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T_H17 Cells in Asthma and COPD

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Key Words

IL-17, allergy, inflammation

Abstract

Asthma and chronic obstructive pulmonary disease (COPD) represent two classes of chronic obstructive lung disorders that may share some similar immunologic mechanisms of disease. Asthma is a complex human disease characterized by airway hyperresponsiveness (AHR) and inflammation, whereas COPD is marked by progressive emphysematic changes in the lung. Recently it has been shown that advanced COPD is characterized by lymphoid follicles, drawing attention to immunological mechanisms in COPD. Despite numerous studies in mice to elucidate the immunologic mechanisms of asthma, sufficient current treatment options are limited. Clinically, many asthma patients fail to satisfactorily respond to standard steroid therapy, and this type of steroid-resistant, severe asthma has been linked to the presence of neutrophilic inflammation in the lung. The role of neutrophils, macrophages, and their secreted proteases in COPD needs to be better defined. Recently, the T lymphocyte subset T_H17 was shown to play a role in regulating neutrophilic and macrophage inflammation in the lung, suggesting a potential role for T_H17 cells in severe, steroid-insensitive asthma and COPD.

Asthma: a complex chronic airway disease characterized by partially reversible airway obstruction, hyperreactivity, and inflammation; often related to atopic immune response

Cytokine: a broad class of secreted protein molecules involved in cell-cell communication through receptor-ligand interactions

Airway hyperresponsiveness (AHR): describes a hypercontractility (compared with normal subjects) of bronchial smooth muscle in response to cholinergic stimulation

Eosinophil: the effector white blood cell of T_H2 immunity; produces cationic proteins, cytokines, and reactive oxygen species characteristic of atopic immunity

Neutrophil: the most abundant white blood cell; produces numerous proinflammatory cytokines, proteases, and reactive oxygen species essential for pathogen clearance

T_H2 cells: a helper T cell subset characterized by IL-4, IL-5, and IL-13 production; involved in atopic immune responses and parasite immunity

INTRODUCTION

Allergic asthma is a chronic airway disease that affects millions of people in the developed world. The disease is characterized by concurring airway inflammation, cytokine production, airway hyperresponsiveness (AHR) to inhaled antigen, and pulmonary fibrosis. Several cell types, including epithelial cells, eosinophils, neutrophils, smooth muscle cells, alveolar macrophages, dendritic cells, mast cells, and T lymphocytes, have been implicated in the pathogenesis of asthma. Numerous studies in both mice and humans have identified the T_H2 subset of T cells as playing a key role in disease pathogenesis through the production of cytokines and chemokines, which induce airway eosinophilic inflammation and AHR.

The murine ovalbumin (OVA) sensitization and challenge model of allergic airway disease has been well established by many investigators (1–3). In this model, airways accumulate large numbers of eosinophils as measured in bronchoalveolar lavage (BAL) fluid and express increased levels of the T_H2 cytokines interleukin (IL)-4, IL-5, and IL-13. These mice also exhibit B cell-dependent production of OVA-specific IgE and IgG₁. In addition, mice that have been sensitized and challenged with OVA exhibit increased airway resistance following methacholine (Mch) challenge compared with nonsensitized controls, illustrative of the development of AHR. Furthermore, airway remodeling including enhanced deposition of collagen around the airways, increased mucous cell metaplasia, and smooth muscle hyperplasia has been reported. Therefore, the murine OVA model represents several of the key characteristics of human asthma. However, despite the effectiveness of T_H2 cytokine inhibition in mice in abrogating allergic airway disease (4–6), these approaches have proved unsuccessful in treating established asthma in patients (7).

Chronic obstructive pulmonary disease (COPD) shares a common morbidity with asthma, airflow limitation. However, in COPD this loss of lung function is not reversible due

to progressive tissue destruction. COPD represents the fourth leading cause of death in the developed world and is increasingly prevalent in men and women over the age of 40 (8). The disease etiology is invariably linked to cigarette smoking or environmental pollutant exposure. The role of neutrophils and macrophages and their products has been well established in the slow progression of the disease. Inhibitors of neutrophil proteases, such as neutrophil elastase and matrix metalloproteinase (MMP)9, have recently been discussed as potential therapeutic targets (9–11). In addition, antagonists of chemokine receptors, including CXCR2, CCR5, and CCR6, involved in neutrophil recruitment have also been investigated (12–14). These receptors recognize the known neutrophil chemokines KC, GRO, and MIP-2 (categorized as CXCL1–3), which bind CXCR2; the T cell chemokines MIP-1/CCL3 and CCL4, which bind CCR5; and CCL20, which binds CCR6. Numerous studies in mouse models of cigarette smoke exposure have confirmed the roles of these molecules in disease pathogenesis. However, the role of T lymphocytes in COPD is less well defined.

NEUTROPHILIC INFLAMMATION IN ASTHMA

Despite the research focus on T_H2 -driven asthma, studies have shown that as many as 50% of asthmatics are characterized by nonatopic, non-IgE-dependent, and noneosinophilic inflammation (15). Moreover, airway neutrophilia is enhanced in noneosinophilic asthmatics, and the extent of neutrophilia is correlated to asthma severity, suggesting a role for neutrophils in a subset of asthmatics (16–19). Neutrophilic inflammation is largely present in sudden-onset fatal asthma in the absence of eosinophils, and neutrophil numbers are highly elevated in status asthmaticus (20, 21). These data suggest that severe and fatal asthma may be a neutrophil-mediated disease, rather than classical T_H2 -driven eosinophilic asthma. In addition to severe asthma,

steroid-resistant asthma may also feature a neutrophil-dependent component (22). The degree of neutrophilic inflammation correlates with decreased improvement in FEV₁ (forced expiratory volume in 1 s) and Mch responsiveness following glucocorticoid (GC) treatment (23), whereas GC prophylaxis results in increased levels of the neutrophil chemokine IL-8 and increased neutrophil numbers in the airways (24). Furthermore, neutrophils are largely steroid insensitive, and GCs inhibit neutrophil apoptosis (25, 26), perhaps explaining the increase in neutrophilia in severe and steroid-resistant asthmatics. Taken together, these data suggest a role for neutrophils in mediating severe and steroid-resistant asthma (27–29).

