colon mucosa, and cartilage.¹¹ No specific receptors for IL-17C or IL-17D have been identified.¹² IL-17C induces production of proinflammatory cytokines and metalloproteases by certain cells¹² and has been associated with pathologic conditions, such as the paws of mice with collagen-induced arthritis.¹³ IL-17D is highly expressed in the skeletal muscle, brain, adipose tissue, heart, lung, and pancreas.¹⁴

In addition, 2 new subsets of effector T_H cells have been identified according to their cytokine signatures: T_H9 and T_H22 cells. TGF- β in the presence of IL-4 reprograms T_H2 cell differentiation and leads to the development of T_H9 cells that produce IL-9 and IL-10. T_H9 cells lack suppressive function and promote tissue inflammation.¹⁵ T_H22 cells are characterized by IL-22 production and contribute to epidermal hyperplasia in patients with inflammatory skin disease.^{16,17} In addition, a subset of T cells, termed T follicular helper cells, provides a helper function to B cells and represents one of the most numerous and important subsets of effector T cells in lymphoid tissues.¹⁸ To regulate and counterbalance the immune responses, subsets of regulatory T (Treg) cells with distinct phenotypes and mechanisms of action include the naturally occurring, thymus-derived CD4⁺ forkhead box P3 (FOXP3)⁺ Treg cells, inducible CD4⁺FOXP3⁺ Treg cells, and inducible type 1 Treg cells (T_R1 cells).^{19–22} It has been continuously demonstrated that each T-cell subset counterregulates other effector or Treg cell subsets.^{23,24} It must be noted here that the cytokine profile of freshly isolated T cells in human subjects is not as distinctly and clearly skewed as that observed in mice. Most of the human T-cell clones isolated from peripheral blood and tissues show a mixed cytokine pattern, with small shifts in balance toward the dominant cytokine. Fully skewed T-cell clones can rarely be observed in human subjects. However, human naive T cells can be differentiated *in vitro* to all of the above-mentioned subsets equally as well as murine naive T cells.

Investigations of the mechanisms of immune inflammatory cell functions have identified an ever-growing list of interleukins and interactions that contribute to their effector and suppressive functions. Over the last few years, a tremendous advance in the knowledge of T-cell biology has been gained. Here we review the most recent findings in the field of T_H17 and T_H22 cells. The functions of T_H17 and T_H22 cytokines, their receptors, signal transduction pathways, and cellular sources and targets and their roles in immune regulation and cellular networks, host defense and other immune-regulatory conditions, and allergy and asthma are discussed.

MECHANISMS OF T_H17 CELL GENERATION

The discovery of T_H17 cells was essential to increase our understanding of inflammatory processes because it was unclear how T_H1 cells actually mediate inflammation in tissue.¹⁰ Several studies in mice lacking essential components of the T_H1–IFN- γ pathway demonstrated that these mice were not protected against but rather quite susceptible to different types of autoimmune diseases.²⁵ Although the main function of T_H17 cells is supposed to be induction of protection against potentially harmful fungi and extracellular bacteria,²⁶ a large battery of experiments with IL-17 neutralizing antibodies, as well as relatively high levels of IL-17A and IL-17F detected in patients with multiple sclerosis, rheumatoid arthritis, and psoriasis, firmly revealed that T_H17 cells also drive tissue inflammation in patients with several autoimmune diseases and allergy.^{27,28} 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.²⁹ IL-17F binds to the same receptor as IL-17A (IL-17RA), although with lower affinity.³⁰ IL-17A and IL-17F form heterodimers, as expected from their structural similarities. There are 2 isoforms of IL-17F that are both produced by activated T_H17 cells.⁹ Like IL-17A, IL-17F acts on many cell types and induces similar proinflammatory cytokines and chemokines, as predicted on the basis of their structural homology and expression patterns.

