

IL-17-producing T cells in lung immunity and inflammation

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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Activity Objectives

1. To become familiar with current knowledge on the generation and biology of T_H17 cells.
2. To understand the role of T_H17 cells as effector cells in the course of pulmonary immune responses.
3. To recognize the role of T_H17 cells in allergic diseases.

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T_H17 cells are a recently described effector CD4 T-cell subset characterized by the production of IL-17A, IL-17F, and IL-22, which have been implicated in the pathogenesis of several autoimmune diseases. T_H17 and other IL-17A-producing T cells, including a population of $\gamma\delta$ T cells and natural killer T cells, have also been associated with the development of skin, intestinal, and lung inflammatory diseases, such as asthma, granulomatous disease, chronic obstructive pulmonary disease, and cystic fibrosis. On the other hand, IL-17-producing T cells play important roles in protective immunity against some bacterial infections, mainly through the recruitment and activation of neutrophils. Thus, their regulation appears to be critical, and excess or deficient IL-17 elaboration leads either to deficient responses or disease. This review will summarize T_H17 cell differentiation and discuss the host beneficial and detrimental function of IL-17A and related cytokines produced by different subpopulations of T cells. (*J Allergy Clin Immunol* 2009;123:986-94.)

Key words: T_H17 cells, IL-17, neutrophils, autoimmunity, asthma

Adaptive immunity provides the host with a highly specific line of defense against invading pathogens, such as viruses, bacteria, or helminths. CD4 T_H cells orchestrate different aspects of adaptive immune responses through the secretion of distinct cytokines, which exert specific effector functions. Although T_H1 and T_H2 cells confer protection against intracellular microbes and nematodes, respectively, T_H17 cells have been implicated in the defense against certain bacteria and fungi. In addition to their beneficial roles in the control of pathogens, T_H subset effector responses can also induce pathology. Specifically, T_H2 cells mediate allergic and asthmatic diseases, whereas T_H1 and T_H17 cells contribute to acute and chronic inflammation associated with tissue damage through the activation of macrophages and neutrophils. In addition, a unique role for T_H17 cells in the development of autoimmunity and chronic lung disorders has been postulated.

Mouse T_H17 cells express the lineage-specific cytokines *IL-17A* (also termed IL-17), *IL-17F*, and *IL-22*, in addition to other inflammatory cytokines, such as IL-21, TNF- α , and GM-CSF.¹ Human T_H17 cells also secrete the IL-22-related cytokine IL-26.² IL-17A and IL-17F display high sequence homology and can be secreted as homodimers, as well as IL-17A/F heterodimers, by both mouse and human cells.^{3,4} The cognate receptor for IL-17A is IL-17RA, which also binds IL-17F, albeit with a lower affinity. In mice the cognate receptor for IL-17F is IL-17RC, and

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Terms in boldface and italics are defined in the glossary on page 987.

Abbreviations used

CIA: Collagen-induced arthritis
CXCL: Cysteine-X-cysteine chemokine ligand
EAE: Experimental autoimmune encephalomyelitis
FoxP3: Forkhead box protein 3
G-CSF: Granulocyte colony-stimulating factor
NK: Natural killer
MMP: Matrix metalloproteinase
OVA: Ovalbumin
ROR γ t: Retinoic acid–related orphan receptor γ t
Treg: Regulatory T

in human subjects IL-17RA and IL-17RC can form a heterodimer that is able to bind both IL-17A and IL-17F.^{1,5} IL-17RA and IL-17RC are expressed to different extents by hematopoietic cells, as well as nonimmune cells, such as fibroblasts, smooth muscle cells, and epithelial cells.¹ The broad expression of their receptors underscores the role T_H17 effector cytokines have been suggested to play in the course of immune responses and diseases.

