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The Potential Role of Interleukin-17 in Severe Asthma

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Abstract Asthma has long been characterized as a disease of dysregulated T-helper type 2 immune responses to environmental allergens. Clinical studies suggest that asthma is a heterogeneous disorder with distinct types of inflammatory processes. Accumulating evidence suggests that aberrant interleukin (IL)-17 production is a key determinant of severe forms of asthma. However, the identity of IL-17–producing cells and the factors regulating IL-17 production during the course of allergic inflammation remain elusive. In this review, we summarize the potential IL-17–producing cells and their involvement in the inflammatory responses that mediate distinct features of asthma. The role of proinflammatory cytokines and the complement pathway in regulating the generation of IL-17–producing T cells is also discussed. Understanding the biology of IL-17 in the context of allergic inflammation may be informative in the development of novel approaches to the diagnosis and treatment of asthma.

Keywords Interleukin-17 · IL-17 · T cells · Asthma

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Introduction

Allergic asthma is a chronic and heterogeneous disorder of the airways that affects 5% to 10% of the population in the United States. The cardinal features of asthma include chronic airway inflammation, mucus hypersecretion, airway hyperresponsiveness (AHR) to inhaled allergens, and subepithelial fibrosis [1]. Studies from patients and animal models have demonstrated that upon allergen exposure, lung resident T-helper type 2 (Th2) cells release Th2 cytokines to initiate a cascade of immunologic events, resulting in the pathogenesis of asthma [2]. The Th2 cytokine interleukin (IL)-4 is critical for the generation of Th2 cells and mediating allergen-specific B cells to undergo isotype class switching to IgE [3]. IL-5 promotes airway eosinophilia, and IL-13 mediates the induction of AHR, goblet cell hyperplasia, and mucin production [2]. Although Th2 cells are thought to drive asthma in patients with eosinophilic inflammation, asthma patients often appear to manifest different patterns of airway inflammation that cannot be explained by the Th2 immune response alone. Specifically, recent cluster analyses have led to the classification of asthma into subgroups depending on the nature of the inflammatory response, including the following: 1) eosinophilic, 2) neutrophilic, 3) mixed (both neutrophils and eosinophils found), and 4) paucigranulocytic (few or no granulocytes) [4, 5]. Patients with asthma who have elevations in eosinophils as well as neutrophils in their airways have the lowest lung function, worse asthma control, and increased exacerbations [5, 6•]. Given that Th17-derived cytokines such as IL-17A and IL-17F are important regulators of neutrophilic inflammation, it has been postulated that aberrant IL-17A/F production may drive severe forms of the disease. Indeed, recent studies demonstrated that individuals with severe asthma display

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not only severe AHR but also robust neutrophilia and increased IL-17A/F production [6•, 7]. These discoveries have led to the revision of the Th1/Th2 paradigm. They provide new perspectives on the immunopathogenesis of allergic asthma and highlight the importance of understanding the regulation of IL-17 production and the identity of IL-17–producing cells in the lung during the course of allergic inflammation. Herein we discuss recent advances in our understanding of the role of IL-17A in asthma.

Interleukin-17 and Its Signaling

IL-17 (IL-17A) was originally identified from activated T-cell clones and named *cutaneous lymphocyte-associated antigen-8* [8–10]. Subsequently, genomic approaches led to the discovery of five additional family members, designated as IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F [11–13]. Among IL-17 family members, the expression patterns and function of IL-17, IL-17F, and IL-17E (IL-25) are better characterized. Alignment of the predicted amino acid sequence of IL-17 and the other family members revealed that IL-17F shares the greatest similarity with IL-17 (55% identity), whereas IL17E (IL-25) shares the least (17%) [14]. IL-17 is a disulfide-linked homodimeric glycoprotein with a molecular weight of 35 kD whose C-terminus possesses a cysteine knot structure similar to that found in transforming growth factor (TGF)-β and nerve growth factor [15]. Recent reports demonstrated that IL-17 can also form heterodimers with IL-17F, termed *IL-17A/F* [16, 17]. Studies of the IL-17 receptor family (IL-17RA-E) showed that the cognate receptor for IL-17 is IL-17RA, which is ubiquitously expressed [18]. However, the biological activity of IL-17 is dependent on the heterodimeric receptor complex composed of IL-17RA and IL-17RC [19]. Bioinformatic analyses identified a conserved cytoplasmic motif of IL-17R family members, termed *SEFIR* (similar expression to fibroblast growth factor receptor and IL-17R), that is homologous to the Toll/IL-1R domains common to Toll-like receptors and IL-1 receptors [20]. The signaling adaptor ACT1, which also contains the SEFIR domain, is essential for mediating IL-17R signaling [21]. The homotypic interaction between IL-17RA and ACT1 through the SEFIR domain recruits tumor necrosis factor (TNF) receptor–associated factor 6, which activates downstream canonical nuclear factor-κB and mitogen-activated protein kinase pathways [18].