T_H17 cells were definitely recognized as an independent effector T_H cell subset after the identification of the retinoic acid receptor–related orphan receptor (ROR) $\gamma t/C2$ in mice and human subjects, respectively, which is the master transcription factor involved in their development.²⁷ Generation of human T_H17 cells and expression of IL-17A, IL-17F, and IL-26 are driven by RORC2, a nuclear transcription factor that belongs to the family of ROR proteins, which encompasses RORA, RORB, and RORC. Several isoforms varying on the N-terminal domain are described for all ROR genes. In contrast to other nuclear receptors, ROR family proteins bind as monomers to DNA containing ROR response elements through a highly conserved DNA-binding domain. A hinge domain and a C-terminal ligand-binding domain that can interact with both coactivators and corepressors and positively or negatively regulate transcription of target genes are also distinguished in this family of transcription factors.³¹ Recent findings have demonstrated that T_H17 differentiation is impaired by small chemical compounds, such as *digoxin* and SR1001, that directly target ROR γt .^{32,33} Also, a potent synthetic retinoid, Am80, has been demonstrated to improve *chronic graft-versus-host disease* by regulating T_H1 and T_H17 cells.³⁴ Previous studies indicated that the aryl hydrocarbon receptor, a ligand-dependent transcription factor involved in mediating the toxicity of dioxin, was involved in T_H17 cell-mediated autoimmunity to environmental toxins and that their natural agonists were essential for optimal T_H17 cell differentiation.^{35,36} Altogether, these novel advances suggest that the development of small-molecular-weight compounds inhibiting or interfering with ROR γt /RORC2 functions might well represent a promising therapeutic alternative for preventing T_H17 -mediated tissue inflammation and autoimmunity. The identification of TGF- β and IL-6 as essential factors for T_H17 differentiation in mice also contributed to supporting the existence of a new functional T_H cell subset.^{37–39} In human subjects, although initial studies pointed out TGF- β as not being a key factor for T_H17 differentiation,^{40,41} more recent findings indicate that the presence of TGF- β is essential for the generation of functional T_H17 cells.⁴² Other key cytokines involved in T_H17 cell differentiation and expansion are IL-21 and IL-23.^{43–45} Because T_H17 cells have been described as a source of IL-21, a potential positive feedback loop serving as an autocrine mechanism of T_H17 polarization has been suggested for this cytokine,^{8,46} with IL-23 recognized as an essential cytokine for the terminal differentiation and pathogenicity of T_H17 cells.⁴⁵

Crossover inhibition of T-cell subsets during differentiation has been demonstrated as an essential mechanism to ensure polarization and clonal expansion of the most efficient subset, thus contributing to delineation of the proper immune response. The molecular mechanisms of such pathway crosstalk have previously been shown to take place on the level of pathway-specific transcription factors, such as GATA3 for T_H2 cells, T-box transcription factor (T-bet) for T_H1 cells, FOXP3 for Treg cells, and ROR γt for T_H17 cells.^{47,48} Runt-related transcription factor (RUNX) 1 and 3 promote Treg cells^{20,49} and inhibit differentiation of T_H2 cells.⁵⁰ RUNX1 is also involved in the regulation of IL-17 expression by forming a complex with ROR γt to activate transcription.⁵¹ T-bet interferes with T_H17 cells and directly blocks GATA3 to bind its targets.⁵² Interestingly, it has been recently shown that T-bet also inhibits the expression of ROR γt by sequestering the transcription factor RUNX1.⁵³ The

differentiation of both T_H17 and Treg cells requires TGF- β , and it is often reciprocal.³⁷ This interesting dichotomy in the generation of T_H17 and Treg cells has been explained at the molecular level by experiments demonstrating that FOXP3 inhibits ROR γt function through physical interactions.⁵⁴ In addition, RORC2 inhibits FOXP3 expression by directly binding to the FOXP3 promoter.⁵⁵ These counterregulatory mechanisms involving lineage-specific transcription factors together with the existence of positive feedback loops for all differentiation pathways synergistically cooperate to fine tune the generation and maintenance of specific T-cell subsets. The dysregulation of such fine balances leads to immune tolerance–related diseases, such as allergy, autoimmunity, tumor tolerance, and rejection of organ transplants.⁵⁶

Although the knowledge about the mechanisms operating in T_H17 cell differentiation has experienced a tremendous advance within the last few years, the role of the specific DC subsets involved in such processes still remains poorly understood. In this context it has been shown that different subsets of myeloid DCs contribute to orchestrate the plasticity of T_H17 and Treg cells.⁵⁷ In particular, the expression of CD11b on murine antigen-presenting cells is essential to induce oral tolerance by suppressing T_H17 differentiation.⁵⁸ In human subjects slan (6-sulfo LacNac) inflammatory dermal DCs were described as potent inducers of T_H17/T_H1 responses in patients with psoriasis.⁵⁹ In addition, TNF-related apoptosis-inducing ligand–positive inflammatory myeloid DCs isolated from psoriatic lesional skin express a wide range of inflammatory molecules. However, their precise role in disease pathogenesis and T_H17 differentiation remains to be elucidated.⁶⁰ Different DC-specific costimulatory molecules positively or negatively influence T_H17 cell development. For example, the Syk-couple C-type lectin receptors Dectin-1 and Dectin-2 have been demonstrated to be essential pattern-recognition receptors to induce T_H17 cell-mediated antifungal immune responses.^{61,62} In the same way, the expression of $\alpha v \beta 8$ integrin on DCs is crucial for T_H17 -driven autoimmune diseases in mice.⁶³ In contrast, the PDL1-PD1 and B7–cytotoxic T lymphocyte–associated antigen 4 axis involving DCs and T cells inhibits T_H17 differentiation, thus suppressing T_H17 -mediated autoimmunity.^{64,65} Recent findings showed that in human tonsils *plasmacytoid DCs* drive the generation and maintenance of allergen-specific FOXP3⁺ Treg cells,⁶⁶ but the contribution of plasmacytoid DCs in T_H17 cell development is still controversial.⁶⁷ Another striking finding is that skin-derived DCs isolated from the lesional skin of patients with atopic dermatitis (T_H2/T_H22 dominant) and patients with psoriasis (T_H1/T_H17 dominant) show very similar induction of T_H1 and T_H2 subsets.⁶⁸