Activated neutrophils secrete a variety of cytokines and proteases that may play a role in the AHR and mucus metaplasia observed in asthma (30, 31). The extracellular matrix proteases elastase and MMP9 are elevated in asthmatics (28, 32, 33). These proteases are thought to be involved in the airway remodeling seen in asthma, which may relate to the decline in lung function in these patients. Inhibition of neutrophil elastase with a specific peptide inhibitor abrogated AHR in allergic sheep (34), whereas treatment with exogenous neutrophil elastase enhanced AHR in guinea pigs (35). These data suggest that neutrophil elastase is an important mediator of AHR in asthma. However, inhibition of early neutrophil influx by inhibiting IL-1 or IL-18 signaling in the OVA model had no impact on AHR (36). The effects of altering neutrophil numbers or elastase production on AHR are still unclear. In addition to potentially impacting AHR, neutrophil elastase stimulates mucin production and secretion by airway epithelial cells (37, 38). Another key neutrophil protease, MMP9, is a primary MMP enhanced in asthmatics, and levels of MMP9 correlate with asthma severity (39, 40). Furthermore, IL-17 increases MMP9 levels via recruitment of neutrophils to the lung (41). The role of these proteases has not been fully examined in a model of neutrophilic asthma in mice.

DISCOVERY AND CELLULAR SOURCES OF INTERLEUKIN-17

IL-17, also known as IL-17A, was first cloned in 1993 and identified as cytotoxic T lymphocyte-associated antigen (CTLA)-8 (42). It was found to have high similarity with open reading frame 13 of *Herpesvirus saimiri*, a virus capable of inducing T cell lymphomas in several species of primates. In humans, the gene for IL-17 was mapped to chromosome 2q31 (42, 43). However, subsequent studies have identified the gene on chromosome 6p12 (44, 45). Mouse IL-17 and human IL-17 exhibit 63% amino acid homology (46). Since the discovery of IL-17, several other homologous proteins have been identified, resulting in an IL-17 cytokine family in which the members are designated as IL-17A through IL-17F (**Figure 1**) (45, 47, 48). The IL-17 family members exhibit four conserved carboxy-terminal cysteine residues involved in dimerization. IL-17A and IL-17F share the greatest homology and are perhaps the best-characterized cytokines in the family (44). These two molecules may also heterodimerize (49). In contrast, IL-17E, also referred to as IL-25, is the most divergent member (50).

IL-17 was first shown to be produced by activated CD4⁺ memory T cells (51). Since that discovery, it has been determined that CD4⁺ T cells producing IL-17 constitute a distinct lineage, referred to as T_H17 cells (in contrast to T_H1 or T_H2 cells) (52–54). T_H17 cells produce both IL-17A and IL-17F (along with other cytokines), although subsets producing only IL-17A or IL-17F have also been described (55).

In addition to T_H17 cells, other cell types have also been described to produce IL-17. These include invariant natural killer T (iNKT) cells (56), CD8⁺ T cells (57), and lymphoid tissue inducer (LTi)-like cells (58). Additionally, a recent report has identified a subset of CD8⁺ cells that produces IL-17 and termed them T_C17 cells (59), following the convention of CD4⁺ T cell subsets. Gamma delta T (γδT) cells have also been described as an important

Ovalbumin (OVA)

model: ovalbumin immune sensitization and subsequent challenge model utilized in mice to mimic atopic asthma

Chronic obstructive pulmonary disease (COPD):

characterized by concurring bronchitis and emphysema resulting in irreversible airflow limitation; often associated with smoking

Atopy: the capacity to generate allergic responses to antigen; characterized by IgE production

Severe asthma:

asthma characterized by frequent exacerbations, significant decline in FEV₁ (<60%), and impairment of daily physical function

Forced expiratory volume in 1 s (FEV₁):

considered a primary indicator of lung function

Steroid-resistant asthma:

asthma in which airway hyperreactivity is not reversible (less than 15% of FEV₁) by standard glucocorticoid treatment; often neutrophil associated

Glucocorticoids (GCs):

a class of steroid hormones (including dexamethasone) that generally inhibit immunity and inflammation

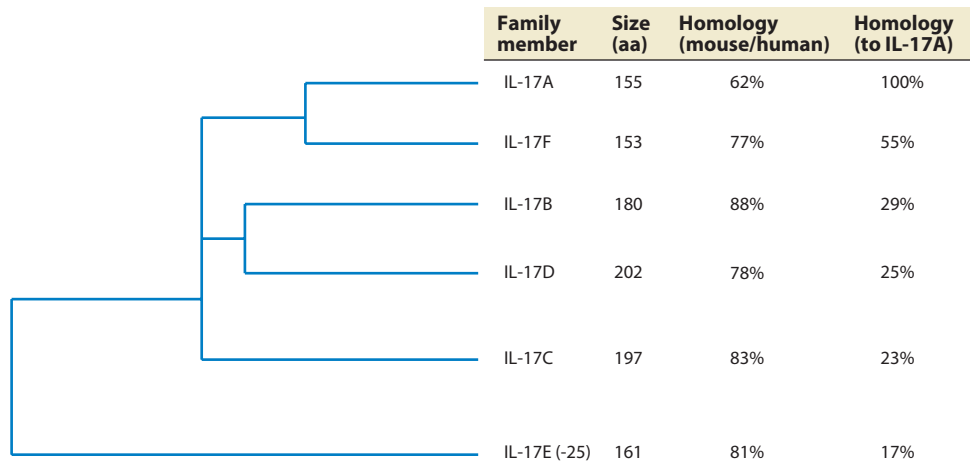


Figure 1
The IL-17 cytokine family. The six cytokine members of the IL-17 family are depicted in a dendrogram revealing relative homology to each other and between mouse and human proteins. Homology to IL-17A is based on the respective human proteins. aa, amino acids.

source of IL-17 in naive mice and bacterial infection (60–63). In addition to T cell sources, IL-17 mRNA has been measured in neutrophils in response to challenge with lipopolysaccharide (LPS) (64), although production and secretion of IL-17 protein by these cells have not been described.