CYTOKINE MILIEU, MICROBIAL STIMULI, AND ANTIGEN DOSE IN T_H17 DEVELOPMENT

Differentiation into T_H1 and T_H2 cell subsets has been extensively studied. *IL-12* and *IFN- γ* are the key cytokines that drive T_H1 differentiation, whereas *IL-4* is crucial for the development

of T_H2 cells. Specifically, *IFN- γ* and *IL-4* regulate the induction of the lineage-specific transcription factors *T-box transcription factor* and *GATA-3*, respectively.⁶ In addition to polarizing cytokines, the strength of T-cell receptor signaling (or antigen dose), costimulatory molecules, and the stimulation of *pattern-recognition receptors* by *pathogen-associated molecular patterns* strongly influence T_H1 and T_H2 differentiation.⁷⁻⁹

Similar to T_H1 and T_H2 cells, the development of T_H17 and inducible regulatory T (Treg) cells from naive CD4⁺ T cells is cross-regulated by cytokines. In mice, TGF- β alone induces the transcription factor forkhead box protein 3 (FoxP3) and development of inducible Treg cells¹⁰; however, the combination of IL-6 and TGF- β skews the balance toward T_H17 cell differentiation through the suppression of FoxP3 and the induction of the nuclear receptor retinoic acid–related orphan receptor γ t (*ROR γ t*).¹¹⁻¹⁴ Of note, IL-6–deficient mice display impaired frequencies of T_H17 cells and enhanced FoxP3⁺ Treg cells in the course of experimental autoimmune encephalomyelitis (EAE).^{15,16} The presence of fungal components, such as β 1-3 glucan (curdian) and zymosan, or bacterial pathogen-associated molecular patterns, such as LPS, CpG, and muramyl dipeptide, leads to an inflammatory microenvironment rich in IL-6, promoting the generation of IL-17A–producing CD4 T cells both in mice and human subjects.^{13,17-22}

The role of antigen dose in regulating mouse T_H17 development has recently been described. High antigen doses and microbial stimuli synergistically promote T_H17 differentiation through

GLOSSARY

CXCL1, CXCL5, CXCL9: All are members of the chemokine family that signals through G-coupled receptors. CXC members are classified by the presence of an amino acid between the 2 N-terminal cysteines. CXCL1 (Gro α) is important for neutrophil recruitment. CXCL5 is made by epithelial cells, activates neutrophils, and binds to the chemokine receptor CXCR2; CXCL9 (MIG) binds CXCR3, which is expressed by T_H1 cells.

$\gamma\delta$ T CELL: $\gamma\delta$ T cells recognize nonpeptide or unprocessed antigen, can respond directly to pathogen-associated molecular patterns, and interact with antigen independent of MHC. They are localized on mucosal surfaces, as well as in the skin, and can produce T_H1-, T_H2-, and T_H17-associated cytokines.

GATA-3, IL-4: Both are factors critical in determining T_H2 phenotype. GATA-3 is a member of the GATA family of transcription factors and activates the transcription of the *IL4*, *IL5*, and *IL13* genes. The *GATA3* gene is activated by IL-4 and signal transducer and activator of transcription 6. IL-4 induces B-cell IgE switching, T_H2 cell differentiation, and effector responses, including IL-5–mediated eosinophilia and IL-13–mediated goblet cell hyperplasia.

IL-8: Also known as CXCL8, IL-8 is important for the recruitment of neutrophils to sites of injury.

IL-12, IFN- γ : Part of the T_H1 cytokine/interleukin profile, IL-12 and IFN- γ are important for the clearance of infectious organisms, including viruses, bacteria, fungi, and protozoan parasites. IL-12 is composed of biologically active p40/35 heterodimers and stimulates the production of IFN- γ . IL-12p40, IL-12 receptor β 1, and IFN- γ receptor deficiency all lead to severe nontuberculous mycobacterial infections.

IL-17F, IL-17A: The IL-17 family is comprised of IL-17A through IL-17F. IL-17A and IL-17F are typically expressed by T_H17, NK T, and $\gamma\delta$ T cells; IL-17E (IL-25) is made by T_H2 cells and promotes allergic T_H2 responses. IL-25 can suppress IL-17–mediated inflammatory disease.

IL-22: IL-22, although coproduced by T_H17 cells, is differentially regulated from IL-17A and IL-17F. It is also produced by a population of NK cells. IL-22 receptor is expressed on epithelial cells and triggers release of antimicrobial peptides. IL-22 promotes host defense against bacterial infection at contact points with the environment (skin, airway, and intestinal cells).

IL-23: IL-23 is secreted by dendritic cells and macrophages. It is essential for maintenance of T_H17 cells. IL-23–deficient mice are completely protected from autoimmune inflammatory diseases, whereas IL-17A– and IL-17F–deficient mice are only partly protected.