T_H17 CELL-RELATED CYTOKINES

Cytokines involved in T_H17 cell differentiation

Collectively, the main cytokines that have been described as essential for T_H17 development and expansion encompass TGF- β , IL-6, IL-1 β , IL-21, and IL-23.^{8,9} The key role of TGF- β in T_H17 cell differentiation, especially in human subjects, was a matter of debate for a long time. Considering the ubiquitous expression of TGF- β and its receptor by immune and nonimmune cells, it is indeed difficult to imagine an *in vivo* scenario in which T_H17 cells might arise in the complete absence of this cytokine. Recent studies have added more complexity by demonstrating that T_H17 cells represent a more heterogeneous population than

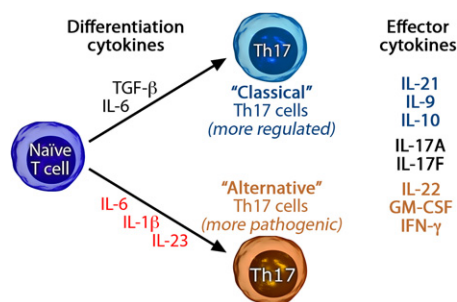


FIG 2. Th17 cell plasticity. In the presence of TGF- β and IL-6, naïve CD4⁺ T cells differentiate into more regulated classical Th17 cells characterized by the production of more IL-21, IL-9, and IL-10. In contrast, without TGF- β but in the presence of IL-6, IL-1 β , and IL-23, more pathogenic alternative Th17 cells producing high levels of IL-22, GM-CSF, and IFN- γ are generated. Both subsets produce IL-17A and IL-17F.

initially anticipated⁶⁹ because phenotypically and functionally different Th17 cell subsets can be generated depending on the presence of TGF- β (Fig 2). In the absence of TGF- β but in the presence of IL-6, IL-1 β , and IL-23, alternative Th17 cells producing higher levels of IFN- γ , GM-CSF and IL-22 are generated. In contrast, in the presence of TGF- β , the generation of classical Th17 cells characterized by the production of higher levels of IL-10 is favored. The relative amount of TGF- β and IL-23/IL-1 β together with the expression of a specific network of transcription factors determine the final outcome of the induced Th17 cell population. Other cytokines, such as IL-10, IL-21, IFN- γ , and GM-CSF, might also play a role in the development of the effector Th17 cell phenotype, directing the bidirectional pathway of cellular conversion and commitment between more regulatory classical and more pathogenic alternative Th17 cells.²⁷

IL-6 and IL-1 β represent key cytokines involved in Th17 cell differentiation. The receptor of IL-6 consists of an IL-6-binding chain, IL-6R α , and the signal-inducing component glycoprotein 130.⁴³ IL-1 β is a potent proinflammatory cytokine that exerts its effects by binding to the IL-1 type I receptor (IL-1RI).⁴³ IL-21 and IL-23 are decisive cytokines for the expansion and terminal differentiation of pathogenic Th17 cells. IL-21, a common γ chain cytokine, is produced by initially differentiated Th17 cells and is involved in a positive feedback loop in Th17 generation.⁴⁶ The receptor for IL-21 (IL-21R α and CD132, the common γ c receptor) is expressed on various cells, suggesting a broad spectrum of action.