Other members of the IL-17 family have different expression patterns. In the case of IL-17B, mRNA has been detected in a wide variety of tissues, including the gastrointestinal tract, prostate, ovary, testis, and spinal cord (47). In contrast, IL-17C expression is much rarer, having been identified only in prostate and fetal kidney (47). IL-17D is expressed in muscle and adipose tissue as well as brain, lung, and pancreas (48, 65). IL-17E (IL-25), like IL-17A and IL-17F, is expressed most abundantly by T cells, especially T_H2 -polarized $CD4^+$ T cells (66). In addition, lung epithelial cells express IL-25 in response to allergic stimuli (67).

REGULATION OF IL-17 PRODUCTION IN T_H17 CELLS

Of the various cell types that are capable of producing IL-17, $CD4^+$ T_H17 cells are

the best characterized. Antigen-specific production of IL-17 by these cells is dependent upon polarization to a T_H17 phenotype. T_H polarization is guided by antigen costimulation and cytokine-dependent signaling (Figure 2). Polarization to the T_H1 subset occurs in the presence of IL-12 signaling through signal transducer and activator of transcription (STAT) 4 and results in a T cell population that expresses the transcriptional regulator T-bet and the cytokine interferon (IFN)- γ . Polarization to the T_H2 subset generally requires the presence of IL-4 signaling through STAT6 and results in a cell population marked by GATA3 expression and production of IL-4, IL-5, and IL-13 (68–70). In the presence of transforming growth factor (TGF)- β alone, T cells polarize to regulatory T cells, which express Foxp3 and produce TGF- β and IL-10 (71, 72). In mice, the presence of TGF- β and proinflammatory cytokines IL-1 β and IL-6 signaling through Smad2/3, STAT3, nuclear factor- κ B (NF- κ B), and AP-1 induces T cell polarization to a T_H17 phenotype, which expresses ROR γ T and ROR α and produces IL-17A and IL-17F, along with IL-21 and IL-22 (72–75). ROR α and ROR γ T are required for IL-17A production, whereas only ROR γ T is necessary for

Interleukin-17

(IL-17): refers to a family of six cytokines (A–F); characterized by four conserved carboxy-terminal cysteines and are involved in tissue inflammation

T_H17 cells: a helper T cell subset characterized by IL-17A, IL-17E, and IL-22 production; involved in host response to extracellular pathogens and autoimmunity

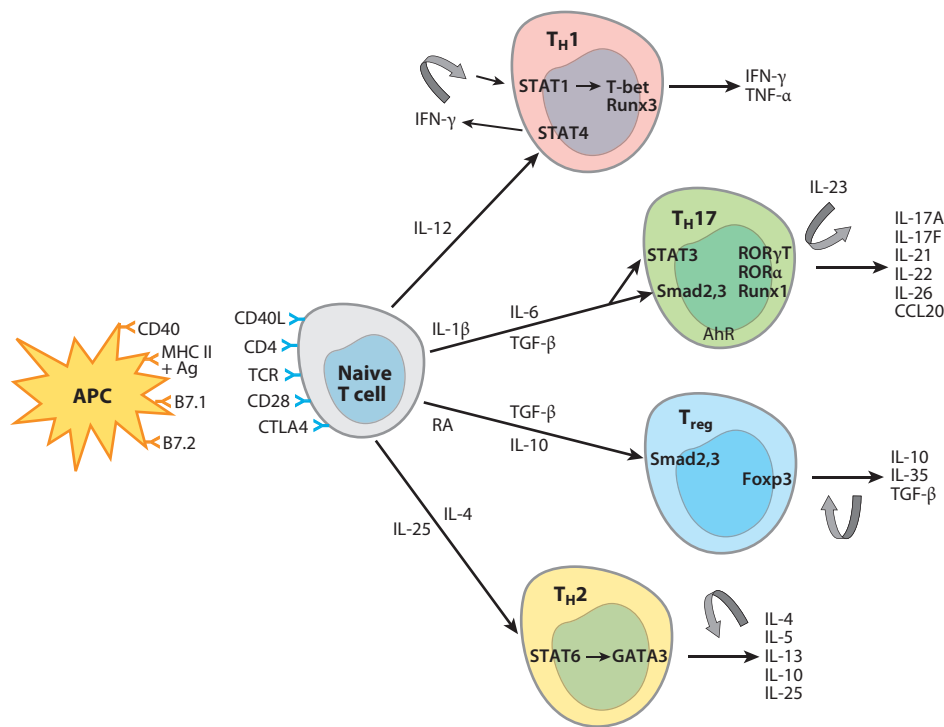


Figure 2

Naive T cell polarization. Complex cytokine networks drive T_H subset polarization in the presence of antigen stimulation of the T cell receptor. Signaling and transcriptional molecules specific for each T_H cell lineage are depicted intracellularly. Each T_H cell lineage is characterized by specific cytokine production. Ribbon arrows indicate autocrine or paracrine effects of cytokines on polarization and cytokine production. Ag, antigen; APC, antigen-presenting cell; T_{reg} , regulatory T cell.

IL-17F (76). Other studies have identified the T cell cytokine IL-21 as being capable of driving T_H17 differentiation along an autocrine or a paracrine alternative pathway (77, 78). A recent study suggests that T_H17 cells retain a degree of plasticity upon differentiation (79). This study showed TGF- β to be critical for sustained IL-17A and IL-17F production by T_H17 cells. In the absence of TGF- β , IL-12 and IL-23 can induce polarized T_H17 cells to produce IFN- γ in a STAT4- and T-bet-dependent manner. These data indicate that T_H17 cells can retain the ability to adjust cytokine production based on the local inflammatory milieu.

Initially, it was believed that T_H17 polarization in mice also requires IL-23. However, investigators showed that receptors for IL-23 are not present on naive T cells (80) and

subsequently demonstrated that IL-23 is not responsible for polarization of naive T cells to a T_H17 phenotype (74, 75). Despite this, IL-23 is important for T_H17 cells, as loss of IL-23 results in decreased production of IL-17. IL-6 and TGF- β synergize to induce expression of IL-23 receptor, and IL-23 is responsible for the expansion and maintenance of T_H17 cells as well as the expression of chemokine receptors on these cells (81–83). Furthermore, loss of IL-23 results in a decrease in IL-7 receptor alpha (IL-7R α), which is necessary for survival of memory T_H17 cells, suggesting that IL-23 supports T_H17 memory (83).