OVA CHALLENGE: In allergen-induced models of allergic disease, mice are first sensitized to OVA (eg, through intraperitoneal injection) and then challenged (eg, intranasally or orally) to create a T_H2 response in the appropriate target organ.

PATHOGEN-ASSOCIATED MOLECULAR PATTERN, PATTERN-RECOGNITION RECEPTOR: Pathogen-associated molecular patterns are evolutionarily conserved structural motifs on bacteria, viruses, fungi, and other invading pathogens that are recognized by germline-encoded, nonadaptive receptors (pattern-recognition receptors) on cells of the innate immune system. Pathogen-associated molecular patterns function as danger signals that activate innate immune cells. Toll-like receptors are an important family of pattern-recognition receptors.

ROR γ T: ROR γ t is a lineage-specific transcription factor essential for T_H17 cell development. ROR γ t^{−/−} mice lack T_H17 cells, and overexpression of ROR drives naive T cells to a T_H17 phenotype.

T-BX TRANSCRIPTION FACTOR: T-box transcription factor (T-bet) is a transcription factor that is essential for T_H1 cell induction and IFN- γ expression; isolated expression of T-bet can cause a shift of T_H2 to T_H1 cells. T-bet/signal transducer and activator of transcription 6–deficient mice have augmented autoimmune colitis, with CD4 cells that lack IL-10 production.

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the upregulation of CD40 ligand on T cells and CD40-mediated IL-6 production by dendritic cells.¹⁹ Accordingly, abrogation of CD40–CD40 ligand interaction inhibited the differentiation of T_H17 cells both *in vitro* and *in vivo*.

In addition to IL-6, IL-1 β , TNF- α , and IL-21, together with TGF- β have been described to support T_H17 polarization.^{13,16,23–25} IL-21 produced by T_H17 cells provides a positive feedback loop for the further expansion of differentiated cells and, together with IL-6, induces the expression of IL-23 receptor.¹ However, a mandatory role of IL-21 *in vivo* has been questioned by the finding that T_H17 cells and autoimmune diseases develop normally in the absence of IL-21 or IL-21 receptor.^{26,27} In contrast, IL-23 is absolutely required for disease pathogenesis in many models of autoimmunity. In mice IL-23 was also originally proposed to initiate T_H17 development^{28,29}; however, IL-23 receptor expression was shown to be induced only on already differentiated T_H17 cells.^{12,25,30} These findings suggest that IL-23 promotes the expansion and maintenance of IL-17A–producing effector T cells.^{31,32} Of note, GM-CSF has also been shown to promote the generation and survival of T_H17 cells by stimulating IL-6 and IL-23 production.³³

In contrast to mice, the conditions favoring the development of T_H17 cells in human subjects are not yet fully elucidated; in particular, the role of TGF- β remains controversial.^{34–36} As opposed to TGF- β , IL-1 β , together with IL-6 or IL-23, was shown to primarily direct IL-17A production by human CD4 T cells.^{17,37,38} A recent publication by Cosmi et al³⁸ further indicates that in human subjects T_H17 cells develop in response to IL-1 β and IL-23 from a thymic CD161⁺ CD4 T-cell precursor, which constitutively expresses ROR γ t and IL-23 receptor.³⁸ However, more recently, TGF- β in combination with IL-6, IL-1 β , or IL-21 has also been shown to contribute to the development of human T_H17 cells under certain conditions.^{34,39}

THE PATHOGENICITY OF T_H17 CELLS IN AUTOIMMUNE DISEASES

The description of T_H17 cells as a distinct T-cell subset originated from observations based on mouse models of autoimmune disorders.^{31,32} It was shown that mice deficient for the IL-23 subunits p40 or p19 were protected from the development of EAE, a model for human multiple sclerosis, as well as from collagen-induced arthritis (CIA).^{40,41} Protection from disease was attributed to the impaired development of IL-17A–producing CD4 T cells, whereas T_H1 responses were shown to be normal in the absence of IL-23. The detrimental role of T_H17 in these models was further suggested by experiments performed in mice lacking IL-17A, which were less susceptible to the development of the autoimmune diseases.^{42,43} Furthermore, inhibition of IL-17A by active vaccination resulted in impaired development of EAE, CIA, and autoimmune myocarditis.^{44,45} In further support of these data, increased levels of T_H17-polarizing and effector cytokines both in the blood and at the inflammation site have been linked with several human autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease.³⁶ Of note, levels of IL-17A were shown to correlate with the severity of the disease.^{46–48}