IL-23 shares the IL-12p40 subunit with IL-12 and possesses a distinct IL-23p19 subunit.⁷⁰ A role for IL-23 is proposed for the terminal differentiation and final phenotype of Th17 cells.^{27,45} IL-23 is mainly produced by phagocytic cells, macrophages, and activated DCs from peripheral tissues, including the skin, intestinal mucosa, and lungs. Because of a common p40 subunit, IL-23 and IL-12 also share the IL-12R β 1 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 receptor.⁴³

Cytokines involved in Th17 cell effector functions

Th17 cells are essential for the elimination of extracellular pathogens.^{71,72} IL-17A and IL-17F coordinate tissue inflammation through the induction of proinflammatory cytokines and chemokines, such as IL-1 β and IL-6 (Fig 3).^{8,9} Activated Th17 cells

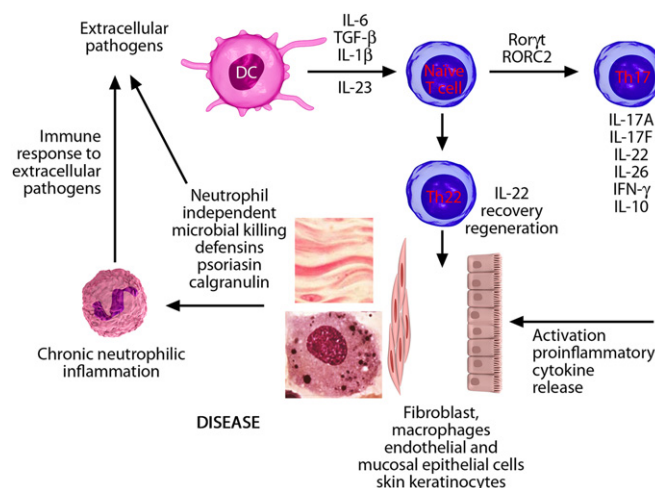


FIG 3. Role of Th17 and Th22 cells in inflammation and immunity. On infection with extracellular pathogens, DCs will be primed to secrete IL-6, TGF- β , IL-1 β , and IL-23 when presenting microbial antigens to naïve T cells. This drives Th17 differentiation. On activation, Th17 cells produce a range of proinflammatory cytokines and chemokines that act on fibroblasts, endothelial cells, mucosal epithelial cells, and skin keratinocytes, as well as macrophages, to secrete antimicrobial peptides, such as defensins and psoriasin, leading to clearance of the pathogens in a neutrophil-independent manner. On the other hand, the same cells produce IL-6 and IL-8, leading to the recruitment of neutrophils to the site of inflammation.

produce the proinflammatory effector cytokines IL-17A, IL-17F, IL-22, and IL-26.^{9,43,73} IL-17A binds as a homodimer or alternatively as an IL-17A–IL-17F heterodimer to its receptor IL-17RA,¹⁰ which can be found in various tissues, such as the lung, spleen, kidney, and liver.⁷⁴ IL-17A is also expressed by CD8⁺ T cells, $\gamma\delta$ T cells, NK cells, B cells, neutrophils, fibroblasts, epithelial cells, vascular endothelial cells, myelomonocytic cells, and bone marrow stromal cells.^{10,75} Consistent with the broad expression pattern of its receptor, IL-17A acts on a large variety of cells, which respond with upregulation of proinflammatory cytokines, chemokines, and/or metalloproteases. IL-17A attracts neutrophils through induction of certain chemokines and is thereby crucial for defense against many different extracellular pathogens. IL-17F shows 50% identity to its homologous IL-17A and also binds to IL-17RA, although with lower affinity. Like IL-17A, IL-17F acts on a large variety of cells and induces a similar panel of proinflammatory cytokines and chemokines.⁴³ IL-6 and IL-8 are strong proinflammatory cytokines that play a crucial role in the effector functions of Th17 cells. IL-6 is a multifunctional pleiotropic cytokine involved in the regulation of immune responses, acute-phase responses, hematopoiesis, and inflammation. Endothelial and epithelial cells, fibroblasts, and monocytes/macrophages triggered by different stimuli (IL-1, IL-17, and TNF- α) during systemic inflammation are the main source.⁴³ IL-8 is a neutrophil-specific chemotactic factor classified as a member of the CXC chemokine family that is produced by a wide variety of cells, such as monocytes and macrophages, neutrophils, lymphocytes, endothelial cells, and epithelial cells, after stimulation with IL-1 α , IL-1 β , IL-17, TNF- α , or Toll-like receptors.⁷⁶ The 2 receptors for IL-8 are CXCR1 (IL-8RA) and CXCR2 (IL-8RB).⁷⁷ The major effector function of IL-8 is the activation and recruitment of neutrophils, NK cells, T cells, basophils, and GM-CSF- or IL-3–primed eosinophils to the site of infection or injury.⁷⁸ IL-22 is also substantially released by