In humans, T_H17 development can be driven by IL-1 β and IL-23 (84, 85) and can be enhanced by IL-6 (86). The role of TGF- β in human T_H17 development is unclear. Some

Gamma delta T ($\gamma\delta$ T) cell:

a lymphocyte that expresses the $\gamma\delta$ T cell receptor, generally resides in mucosal tissues, and plays a role in innate immunity

Invariant natural killer T (iNKT cell) lymphocytes:

recognize lipid and glycolipid antigens presented on CD1d; play a role in innate and autoimmune responses

reports suggest TGF- β may actually suppress the generation of human T_H17 cells (84–86). However, other studies have shown that TGF- β is necessary for human T_H17 development (87, 88). Moreover, one study has shown that TGF- β plus IL-21 can drive human T_H17 polarization (89), whereas another study shows no IL-17 production under those conditions (88). A recent study has shown that TGF- β , IL-1 β , IL-6, and IL-23 are required for T_H17 production of IL-17 and subsequent induction of IL-6 and IL-1 β in epithelial cells, although TGF- β alone is sufficient to induce ROR γ T (RORC2) (90). In this study, ROR γ T expression was not limited to T_H17 cells; rather, it was also expressed in regulatory T cells, iNKT cells, and cytotoxic T (T_C) cells. Reasons behind these discrepancies must be further explored but may be due to differences in culture media (serum versus serum free) and time of the culture (91).

Induction of T_H17 cells requires signaling through STAT3 (92, 93) and activation of transcription factors ROR γ T and ROR α (76, 88). STAT3 is activated by both IL-6 and IL-23. Ablation of STAT3 specifically in T cells resulted in a failure of T_H17 polarization and reduced IL-17 production (92, 94). Additionally, aryl hydrocarbon receptors can stimulate T_H17 differentiation (95). This cytosolic receptor, once bound to an aryl hydrocarbon ligand, translocates to the nucleus and serves as a transcription factor that works synergistically with ROR γ T and ROR α . More recently, it has been shown that prostaglandin E₂, acting through prostaglandin EP2 and EP4, regulates T_H17 cell differentiation (96). In addition to these pathways, interferon regulatory factors (IRFs) play a role in T cell polarization. IRF1 and IRF2 are both involved in T_H1 differentiation (97, 98). IRF4, in contrast, not only promotes development of T_H17 cells but antagonizes IRF1. IRF4-deficient mice exhibit decreased levels of IL-17 and IL-21. Under conditions favoring T_H17 differentiation (i.e., TGF- β and IL-6 are present), these mice instead polarize toward a regulatory T cell phenotype (99). Regardless of the requirements for polarization, T_H17 cells characteristically express CCR4 and

CCR6, which respond to TARC and CCL20, respectively, to promote homing to the site of inflammation (100).

REGULATION OF IL-17 PRODUCTION IN $\gamma\delta$ T CELLS

As for T_H17 cells, production of IL-17 by $\gamma\delta$ T cells requires polarization. Subsets of IL-17-producing $\gamma\delta$ T cells have been identified that are distinct from those producing IFN- γ . Furthermore, these IL-17 producers are CD25⁺ CD122⁻, whereas IFN- γ producing $\gamma\delta$ T cells are CD25⁻ CD122⁺. In contrast to the T_H17 cells described above, which leave the thymus as naive cells and polarize in the periphery, the $\gamma\delta$ T cells are capable of undergoing polarization in the thymus (62). It is hypothesized that this allows them to rapidly respond to antigen in the periphery. The precise factors determining $\gamma\delta$ T cell polarization are not as well described as those for T_H17 cells. One report describes the role of thymic selection in polarization of these cells, demonstrating that $\gamma\delta$ T cells that are antigen naive during development produce IL-17, whereas those that encounter antigen during thymic selection instead produce IFN- γ (101). Other studies have demonstrated that, similar to the case for T_H17 cells, IL-17 production by $\gamma\delta$ T cells is supported by IL-23 and that this IL-23 signal is mediated through Tyk2 signaling (63). In contrast to T_H17 cells, IL-6 does not seem to be required for IL-17 production by $\gamma\delta$ T cells (73).

THE IL-17 RECEPTOR FAMILY AND IL-17 SIGNALING

The first known IL-17 receptor, now known as IL-17 receptor A (IL-17RA), is ubiquitously expressed (43). Both IL-17A and IL-17F are capable of binding IL-17RA, but at low affinities (receptor affinity for IL-17F is less than that for IL-17A) (102). However, a second IL-17 receptor, IL-17RC, has a much higher affinity for both IL-17A and IL-17F. Furthermore, cotransfection with IL-17RC and IL-17RA resulted in optimal signaling induced

by both IL-17A and IL-17F. Additionally, these two proteins coimmunoprecipitate, providing evidence of association (103). The precise stoichiometry of this association is not determined. IL-17RA appears to be essential for both IL-17A and IL-17F signaling, as loss of this protein blocks the ability of cells to respond to these cytokines (104). The cytoplasmic portion of this receptor contains a sequence similar to the TIR domains common to Toll-like receptors (TLRs) and IL-1 receptors (105). This region of the protein has been termed a SEFIR domain, and deletions of this region impair IL-17 signaling (106). The signaling protein Act1, which also encodes a SEFIR domain, interacts with IL-17RA and results in activation of NF- κ B and TAK1 (107). However, IL-17RA also activates other signaling pathways, including ERK (107), suggesting that other signaling motifs remain to be described. Interestingly, a soluble form of IL-17RC has been described,

although its potential function as an antagonist is largely unknown (108). The IL-17R is ubiquitously expressed in the lung and other tissues. In the lung, IL-17RA expression has been described on the basolateral surfaces of well-differentiated airway epithelial cells, suggesting that these cells can serve as a target for IL-17 (109).