The mechanisms underlying the detrimental role of T_H17 cells in autoimmune diseases still remain to be fully elucidated. T_H17 cells have been shown both in mice and human subjects to secrete IL-17A, IL-17F, and IL-22, as well as other inflammatory cytokines, such as TNF- α .^{36,49–51} T_H17 effector cytokines in

turn induce the secretion of proinflammatory cytokines and chemokines, such as TNF- α , IL-1 β , IL-6, cysteine-X-cysteine chemokine ligand 1 (CXCL1), CXCL2, and granulocyte colony-stimulating factor (G-CSF), thereby regulating recruitment of neutrophils and other inflammatory leukocytes, tissue inflammation, and damage.^{50,52–54} In the context of multiple sclerosis and arthritis, it was shown that IL-17A and IL-22 induce the disruption of the blood-brain barrier and promote the recruitment of inflammatory cells into the central nervous system,⁵⁵ and a role for IL-17A in mediating osteoclast differentiation and bone destruction has also been described.^{56,57} In addition, IL-22 was shown to act on keratinocytes to induce antimicrobial peptides and proinflammatory molecules, as well as to inhibit their differentiation, thus contributing to the pathogenicity of psoriasis.^{58,59}

Despite the considerable number of investigations describing the role of the T_H17 cell subset in autoimmunity, the question remains whether these cells are the only players in mediating disease. In fact, T_H1 cells were originally described to mediate autoimmune pathology, and this assumption was later challenged by studies in which mice lacking the T_H1-polarizing cytokine IL-12 were not protected from EAE and CIA and even displayed exacerbated disease outcome.^{40,41} However, more recent reports revealed that depending on the method used, T_H17 and T_H1 cells could mediate autoimmune diseases, such as experimental autoimmune uveitis⁶⁰ or EAE, which was then characterized by neutrophil or macrophage infiltration, respectively.⁶¹ Moreover, especially in human subjects, a considerable proportion of IL-17A–producing CD4 T cells also secrete IFN- γ .⁶² These results led to the general assumption that both T_H1 and T_H17 cells and their effector cytokines might substantially contribute to the pathogenicity of autoimmune diseases, a point that becomes particularly important for the development of new therapeutic strategies.^{63,64} Inhibition of TNF- α , which is secreted by both T_H1 and T_H17 cells, has proved to be an effective therapeutic approach in autoimmunity,³⁶ and a neutralizing antibody against the IL-12– and IL-23–common subunit p40 has shown positive results for the treatment of psoriasis,⁶⁵ thus highlighting the involvement of both T_H subsets in inflammation.

T_H17 CELLS AND EFFECTOR CYTOKINES IN PULMONARY IMMUNE RESPONSES

In addition to their role in autoimmunity, T_H17 cells have been associated with the development of protective immune responses in the lung. In mice the importance of IL-17 in conferring protection against pulmonary bacterial infections was demonstrated after intranasal challenge with *Klebsiella pneumoniae*.⁵⁴ In the absence of functional IL-17RA signaling, infected animals displayed increased bacterial dissemination and mortality when compared with their wild-type counterparts. The role of T_H17 cells in this model was supported by Happel et al,⁶⁶ who showed increased susceptibility to disease in IL-23p19– and IL-23p40–deficient mice but decreased bacterial load after administration of IL-17A.⁶⁶ Notably, a similar result was obtained after treatment with IL-22, which also seems to play an important role in immunity against *K. pneumoniae*.⁶⁷ In line with the expected effector function of IL-17A, the increased susceptibility of IL-17RA–deficient mice to bacterial infection correlated with decreased chemokine production and impaired neutrophil recruitment to the site of infection.⁵⁴ Various reports have described the capacity of IL-17A, IL-17F, and IL-22 in inducing the secretion of CXCL8