T_H17 cells. Its characteristics are discussed later in this article. IL-26 expression seems to be restricted to memory T cells, NK cells, and T_H17 cells.⁴¹ The receptor for IL-26 consists of the IL-10R2 chain and the IL-20R1 chain. IL-20R1 is not detected in immune cells but is expressed on several epithelial cells and many tissues, such as the skin, testis, heart, placenta, salivary gland, and prostate.⁷⁹

Other cytokines regulating T_H17-mediated immune/inflammatory responses

Several cytokines produced by activated T_H17 cells, such as IL-10, IL-21, IFN- γ , or GM-CSF, also contribute to modulating the final outcome of T_H17-mediated immune responses. TGF- β induces IL-10 production in T_H17 cells through a mechanism partially dependent on the transcription factor c-Maf, whereas IL-23 inhibits such production.⁸⁰ Two recent studies have shown that IL-10 produced by Treg cells or directly by the more regulatory classical T_H17 cells block T_H17-mediated inflammation (Fig 2), suggesting the existence of regulatory mechanisms to avoid excessive tissue damage.^{81,82} In addition, IL-21, which is also induced by c-Maf and inhibited by T-bet, has been associated to classical T_H17 cells displaying a less pathogenic phenotype.⁸³ It is well known that T_H17 cells coproduce IL-17 and IFN- γ *in vivo*,⁸⁴ and it has been recently shown that all *in vivo*-generated IL-17⁺IFN- γ ⁺ double producers arise from T_H17 cells.⁸⁵

Considering that IL-23 drives the induction of T-bet/IFN- γ and that TGF- β inhibits this induction, the phenotype for the IFN- γ producers would fit better with the more pathogenic alternative T_H17 cells (Fig 2).^{80,86} In contrast, mice lacking IFN- γ have more severe diseases in animal models of autoimmunity,⁸⁷ thus suggesting a potential protective role for IFN- γ in this context. Therefore further research is required to decipher the final role of IFN- γ in T_H17-mediated tissue inflammation and autoimmune diseases. Very recent studies have also demonstrated GM-CSF as an essential cytokine for the increased pathogenicity of alternative T_H17 cells.^{88,89}

Role of T_H17 cells in host defense and autoimmunity

The essential role of T_H17 cells in the elimination of fungi and extracellular bacteria and their implication in autoimmune disorders are well documented.^{9,43,71,72} The identification of several human genetic immunodeficiencies characterized by the loss of T_H17 cell function has contributed to an increase in our knowledge of the role played by these cells in host defense.⁹⁰ Patients with the *autosomal dominant hyper-IgE syndrome* exhibit reduced numbers of T_H17 cells. Patients with hyper-IgE syndrome display high susceptibility to infections, such as staphylococcal pneumonia or abscesses, lung cysts, or chronic mucocutaneous candidiasis (CMC), which have been partially attributed to defects in T_H17 cell function.⁹¹⁻⁹³ In the same way, patients with mutations in the autoimmune regulatory element presented with autoimmunity polyendocrinopathy-candidiasis-ectodermal dystrophy associated with the presence of circulating anti-IL-17 autoantibodies.^{94,95} Other recent studies seem to indicate that T_H17 cells only contribute to antifungal defense and not to antistaphylococcal immunity.^{96,97} Patients with autosomal dominant CMC also present low numbers of functional T_H17 cells.

These patients, as well as others showing specific mutations in the genes encoding IL-17F or IL-17R, only had CMC, although not from other infections. In any case several studies demonstrated that T_H17 cells might partially exert their functions in host defense by inducing the expression of *antimicrobial peptides* in target cells (Fig 3).⁹⁸ Compelling experimental evidence has demonstrated that T_H17 cells play a key role in the initiation and maintenance of several autoimmune disorders, such as rheumatoid arthritis,⁹⁹ multiple sclerosis,¹⁰⁰ systemic lupus erythematosus,¹⁰¹ and inflammatory bowel disease.¹⁰² Complement activation by exogenous or endogenous stimulation is able to initiate T_H17 cell differentiation and expansion, triggering autoimmune arthritis.¹⁰³ Supporting all these results, recent studies demonstrated that administration of intravenous immunoglobulin, a polyclonal IgG used as a therapeutic approach to treat many autoimmune diseases, directly targets T_H17 cells to induce a reciprocal regulation toward Treg cells.¹⁰⁴

Role of T_H17 cells in patients with allergy and asthma

The exact role of T_H17 cells in patients with atopic diseases is apparently more complex. Although characteristics of patients with hyper-IgE syndrome might suggest a potential protective role of IL-17 in patients with atopic dermatitis by preventing staphylococcal infection, a classical feature of this disease, compelling experimental evidence in murine models, as well as human data, suggest that T_H17 cells play a pathogenic rather than a protective role in the development of allergic diseases.^{10,56}