In response to IL-17RA signaling, cells produce several proinflammatory chemokines, cytokines, and growth factors (**Figure 3**). Among the chemokines that are upregulated are CXCL1 (KC), CXCL2 (MIP-2), CXCL5 (LIX), and CXCL8 (IL-8), all of which are chemoattractive for neutrophils (44, 110, 111). Additionally, granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) are upregulated, promoting granulopoiesis, including neutrophil production (44, 112). Other chemokines that are responsive to IL-17

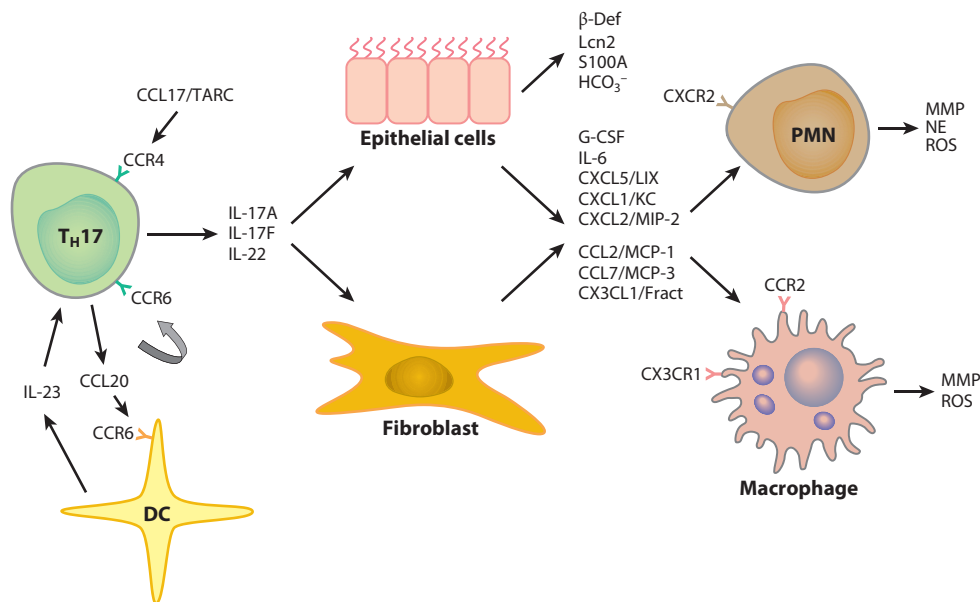


Figure 3

T_H17 regulation of inflammation. T_H17-induced cytokines IL-17A, IL-17F, and IL-22 induce numerous chemokines and growth factors to promote neutrophil and macrophage accumulation at the site of injury. Neutrophil and macrophage products promote inflammation, clearance of infection, and airway remodeling. In addition, T_H17 cytokines stimulate antimicrobial peptide production by the airway epithelium. β-def, β-defensin; DC, dendritic cell; Lcn2, lipocalin 2; MMP, matrix metalloproteinase; NE, neutrophil elastase; PMN, polymorphonuclear cell; ROS, reactive oxygen species.

Table 1 Microarray data sets for T_H17, IL-17, and IL-22 deposited at the NCBI GEO data sets, gene expression omnibus

GSE Number	Title	Species
15029	Gene array for identifying molecules involved in IL-10 regulation during T _H 17 polarization	Mouse
14308	Epigenetic mechanisms underlie T cell plasticity	Mouse
14026	Gene expression comparisons of T helper cells	Mouse
12109	T _H 17 cytokines IL-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways	Human
11367	Effect of IL-17 on human vascular smooth muscle cells	Human
11533	Analysis of gene expression in different T cell clones	Human
11345	IL-17 and IL-22 stimulation of T84 colonic epithelial cell line	Human
10814	Tumor-specific T _H 17-polarized cells eradicate large established melanoma	Mouse
10240	Primary human bronchial epithelial cells stimulated with IL-22 and IL-17	Human
10010	IL-22 plays an indispensable role in early host defense against attaching and effacing (A/E) bacterial pathogens	Mouse
9316	Gene microarray analysis of T _H 17 cells	Mouse
7459	IL-6-induced changes in gene expression in activated CD4 ⁺ T cells	Mouse

signaling include CXCL9 (MIG), CXCL10 (IP-10), CCL2 (MCP-1), and CCL20 (MIP3 α) (113–115). Other proinflammatory cytokines produced in response to IL-17 signaling include tumor necrosis factor- α (TNF- α) and IL-6 (43, 116). IL-17 synergizes with TNF- α to increase cytokine mRNA stability and thus enhance production of inflammatory genes such as IL-6 and IL-8 (117, 118). Additionally, IL-17 up-regulates several acute phase response proteins and antimicrobial proteins, either alone or synergistically with IL-22. These proteins include serum amyloid A, C-reactive protein, lipocalin 2, β -defensins, S100 proteins, and mucins (119–124). A current summary of publicly deposited microarray data regarding IL-17, IL-22, and T_H17 cells is presented in **Table 1**.

IL-17 AND LUNG INFLAMMATION

Given the role of IL-17 in the regulation of growth factors that promote granulopoiesis and chemokines that recruit neutrophils, IL-17 plays an important role in the neutrophil response in the lung. Adenovirus expression of IL-17A or IL-17F is sufficient to promote neutrophilia in the lung (125). Recombinant IL-17A administration to the lung induces a robust neutrophil recruitment (111), whereas IL-17A or IL-17F chronic overexpression

(for five months) resulted in increased CCL2 (MCP-1) production and enhanced lymphocyte and macrophage numbers, but not increased neutrophils (53, 55). IL-17-driven production of proinflammatory cytokines and antimicrobial peptides results in significant consequences for lung host defense. Additionally, the IL-17 signaling pathway likely plays an important role in the reduced airflow observed in asthma and other chronic lung diseases, including COPD and cystic fibrosis (CF).