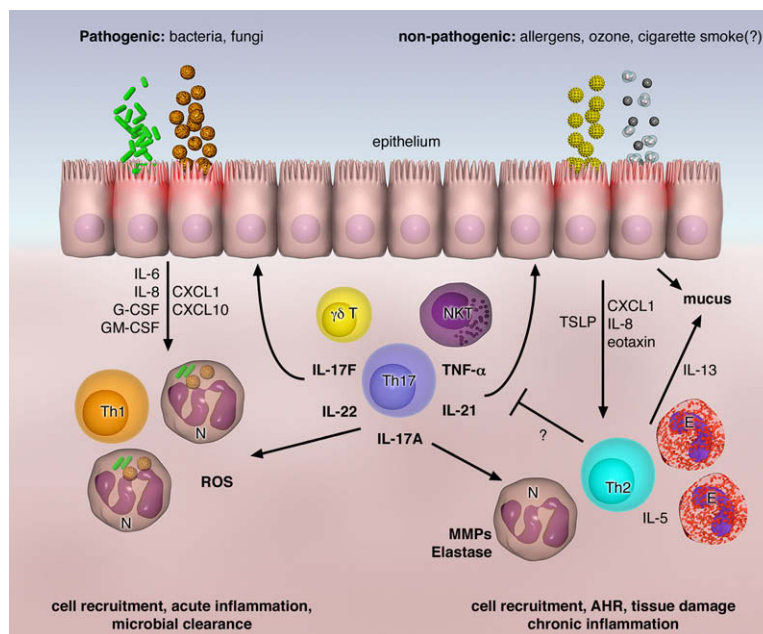


FIG 1. Beneficial and detrimental roles for T_H17 effector cytokines in the course of pulmonary immune responses. Bacterial and fungal infections in the lung trigger generation of T_H1 cells, T_H17 cells, $\gamma\delta$ T cells, and NK T cells, which secrete a panel of proinflammatory cytokines. IL-17A and related cytokines play an important role in inducing mobilization and activation of neutrophils, which contribute to pathogen clearance. However, predominant IL-17 production and associated neutrophil influx and neutrophil-derived products, including metalloproteinases, elastase, and reactive oxygen species, can have host-detrimental roles and contribute to the pathogenesis of severe lung inflammatory diseases, such as chronic asthma, chronic obstructive pulmonary disease, and cystic fibrosis. The effector phase of allergic asthma is determined by T_H2 -mediated allergic responses, including eosinophilia, mucus production, and airway hyperresponsiveness, which can be inhibited by IL-17A. The stimuli and the cellular sources of IL-17A and related cytokines in the course of a particular inflammatory lung disease still remain to be fully elucidated. Notably, the exposure of mice to ozone has been shown to lead to the expression of IL-17A by NK T cells. N, Neutrophils; E, eosinophils; ROS, reactive oxygen species; TSLP, thymic stromal lymphopoietin.

(IL-8), CXCL1, CXCL5, IL-6, G-CSF, and GM-CSF by airway epithelial cells.⁶⁷⁻⁷² These factors all contribute to the expansion of neutrophils from the bone marrow, as well as their survival and recruitment to the airways, thus highlighting the importance of T_H17 effector cytokines in regulating inflammation and immunity in the lung.⁷³

A protective effect of T_H17 immune responses has also been described for other bacterial strains infecting the lung, such as *Mycoplasma pneumoniae* and *Bordetella pertussis*,^{74,75} and IL-23 and IL-17A are readily induced in *Mycobacterium tuberculosis* infections in mice. Of note, $\gamma\delta$ T cells, and not T_H17 cells, were shown to be the initial source of IL-17A during primary infections with *M. tuberculosis* or *Mycobacterium bovis* BCG.^{76,77} After infection with BCG, IL-17A-deficient mice displayed decreased CXCL1, CXCL2, G-CSF, and TNF- α levels and, accordingly, decreased neutrophil infiltration in the early phase of the immune response. However, absence of IL-17A did not affect bacterial counts in the lung and susceptibility to disease. A protective role of CD4 T cell-derived IL-17A was described for *M. tuberculosis* infection after vaccination with BCG. IL-17A production by memory T_H17 cells generated upon vaccination was required for the induction of the chemokines CXCL9, CXCL10, and CXCL11 and for the rapid recruitment of memory T_H1 cells, which eventually control bacterial growth and protection after *M. tuberculosis* infections.^{78,79} Evidence for the role of T_H17 cells in mediating host protection against infections in

human subjects is still missing; however, increased frequencies of antigen-specific IL-17A- and IL-22-producing CD4 memory T cells have been detected in healthy individuals previously exposed to *M. tuberculosis* compared with those seen in infected patients.⁸⁰