Several experimental models showed T_H17 cells to be important for neutrophilic inflammation in patients with acute airway inflammation.^{105,106} Neutrophilic infiltration was also observed in acute asthmatic conditions, and IL-17 was demonstrated as indispensable to induce granulocyte influx into the lungs in allergic asthma models.^{107,108} In human subjects it has been also shown that T_H17 cells contribute to allergic airway disease by inducing airway smooth muscle cell migration,¹⁰⁹ and it has been demonstrated that IL-17 induced B-cell class-switching to IgE in human subjects, suggesting a direct mechanism by which T_H17 cells are able to induce atopic phenotypes.¹¹⁰ Interestingly, human studies also revealed an association between serum IL-17 or IL-17RB expression and the severity of allergic rhinitis.¹¹¹⁻¹¹³ Studies on genetic *polymorphisms* have also demonstrated an association between IL-17 and asthma.¹¹⁴

Regarding atopic dermatitis, studies in filaggrin-deficient mice have shown that mice with this disease had spontaneous IL-17-mediated eczematous inflammation.¹¹⁵ T_H17 cells played a key role in the induction of atopic dermatitis in IL-13/IL-4 null mice.¹¹⁶ This study suggested a potential role for T_H2 cytokines in suppressing allergic inflammation caused by T_H17 cells. In human subjects some studies demonstrated lower frequencies of T_H17 cells in the periphery of patients with atopic dermatitis compared with those seen in healthy subjects,¹¹⁷ whereas others have shown increased circulating T_H17 cell numbers¹¹⁸ or increased levels of IL-17 in atopic dermatitis lesions.^{119,120} When patients with atopic dermatitis and psoriasis are compared with each other, increased levels of circulating T_H17 cells can only be found in patients with psoriasis. In patients with atopic dermatitis, relatively more circulating T_H2 cells are found compared with T_H1 and T_H17 cells.¹²¹ This divergence could be due to distinct roles of T_H17 cells at different

stages of the disease (acute or chronic). Interestingly, it has been also shown that T_H2 cytokines in human subjects counteract IL-17 expression by T_H17 cells.¹²²

T_H22 CELLS: DIFFERENTIATION AND FUNCTION

T_H22 cells are characterized by particularly high IL-22 production. IL-22 was identified in mice during a search of genes that are induced by IL-9 in T cells and was termed IL-10-related T cell-derived inducible factor (IL-TIF; Fig 1).¹²³ It was first classified as an IL-10 family cytokine that binds to a complex of IL-22R1 and IL-10R2.^{123,124} The human gene encoding IL-22 is located on 12q15, which is close to IL-26 and IFN- γ .¹²⁵ The secreted IL-22 is 146 amino acids in length, is approximately 70 kDa in weight, and shares 80.8% identity with murine IL-22.¹²⁶ As a member of the IL-10 family, it has 22.8% identity to IL-10 and shares the anti-parallel α -helical structure with its family members.¹²⁷ Four cysteine residues, 3 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.¹²⁸

The IL-22R complex is built of IL-22R1 and IL-10R2, the second chain of the IL-10 receptor.¹²⁴ IL-22R1 has a long intracellular tail containing 4 putative signal transducer and activator of transcription recruiting sites.¹²⁴ Evidence suggests that IL-22 undergoes conformational change during interaction with its receptor chains.^{128,129} Recently, the crystal structure of the IL-22/IL-22R1 complex has been solved, and residues important for binding have been identified.¹³⁰ Both components of the receptor, IL-10R2 and IL-22R1, are upregulated by IFN- γ . Interestingly, a soluble form of IL-22R exists: IL-22 binding protein (IL-22BP).¹³¹⁻¹³³ Although soluble receptors are in principle generated most often through proteolytic cleavage or alternative splicing, IL-22BP is encoded by an independent gene. IL-22BP is mainly expressed by resting DCs and, to a lesser extent, by activated DCs, resting and activated T and B cells, and activated mast cells.¹³⁴ It binds to IL-22 but not to other members of this cytokine family. *In vitro* IL-22BP can inhibit the function of IL-22 and is therefore frequently used in *in vitro* experiments as a naturally occurring antagonist.