Mice lacking either IL-17 or IL-17RA have increased susceptibility to Gram-negative bacteria, including *Klebsiella pneumoniae* (126) and *Mycoplasma pneumoniae* (127). In the *K. pneumoniae* model, IL-17RA knockout mice showed decreases in granulopoiesis and neutrophil recruitment and higher bacterial burdens in the lung as well as increased dissemination to the spleen (126). IL-23p19-deficient mice, which have decreased levels of IL-17, exhibit a similar phenotype. In these mice, treatment with recombinant IL-17 restores chemokine production and neutrophil recruitment and results in reduced bacterial burden (128). Results in the *M. pneumoniae* model are similar; lower levels of IL-17 correlate with decreased neutrophil recruitment and higher bacterial burden (127). In contrast, reports suggest that IL-23 and IL-17 are dispensable for protection against infection by primary *Mycobacterium tuberculosis*, an

Cystic fibrosis (CF): a genetic disorder resulting in diminished mucociliary clearance in the lung; associated with chronic inflammation and tissue destruction

intracellular pathogen. Loss of IL-17RA does not decrease clearance of *M. tuberculosis* (129). However, IL-23 is induced by *M. tuberculosis*, and use of IL-23 as a vaccine adjuvant in *M. tuberculosis* vaccination results in a more robust antigen-specific T cell response (113, 130, 131). Use of IL-23, although decreasing mycobacterial burden, increases both T_H1 cells and T_H17 cells (130, 131). Furthermore, $\gamma\delta$ T cells are a major source of IL-17 in the tuberculosis model (60).

Aside from the aforementioned report on T_C17 cells in the setting of influenza infection (59), there are fewer data on the role of IL-17 in host defense against viral pneumonias. IL-17RA knockout mice display impaired neutrophil recruitment following influenza challenge and as a consequence have reduced lung injury, despite no changes in viral clearance (132). There is ample evidence that, in addition to its role in viral immunity, IL-17 signaling regulates fungal host defense in the lung. In a model of *Pneumocystis carinii* pneumonia (PCP), mice with reduced levels of IL-17 have higher fungal burdens, suggesting a beneficial role for IL-17 in fungal clearance (133). However, in apparent contrast to this observation, decreases in IL-23 result in more efficient clearance of *Aspergillus fumigatus*. Further studies suggested this result was because IL-17 may actually inhibit fungicidal activity of neutrophils (134). This apparent dichotomy in protective versus detrimental roles of IL-17 in fungal clearance is reflected in other extrapulmonary models of fungal infection, including *Candida albicans* [a protective role in intravenous infection and a detrimental role in intragastric infection (134–136)] and *Cryptococcus neoformans* [a protective role (137)]. Recently, the T_H17 pathway was shown to be critical for protection against oral candidiasis, as IL-23 or IL-17R knockout mice had a more severe fungal burden compared with controls (138). Interestingly, the T_H17 cytokine IL-22 was not required in this model, suggesting a key role for IL-17. Further studies are needed to clarify the factors that determine whether IL-17 is protective or detrimental in the antifungal immune response.

Evidence for the role of IL-17 in human host defense is apparent in Job's syndrome (also known as hyper-IgE syndrome) patients. These patients have a defect in STAT3, which is important in both IL-6 and IL-23 signaling and is therefore key to polarization toward T_H17 cells (139). As a result, these patients exhibit decreases in T_H17 cells and IL-17 production (140, 141). These patients come to medical attention with chronic, recurrent infections of the skin and lung by *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, as well as other pathogens (139–141).

Importantly, the neutrophil response is not the only mechanism by which IL-17 aids in host defense. As mentioned above, IL-17 results in the induction of several antimicrobial peptides. These include β -defensins and S100 proteins (S100A7, S100A8, S100A9). The expression of these antimicrobial peptides is enhanced by the synergistic expression of IL-17 and IL-22, another T_H17 cytokine (119–124). Like IL-17, IL-22 has an important role in host defense against bacterial pneumonia, as loss of IL-22 results in increased susceptibility to *K. pneumoniae* (121). The ability of antimicrobial peptides to kill pathogens is regulated by carbonate concentrations in physiological buffers (142). Interestingly, IL-17A induces bicarbonate secretion by human bronchial epithelial cells (143), suggesting that IL-17A may regulate both production and activity of antimicrobial peptides. In addition to these functions, IL-17 plays a role in upregulating mucus production in the airway. MUC5B and MUC5AC, two mucin proteins that constitute much of the mucus in respiratory secretions, are both inducible by IL-17 (124). These proteins play key roles in mucociliary clearance of particles in the lung. Several chronic lung diseases are characterized by hypersecretion of mucus, including CF, COPD, and asthma; therefore, it is important to understand what role, if any, IL-17 might play in these disease states.

CF is a chronic inflammatory disease of the lung in which patients have an excess of mucus in the airway. CF is attributed to mutations in an ion channel—cystic fibrosis transmembrane

conductance regulator (CFTR)—that results in decreased amounts of airway surface liquid. This in turn prevents normal function of cilia and leads to the accumulation of mucus, which leads to recurrent pulmonary infections (144). CF patients undergoing pulmonary exacerbations were found to have increases in IL-17 in their sputum. These IL-17 levels correlated with colonization by *Pseudomonas aeruginosa* and declined with antibiotic treatment (104). This suggests that IL-17 plays a role in host defense under chronic inflammatory conditions. Because IL-17 is capable of inducing bicarbonate secretion (143), this finding may have important consequences in regulating the volume of the airway surface liquid and, combined with the ability of IL-17 to induce mucus production (124), suggests that IL-17 may play an important role in mucociliary clearance in both the CF and healthy lung.

IL-17 AND ASTHMA

The role of IL-17 in asthma is an area of much current investigation. Asthmatics have elevated levels of IL-17A mRNA and protein (145–148). Furthermore, increased IL-17A and IL-17F levels are positively correlated to disease severity, suggesting an important role for IL-17A and IL-17F in severe asthma (149, 150). Indeed, elevated IL-17A levels also correlate to increased neutrophilic inflammation, a characteristic of severe and steroid-resistant asthma (146). Increased IL-17A has also been correlated to increased AHR in response to Mch in asthmatics (151). These data implicate IL-17A as an important mediator in neutrophilic asthma. In addition, a polymorphism in IL-17F that results in a loss-of-function mutation is inversely related to asthma risk, suggesting that IL-17F may also play an important role in the development of asthma (152, 153). The cellular source of IL-17A in asthma is unclear, although a recent study has shown the presence of a significant number of IL-17A-producing CD4⁺ cells (potentially T_H17) in asthmatic tissues (154). Interestingly, IL-17 expression by T cells may be restricted to allergic

asthma as opposed to nonatopic asthma (155). These studies implicate IL-17 in the pathogenesis of asthma, particularly severe, neutrophilic asthma.