A protective role of T_H17 cells and IL-17A in defense against fungal infection has been implicated by the identification of IL-17A-producing CD4 memory T cells specific for *Candida albicans* in human subjects⁸¹ and enhanced susceptibility of IL-17RA-deficient mice to *C. albicans* infection.⁸² However, studies by Zelante et al⁸³ suggest that IL-23 and IL-17A have a largely negative role in fungal infection. Gene deletion or neutralization of IL-23 and IL-17A improved immunopathology and fungal control after pulmonary *Aspergillus fumigatus* and systemic *C. albicans* infection.⁸³ Stimulation of neutrophils with IL-23 or IL-17A led to impaired fungicidal activity along with increased secretion of matrix metalloproteinase (MMP) 9 and myeloperoxidase. Cytokine treatment further prevented the initiation of an indoleamine 2,3-dioxygenase-dependent anti-inflammatory program in neutrophils. These results indicate that T_H17 responses can exert a detrimental effect in the course of fungal infections at mucosal surfaces by affecting fungal clearance and by promoting chronic inflammation and tissue damage.

In addition, T_H17 cells have also been implicated in the pathogenesis of inflammatory lung diseases, such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis,⁸⁴⁻⁸⁶ which are

TABLE I. T_H17 effector cytokines in pulmonary infections and diseases

Infection/disease	Cytokine effect	References
Mouse		
<i>Klebsiella pneumoniae</i>	Protection, neutrophil recruitment	54, 66, 67
<i>Mycobacterium tuberculosis</i>	Neutrophil recruitment	77
	Protection, regulation of T _H 1 responses	78
<i>Aspergillus fumigatus</i>	Exacerbation of inflammation, impaired fungal clearance	83
Nonallergic airway inflammation	Neutrophil influx, induction of airway hyperresponsiveness	98, 124
Allergic airway inflammation	Sensitization phase:	
	Induction of antigen-specific T cells	109, 110
	Induction of eosinophilia and T _H 2 responses	110
	Effector phase:	
	Suppression of inflammation	110
	Normal eosinophilia, neutrophils in bronchoalveolar lavage	111
Human		
<i>In vitro</i>	Induction of inflammatory chemokines and cytokines by airway epithelial cells, fibroblasts, smooth muscle cells, eosinophils	68-70, 88, 93, 94, 106, 107
<i>M tuberculosis</i>	Protection?	80
Severe chronic asthma, chronic obstructive pulmonary disease, cystic fibrosis	Neutrophil infiltration, inflammation, disease exacerbation?	84-89
Allergic asthma	?	104, 105

characterized by the influx of neutrophils into the airways. Increased levels of IL-17A and IL-17F could be detected in the airways of patients with asthma or cystic fibrosis compared with those seen in healthy individuals.^{69,71,87,88} In asthmatic individuals IL-17A levels were shown to correlate with the incidence of airway hyperresponsiveness and the severity of disease.^{89,90} Specifically, IL-17A expression appears enhanced in individuals with severe and chronic forms of asthma, in which the cellular infiltrate largely consists of neutrophils as opposed to the eosinophil influx observed in patients with moderate allergic asthma.^{87,91,92}

As previously mentioned, IL-17A acts directly on epithelial cells but also airway fibroblasts and smooth muscle cells to induce the secretion of neutrophil-recruiting chemokines, such as CXCL8.^{88,93-95} Moreover IL-17A and TNF- α strongly stimulate pulmonary cells to produce IL-6, a survival and activation factor for neutrophils.^{94,96} In rats direct administration of IL-17A into the airways was shown to induce neutrophil recruitment and activation.⁹⁷ Liang et al³ could additionally show that in mice T_H17 cells secrete IL-17A/A homodimers, as well as IL-17A/F heterodimers, which in the lung potentially induce the infiltration of neutrophils. Furthermore, the adoptive transfer of T_H17 cells induced neutrophil infiltration and steroid-resistant airway hyperresponsiveness on intranasal antigen challenge, and this response was inhibited in the absence of IL-17RA signaling.⁹⁸