Cellular sources and targets of IL-22

Among T cells, IL-22 is mainly expressed by memory $CD4^+$ cells of the T_H0 , T_H17 , and T_H22 lineage.^{73,135-137} Similar to T_H22 cells, a recent report identifies a distinct subset of IL-22-producing NK cells located in the mucosa-associated lymphoid tissues of mice and human subjects, which are referred to as NK-22 cells.¹³⁸ In contrast, IL-22 is not expressed in monocytes and B cells. Because the IL-10R2 chain is ubiquitously expressed, IL-22R1 is likely to determine which cells are targets for IL-22. Interestingly, IL-22R1 could not be detected on primary immune cells, such as monocytes, skin-derived mast cells, macrophages, DCs, T cells, B cells, and NK cells.¹³⁹ In contrast, some organs, such as the kidney, small intestine, liver, colon, and lung and particularly the 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*.

Role of IL-22 in host defense or other immune regulation-related diseases

IL-22 increases the antimicrobial defense of skin keratinocytes by enhancing the expression of β -defensin 2 and β -defensin 3, psoriasin, calgranulin A, and calgranulin B (Fig 3).¹⁴⁰ It synergizes with IL-17A and IL-17F in the induction of antimicrobial peptides in keratinocytes.¹³⁵ IL-22 is important for the defense of *Citrobacter rodentium*,¹⁴¹ a bacterium that induces the appearance of IL-22-secreting NK (NK-22) cells in the lamina propria.¹³⁸ IL-22 knockout mice have increased intestinal epithelial damage, systemic bacterial burden, and mortality on infection with *C rodentium* because of a defective induction of antimicrobial proteins belonging to the Reg family.¹⁴¹ 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. Furthermore, production of IL-22 is strongly induced on stimulation with staphylococcal exotoxins *in vitro*, especially in patients with atopic dermatitis compared with patients with psoriasis and healthy control subjects.¹⁴² IL-22 levels are also increased on infection with *Mycobacterium tuberculosis* and *Klebsiella pneumoniae*, suggesting a role for IL-22 in the defense of these bacteria.^{143,144}

IL-22 can also play a role in defense against viruses, although there are some inconsistencies. For example, IL-22 overproduction has been found in subjects with resistance to HIV-1.¹⁴⁵ In patients with viral hepatitis, hepatocytes upregulate IL-22.¹⁴⁶ Although no effect on viral replication has been observed in this disease, IL-22 might prevent and repair liver injury.¹⁴⁷ Finally, because CMC was found to be associated with significantly lower IL-22 levels, the inability to clear *Candida albicans* might be due to a defect in IL-22 production.¹⁴⁸ Taken together, these studies support an important role for IL-22 in the defense of different pathogens.

Because keratinocytes are a major target for IL-22, its role in keratinocyte-associated diseases has been studied. An important role for IL-22 in patients with psoriasis (ie, mediating dermal inflammation and acanthosis) has been reported.⁷³ Consistently, in a murine model of psoriasis, neutralization of IL-22 prevented the development of the disease, reducing acanthosis (thickening of the skin), inflammatory infiltrates, and expression of T_H17 cytokines.¹⁴⁹ T cells isolated from psoriatic skin of patients produced higher levels of IL-22, and supernatants of lesional psoriatic skin-infiltrating T cells induced an inflammatory response by normal human epidermal keratinocytes.¹⁵⁰ The influence of 2 different drugs on IL-22 was investigated. It was found that etanercept but not acitretin is able to reduce IL-22 levels, as accompanied by a lower psoriasis area and severity index.¹⁵¹ Increased IL-22 levels have been found in patients with inflammatory bowel disease, and intestinal epithelial cells express functional receptors for IL-22.¹⁵²⁻¹⁵⁴ Although further investigations are needed to fully clarify the role of IL-22, it might both contribute to inflammation and also play a beneficial role by promoting wound healing. Such a repair effect of IL-22 is also observed in patients with hepatitis. Injection of recombinant IL-22 attenuated liver injury,¹⁴⁷ whereas hepatocytes from mice deficient in IL-22 were highly sensitive to the detrimental immune response associated with hepatitis,¹⁵⁵ suggesting that IL-22 serves as a protective molecule counteracting the destructive effects of the immune response and limiting tissue damage. Supporting this concept, IL-22-deficient mice showed delayed healing of

mucosal colonic biopsy specimens compared with control subjects.¹⁵⁶ In addition, IL-22 treatment of keratinocytes quickens repair after wounding.¹⁶ Thus IL-22 has many roles in aiding tissue repair. Six single nucleotide polymorphisms have been found in the gene encoding IL-22.¹⁵⁷ Two of these seem to correlate with treatment response and viral clearance, respectively, which is consistent with the reports suggesting a role for IL-22 in the defense against viruses.