IL-17 AND ANIMAL MODELS OF ASTHMA

The role of IL-17 in the murine OVA model has been examined with conflicting results. OVA sensitization in the presence of the adjuvant aluminum hydroxide and subsequent OVA challenge resulted in increased IL-17A and IL-17F mRNA and protein levels in lung homogenates (156–158). IL-17A neutralization prior to OVA challenge worsened airway eosinophilia, increased T_H2 cytokine levels, and decreased neutrophilia and MMP9 levels (157, 159). Similarly, one study showed that exogenous IL-17A decreases eosinophil recruitment to the lung (158). Conversely, other studies showed that IL-17 synergizes with IL-4 and IL-13 to enhance T_H2 cytokines and CCL11 (eotaxin), and a separate study showed that IL-17 neutralization inhibits T_H2 disease (160–163). Furthermore, PPAR γ agonists inhibit T_H2-driven airway disease via downregulation of IL-17 induction (163). IL-17R knockout mice display reduced OVA-induced airway eosinophilia, IgE, and T_H2 cytokines (158). The timing (sensitization or challenge phase) of IL-17 administration or neutralization may likely explain some of the discrepancies in these studies.

Interestingly, IL-17A administration or neutralization resulted in either no change or variable changes in AHR as measured by whole-body plethysmography. In one study, exogenous IL-17A reduced AHR, whereas IL-17A neutralization increased AHR (158). Conversely, IL-17F overexpression by gene transfer enhanced AHR, which was correlated to increased neutrophilic inflammation (164). These data are difficult to evaluate due to the numerous deficits in using Penh to assess AHR in mice (165). Other groups have suggested a direct causative role for IL-17 in inducing AHR. The method of OVA sensitization is critical for IL-17 induction and AHR, implicating a role

for TNF- α in priming the IL-17 response (166). In addition, adenoviral expression of IL-17A was sufficient to induce AHR in mice, and IL-17 produced by iNKT cells is required for ozone-induced AHR (167, 168).

The IL-17 pathway has also been examined in other models of allergic airway disease. IL-17A and IL-17F knockout mice had differing phenotypes in the keyhole limpet hemocyanin (KLH) antigen sensitization and challenge model (55). IL-17A knockout mice displayed inhibited airway eosinophilia, whereas IL-17F knockouts had enhanced eosinophilia and diminished neutrophilia, suggesting differing roles for IL-17A and IL-17F in allergic asthma. However, these reports did not assess the effect of IL-17 manipulation on AHR. Recent studies have shown a critical role for IL-23 in allergic responses. Overexpression of IL-23 in the lung was sufficient to enhance antigen-dependent eosinophilia, T_H2 cytokines, IL-17 production, and AHR (169). IL-23 also promotes T_H17 differentiation under T_H2 -polarizing conditions via TSLP and TLR3 ligand interactions (170). In the house dust mite model, AHR-susceptible mice have enhanced myeloid dendritic cell production of IL-23, which drives T_H17 polarization and subsequent AHR, whereas AHR-resistant mice are characterized by antigen-presenting plasmacytoid dendritic cells and do not develop T_H17 or AHR (171). These data indicate a role for T_H17 and IL-17 in promoting allergic airway disease.

IL-25 AND ANIMAL MODELS OF ASTHMA

The IL-17 family member IL-25 has recently received a great deal of interest for its role in promoting T_H2 disease. Contrary to IL-17A and IL-17F, IL-25 is primarily a product of T_H2 cells and epithelial cells, among other sources. IL-25 signals through an IL-17RA, IL-17RB heterodimeric receptor and through the IL-17 common adapter protein Act1 (172–174). IL-17RB polymorphisms have been associated with both increased and decreased asthma risk (175). The primary impact of IL-25 signaling

is to enhance T_H2 cytokine production, eosinophilia, and AHR (67, 176). Overexpression of IL-25 in the lung enhanced T_H2 disease, whereas antibody neutralization blocked T_H2 cytokine production and AHR (177, 178). Interestingly, IL-25 antagonizes T_H17 development in the intestine and in experimental autoimmune encephalomyelitis (179, 180). This potential regulation of IL-17 immunity has not yet been reported in the lung.

T_H17 CELLS AND STEROID-RESISTANT ASTHMA

Work in our laboratory has established a causative link between T_H17 cells and GC-insensitive allergic airway disease in mice (167). This model is characterized by elevated neutrophil chemokines and growth factors as well as neutrophilic inflammation in the lung. In this study, IL-17A and IL-22 production by T_H17 cells was steroid insensitive *in vitro*. Transfer of OVA-specific T_H17 cells to donor mice resulted in neutrophilic airway inflammation, AHR, and mucus metaplasia following OVA challenge. These components of allergic airway disease were not abrogated by GC treatment, whereas GCs were effective in inhibiting T_H2 -driven disease. In fact, GCs enhanced airway neutrophilia in T_H17 -transferred mice. In contrast to our study, corticosteroids have been shown to inhibit IL-17 induction of cytokines in epithelial cells and fibroblasts *in vitro* (147, 181). These data show that T_H17 cells are sufficient to promote many of the hallmark characteristics of asthma *in vivo* and that this response is steroid insensitive. In addition, the results implicate neutrophilic inflammation as mediating some of the pathology observed in T_H17 -driven allergic airway disease. In support of a causative role for T_H17 cells in allergic airway disease, adoptive transfer of both T_H2 and T_H17 cells to mice further enhanced T_H2 -driven eosinophilia and AHR (169).