These findings suggest that T_H17 cells and effector cytokines might play a prominent role in the pathogenesis of lung inflammatory diseases, such as severe asthma, by promoting the recruitment and survival of neutrophils (Fig 1). Moreover, in the inflamed airways the increased production of cytokines, such as TNF- α , IL-6, and IL-1 β , might also support additional *in situ* CD4 T-cell differentiation to the T_H17 cell subset, leading to further neutrophil infiltration and establishment of chronic inflammation. In asthmatic individuals there is a positive correlation between nonspecific bronchial hyperreactivity and increased frequencies of neutrophils in the airways.⁸⁴ Neutrophils are likely to play a detrimental role in the course of obstructive lung diseases by secreting inflammatory enzymes, such as myeloperoxidase,

MMPs, and elastase⁸⁴; the latter promotes airway wall destruction, whereas MMP-9 mediates both tissue remodeling and mucus hypersecretion.⁹⁹ Of note, IL-17A was also shown to induce the expression of mucin genes from human bronchial epithelial cells *in vitro*.¹⁰⁰

Although allergic asthma can be inhibited by corticosteroids,¹⁰¹ this treatment is not effective against airway inflammatory diseases characterized by enhanced neutrophilia.¹⁰² Corticosteroids might even exacerbate inflammation by enhancing survival and CXCL8-dependent recruitment of neutrophils into the airways¹⁰³; therefore other therapeutic approaches have to be considered. In line with the role of IL-17A and IL-17F in regulating granulopoiesis, recruitment, and survival of neutrophils, it can be speculated that inhibition of T_H17 effector functions represents a promising therapeutic strategy for the treatment of airway inflammatory diseases characterized by exacerbated neutrophil infiltration and activation, such as severe asthma, chronic obstructive pulmonary disease, or cystic fibrosis.¹⁰²

T_H17 EFFECTOR CYTOKINES IN ALLERGIC AIRWAY INFLAMMATION

Accumulating evidence implicates IL-17 in the development and progression of allergic asthma. First, IL-17 expression is upregulated after allergen challenge, and restimulation of allergen-specific T cells from atopic asthmatic patients results in enhanced production of IL-17 compared with that seen in nonallergic control subjects.^{104,105} In addition, IL-17 has also been shown to induce the release of the eosinophil-recruiting chemokine eotaxin from airway smooth muscle cells, and both IL-17 and IL-17F were able to induce the release of inflammatory mediators from human eosinophils *in vitro*.^{106,107} Interestingly, allergic individuals display lower frequencies of allergen-specific IL-10-producing Treg cells.¹⁰⁸ Considering that Treg and T_H17 cell differentiation is crossregulated, it can be speculated that in allergic individuals the balance is skewed toward inflammatory T_H17 cells. Regulation of the balance between these cell subsets might play an important role in determining the development of

tolerance or disease in the lung. However, models of ovalbumin (OVA)-induced allergic asthma in mice treated with IL-17-neutralizing antibodies or genetically deficient for IL-17A, IL-17F, or IL-17RA have provided a more complex picture. Mice deficient for IL-17A or IL-17RA showed impaired induction of OVA-specific T cells upon sensitization and reduced T_H2-type allergic airway inflammation (with a more pronounced defect in IL-17RA knockout animals), suggesting that IL-17A and possibly IL-17F contributed to the development of asthma in the sensitization phase.^{109,110} Conversely, IL-17A appears to inhibit asthma responses (eg, airway hyperresponsiveness, eosinophilia, and mucus production) in the effector phase, as suggested by results obtained from intranasal administration of recombinant IL-17 to OVA-sensitized mice and from neutralization of IL-17A during the challenge phase.¹¹⁰ Intriguingly, the route of sensitization seems to play an important role in IL-17-driven pulmonary inflammatory response considering that epicutaneous sensitization resulted in much stronger T_H17 responses compared with those seen after intraperitoneal sensitization, whereas T_H1 and T_H2 responses were comparable. Accordingly, OVA inhalation by mice that were sensitized epicutaneously (by using patches for delivery of antigen through shaved skin) induced neutrophil influx in the lung along with bronchial hyperreactivity, which were reversed by IL-17 blockade.¹¹¹