Role of IL-22 in patients with allergic disease

To date, only few reports investigated the role of IL-22 in allergic diseases. Inflamed skin of nickel-challenged allergic subjects was observed to contain infiltrating cells expressing IL-22 and IL-22R.¹⁵⁸ Asthma is a chronic inflammatory disease of the airways characterized by structural airway changes, which are known as airway remodeling, including smooth muscle hypertrophy, goblet cell hyperplasia, subepithelial fibrosis, and angiogenesis.^{159,160} Migration of airway smooth muscle cells might contribute to increased airway smooth muscle mass in asthmatic patients. This was recently linked to T_H17 and T_H22 cells in which IL-17A, IL-17F, and IL-22 promote migration in a dose-dependent manner.¹⁰⁹ These structural changes could influence the reversibility of airway obstruction in certain subgroups of asthmatic patients and correlate with asthma severity. The pathogenesis seems to be very complex and involves multiple cytokines at different stages of disease development and chronicity. It was reported that T_H17 cells induce airway hyperresponsiveness in patients with steroid-resistant asthma. It remains to be determined whether this effect is due to IL-22 or due to other T_H17 cytokines.¹⁶¹ In an allergen-induced T_H17-dependent airway hyperresponsiveness murine model, it was shown that that FoxP3⁺ inducible costimulator-positive Treg cells could suppress airway hyperresponsiveness by expressing IL-35, IL-10, and TGF- β , although IL-10 and TGF- β were dispensable for suppressing IL-17 production.¹⁶² The T_H17 cytokines IL-17A and IL-17F play a critical role in the activation and recruitment of neutrophils at airway inflammation, mainly through the induction of CXC chemokines in the lungs.¹⁶³ IL-22, which is produced by T_H17 and not T_H22 cells during allergic airway inflammation, inhibits allergic airway inflammation in the effector phase by altering the function of DCs and inhibiting IL-25 production from lung epithelial cells.¹⁶⁴ Both beneficial and detrimental effects of IL-17 have been reported in asthma models. *Toll-like receptor 6* activation is critical for IL-23 production and TH17 responses, which both regulate the allergic inflammatory response in patients with chronic fungus-induced asthma.¹⁶⁵

In patients with atopic dermatitis, development of eczematous skin reactions depends on dermal migration of T lymphocytes and initiation of inflammation through various cytokines and chemokines, leading to dermatitis and eczema. T_H17 and T_H22 cells are essential in this process mainly with their interaction with resident tissue cells.¹²⁰ Both of the T-cell subsets, T_H17 and T_H22 cells, are enriched in patients with atopic dermatitis, allergic contact dermatitis, and psoriasis. They particularly activate keratinocyte innate immune defenses, such as formation of antibacterial peptides. Together with IFN- γ , IL-17 strongly enhances adhesion molecules on keratinocytes, thus promoting T cell-keratinocyte adhesion and T cell-mediated cytotoxicity and resulting in keratinocyte apoptosis as the key mechanism of eczema.^{166,167} Whereas T_H17 cells contribute to inflammation

and injury, T_H22 cells support skin integrity by inducing keratinocyte proliferation.¹⁶ It seems that in both patients with atopic dermatitis and those with allergic contact dermatitis, IL-17, IL-22, and IL-10 display inflammatory, tissue-protective, immunoregulatory roles, and sometimes all 3 can exist in the same biopsy specimen, demonstrating the complexity of the inflammation.¹⁶⁸

CONCLUSION AND FUTURE DIRECTIONS

Our knowledge on T_H17 and T_H22 cell biology and the roles of these cells in host defense and inflammatory diseases has advanced over the last few years, but still, many complex aspects of these novel and exciting T_H cell subsets remain unresolved. Many new findings shed light on the mechanisms of their generation. The key cytokines involved in such processes and their specific functions revealed the existence of different subsets of T_H17 cells classified as more regulatory classical or more pathogenic alternative T_H17 cells. The identification of the specific DC subsets orchestrating T_H17 and T_H22 cell differentiation and the mechanisms operating in the potential interconversion of these different T-cell subsets in the context of specific diseases will offer a great opportunity to develop alternative therapeutic interventions. Both T-cell subsets play a pivotal role in host defense against fungi and extracellular bacteria, but whether they specifically sense different types of pathogens and identification of the mechanisms involved in such processes remain unresolved. A large battery of murine and human studies have contributed to clarifying the role of T_H17 and T_H22 cells in the initiation and maintenance of immune and inflammatory diseases. However, their role in allergy and asthma still remains to be elucidated. IL-17 induces an inflammatory tissue response and is involved in the pathogenesis of several autoimmune diseases, whereas IL-22 plays a role in tissue protection and regeneration. Future research to elucidate their exact role at different stages of inflammatory diseases will be of great benefit to better understand their pathophysiology and to develop alternative more efficient and safer treatments.

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