IL-17, T_H17 CELLS, AND COPD

The role of IL-17 and T_H17 cells in COPD remains largely speculative, although the

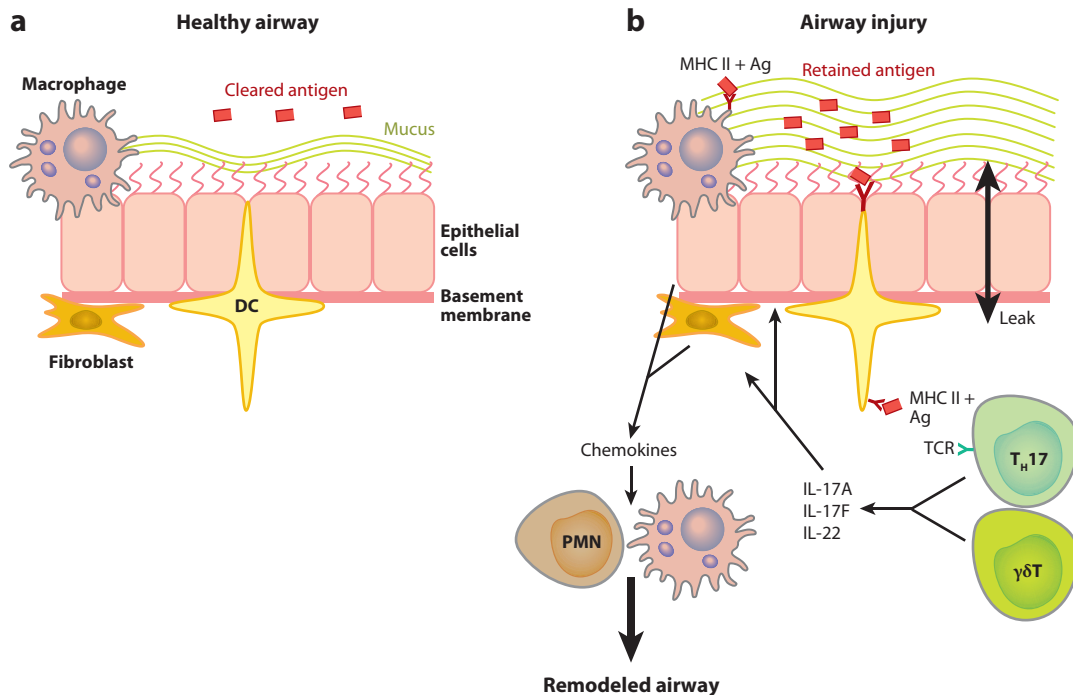


Figure 4

Model for IL-17-regulated airway remodeling. IL-17, produced by T_H17 cells and $\gamma\delta T$ cells, promotes remodeling through recruitment of macrophages and neutrophils to the airspaces. This paradigm may be relevant in the airway changes observed in chronic inflammatory diseases such as asthma and COPD. Ag, antigen; DC, dendritic cell; PMN, polymorphonuclear cell.

importance of IL-17 in stimulating chemokine production and the role of neutrophils and macrophages in promoting COPD pathogenesis have led to interest in a potential connection (182). In addition, another possible link derives from IL-17's ability to drive MMP9 production, which may directly link to the tissue destruction observed in COPD (41). In humans with COPD, IL-17 protein in sputum was detectable, but at significantly lower levels than those of asthmatics (151). Recently, patients with stable COPD exhibited elevated numbers of IL-22- and IL-23-staining cells in the bronchial epithelium and IL-17-positive cells in the submucosa (183). Furthermore, airway smooth muscle strips from COPD patients express IL-17RA and respond to IL-17 by inducing IL-8 production (184). These data further suggest a potential role for

IL-17 in COPD. Mice exposed to cigarette smoke exhibit enhanced IL-17 production; increased IL-17-dependent gene products IL-6, IL-8, G-CSF, and MCP-1; and increased neutrophilia (185, 186). Unpublished observations in our laboratory have shown that IL-17RA knockout mice are protected from lung emphysema induced by cigarette smoke exposure. A great deal of additional work will be required to elucidate the role of IL-17 and T_H17 cells in COPD pathogenesis.

CONCLUSIONS

The role of IL-17 in promoting neutrophil and macrophage recruitment to the lung in a variety of models has become clear, although the identity of IL-17 cellular sources in human disease and mouse models is only now

emerging. Additional work will be required to determine the exact role of T_H17 cells in lung immunity versus disease pathogenesis (see model, **Figure 4**). Current data support a role for the T_H17 /IL-17 axis in asthma and most likely COPD. However, whether this is due to an increase in proximal signals such as IL-6 or IL-23, which may drive T_H17 inflammation, or to a lack of negative signaling by IL-27 to terminate a normal T_H17 response remains to

be determined. Although airway neutrophilia is readily observed in a subset of severe and steroid-insensitive asthmatics and COPD patients, the causative nature of these cells in the disease pathogenesis is still controversial. If, indeed, T_H17 /IL-17 are critical in humans, then they are likely exerting their actions through the effects of neutrophils and their products on the airways. Research in this field will likely address these questions in the years to come.

SUMMARY POINTS

1. Neutrophils and their products (cytokines, proteases, and reactive oxygen species) have been implicated in the disease pathogenesis of severe and steroid-resistant asthma, in addition to COPD.
2. The cytokine IL-17 promotes airway neutrophilia through the induction of granulocyte chemokines and growth factors.
3. IL-17 is critical for host defense against a wide range of pathogens, including bacteria, fungi, and viruses, through the recruitment of neutrophils and direct effects on structural lung cells.
4. IL-17 levels are elevated in asthma and COPD and correlate with the presence of neutrophils and the severity of loss of lung function.
5. In mouse models of allergic airway disease, IL-17 has controversial effects (either enhancing or inhibiting) on the degree of airway inflammation and airway hyperresponsiveness.
6. The IL-17 family member IL-25 promotes canonical T_H2 signaling pathways and enhances allergic responses.
7. T_H17 cells are IL-17-producing cells that form a unique lineage of ROR γ T-expressing lymphocytes derived under polarization driven by TGF- β , IL-6, IL-1 β , and IL-23.
8. Cytokine production, neutrophil recruitment, and airway hyperresponsiveness driven by T_H17 cells are steroid resistant, suggesting a role in this subset of asthmatics.

DISCLOSURE STATEMENT

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Errata

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