T_H2 cells are known to drive allergic asthma, and IL-4, the key T_H2 cytokine, has been described as a potent inhibitor of T_H17 development.^{28,112} Consistently, IL-4 receptor-deficient mice, which are protected from allergic asthma, showed increased IL-17 levels in the lungs that were partially responsible for suppression of lung eosinophilia.¹¹⁰ This argues that the balance of IL-17 and IL-4 levels in the lung determines the severity of allergic asthma. An overall inhibitory role of T_H17 cells in patients with allergic asthma might also be suggested by the exacerbated lung eosinophilia and frequencies of T_H2 cells in IL-6-deficient mice, which are defective in development of T_H17 cells (unpublished data).¹¹³

Taken together, these results clearly implicate IL-17 in asthma; however, no firm conclusions can be drawn. Given such disparate data, it is tempting to speculate that IL-17 does not play a dominant role in allergic asthma and its function might be more limited to diseases in which neutrophils play a critical role. Further focus on human studies or more relevant mouse models of allergic asthma (eg, purified allergens as opposed to innocuous proteins, such as OVA, and inhalation sensitization rather than systemic protein/adjuvant sensitization) might be the key to bringing clarity to the role of IL-17 in allergic asthma.

IL-17-PRODUCING $\gamma\delta$ T CELLS AND NATURAL KILLER T CELLS IN THE RESPIRATORY TRACT

In addition to T_H17 cells, $\gamma\delta$ T cells and natural killer (NK) T cells have also been shown to produce IL-17A in the lung. Pulmonary IL-17A-producing $\gamma\delta$ T cells have been detected after infection with *M tuberculosis*,⁷⁶ as well as in response to bleomycin-induced tissue damage.¹¹⁴ Notably, $\gamma\delta$ T cells have been associated with innate immune responses against bacterial infections and the regulation of lung tissue homeostasis and repair against infectious and noninfectious insults.¹¹⁵⁻¹¹⁷ Conversely, a particular subset of $\gamma\delta$ T cells secreting IL-17A has been shown to contribute to hyperinflammatory granulomatous disease and fatal lung tissue damage during pulmonary aspergillosis.¹¹⁸

NK T cells represent another T-cell subset, which was recently described to produce IL-17A in mice.¹¹⁹ These invariant IL-17A-secreting NK T cells were shown to be frequent in the lung, to induce the recruitment of neutrophils into the airways in response to α -galactosylceramide or LPS, and to express the lineage-specific transcription factor ROR γ t.¹²⁰ NK T cells play an important role in the regulation and amplification of immune responses through the rapid production of inflammatory cytokines.¹²¹ Of note, NK T cells have been reported to localize in the lungs of asthmatic individuals, and mice lacking NK T cells displayed impaired bronchial hyperreactivity in a model of allergic airway inflammation, suggesting a role for this cell subset in the pathogenesis of asthma and airway hyperresponsiveness.^{122,123} Furthermore, Pichavant et al¹²⁴ proposed a role for NK T cells in the development of airway hyperresponsiveness after exposure to ozone. In this model ozone inhalation induced infiltration of neutrophils, IL-17A-producing NK T cells, and airway hyperreactivity. Of note, the development of ozone-induced asthma was shown to be impaired in the absence of NK T cells and in IL-17A-deficient mice. Although the induction of IL-17A expression in $\gamma\delta$ T cells and NK T cells has yet to be elucidated, these studies do highlight IL-17A-secreting NK and $\gamma\delta$ T cells as potential regulators of allergic and nonallergic asthma.

CONCLUDING REMARKS

In conclusion, IL-17A, IL-17F, and IL-22 are produced by distinct types of T cells, including T_H17 cells, $\gamma\delta$ T cells, and NK T cells, that are involved in the induction and effector phase of a variety of immune responses. The rapid activation of $\gamma\delta$ and NK T cells to secrete IL-17A might represent an important innate mechanism for the recruitment of neutrophils in response to bacterial infection, in particular at mucosal surfaces. Depending on the timing, the tissue, and the local microenvironment, IL-17A-secreting cells appear to play both beneficial and detrimental roles in lung immunity and disease. Given the current controversy on the relevance of IL-17A and related effector cytokines in the respiratory tract (Table I),* further work is certainly required to clarify how this pathway of inflammation could be harnessed for future therapeutics.

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