Interleukin-17–Producing Cells in Asthma

IL-17 was first shown to be produced by activated $CD4^+$ T cells. The analysis of IL-23–mediated immune pathogenesis later led to the delineation of a distinct $CD4^+$ T-helper cell subset, termed the *Th17 cell lineage* [22–25]. Th17 cells produce IL-17, IL-17F, IL-22, and to a lesser extent TNF and IL-6 [26]. The retinoid acid–related orphan receptor (RORγt) was later identified as the master transcription factor controlling the development of the Th17 cell lineage [27–31]. Although the importance of Th17 cells was originally described in driving inflammatory autoimmune disorders [22], accumulating evidence now suggests that Th17 cells and their related cytokines are also involved in the pathophysiology of allergic asthma. IL-17 expression is increased in the lung, sputum, bronchoalveolar lavage fluid (BALF), and sera in patients with asthma, and the severity of AHR is positively correlated with IL-17 expression levels [32, 33]. IL-17 and IL-17F can induce lung structural cells to secrete proinflammatory cytokines (eg, TNF, IL-1β, granulocyte colony-stimulating factor, and IL-6) and chemokines (eg, CXCL1/Gro-α, CXCL2, and CXCL8/IL-8), thereby triggering neutrophil infiltration [34–36]. In a murine model of allergic lung disease, mice lacking IL-17A exhibited a reduced Th2 response to antigen sensitization, and mice lacking IL-17RA exhibited reduced neutrophil and eosinophil recruitment [37, 38]. Although these studies demonstrate the importance of IL-17 in driving the immunopathogenesis of asthma, the identity of IL-17–producing cells during the course of allergic inflammation remains elusive.

In addition to Th17 cells, other innate-like T cells (eg, γδ T cells and invariant natural killer T [iNKT] cells) are also capable of producing IL-17 in the context of allergic asthma [39]. γδ T cells are in close contact with lung epithelium and have served an immunosurveillance function. In mice, IL-17–producing γδ T cells have been shown to play important roles in the pathogenesis of inflammatory granulomatous diseases and in lung tissue damage during pulmonary aspergillosis [40]. These cells can produce IL-17 rapidly, drive the recruitment and activation of neutrophils at the sites of inflammation, and contribute to AHR [41]. In humans, the frequency of γδ T cells in BALF from patients with asthma is higher than that of healthy controls [42]. However, the function of lung resident γδ T cells in the immunopathogenesis of human asthma remains unclear [43]. iNKT cells express restricted T-cell receptor that recognizes lipid antigens in the context of the major histocompatibility complex class I–like molecule CD1d. After activation with synthetic α-galactosylceramide, these cells rapidly produce high levels of IL-17 in vitro. Administration of α-galactosylceramide intranasally in mice activates iNKT cells to produce IL-17, leading to airway neutrophilia [44]. Furthermore, in a murine model of allergic lung disease, mice deficient in iNKT cells failed to develop AHR despite eosinophilic inflammation [45]. In humans, iNKT cells were found in the lungs of asthmatic patients, and the frequency of iNKT cells increased

after allergen challenges [46, 47]. These studies suggest a role for iNKT cells in the development of AHR and of asthma with neutrophilic inflammation.

Recently, a subset of human Th2 memory cells that are capable of producing Th17 and Th2 cytokines concurrently was identified [48••]. These IL-17–producing Th2 cells express both GATA3 and RORγt transcription factors, which are known to be required for the development of the Th2 and Th17 cell lineage, respectively. Notably, the frequency of circulating IL-17–producing Th2 cells within the total $CD4^+$ Th2 memory/effector cell pool is significantly elevated in the blood of patients with atopic asthma. Mirroring these findings in humans, IL-17–producing Th2 cells were found primarily in the inflamed lungs, but not other lymphoid organs, in a murine model of allergic lung disease. Notably, these lung resident IL-17–producing Th2 cells persist in inflamed lungs as the dominant IL-17–producing T cells during the chronic stage of allergic airway inflammation. These intriguing findings suggest that Th2 memory cells may be a dominant cellular source of IL-17 in the chronic stage of asthma (Fig. 1).

Regulation of Interleukin-17 Production

Because IL-17–producing cells play important roles in the inflammatory response at mucosal sites, understanding the regulation of IL-17 production is a key subject for investigations. Although the specific requirements for individual IL-17–producing cell types may vary, extensive studies have identified the key factors or inflammatory cytokines that are crucial for the induction of IL-17 production, summarized as follows.

1. Studies in vitro have shown that the absence of IL-4 and interferon-γ is the primary prerequisite for Th17 cell differentiation from naïve T cells [49].
2. TGF-β is the essential cytokine that induces transcription factor RORγt expression in naïve T cells during Th17 cell development [49–51], although the role of TGF-β in human Th17 cell lineage commitment has been controversial [52–54]. While the role of TGF-β in regulating IL-17 production by γδ T cells and iNKT cells remains to be determined, a recent study demonstrated that TGF-β is not required for the induction of IL-17 production by Th2 memory cells [48••].
3. Amidst the accumulating evidence, the proinflammatory cytokine IL-1β has emerged as the critical factor to trigger IL-17 production [55]. IL-1β can induce Th17 polarization from $CD4^+$ naïve T cells and trigger IL-17 production by classical Th2 memory cells, as well as iNKT cells, by upregulating the transcription factor interferon regulator factor-4 expression [56].
4. Although IL-23 was originally identified as the key cytokine for the development of Th17 cell lineage [22], recent studies suggest that IL-23 is critical for the expansion and maintenance of Th17 cells [57, 58] and functions to promote IL-17 production by γδ T cells and iNKT cells [44]. Notably, IL-23 is not required for the induction of IL-17 production by classical Th2 memory cells due to their lack of IL-23R [48].
5. IL-6 can synergize with TGF-β to induce surface IL-23R expression on Th17 cells, thereby promoting Th17 development in the presence of IL-23. While IL-6 can also enhance the effect of IL-1β on the induction of IL-17 production by Th2 memory cells, IL-6 is dispensable for IL-17 production by γδ T cells and iNKT cells [27, 56].

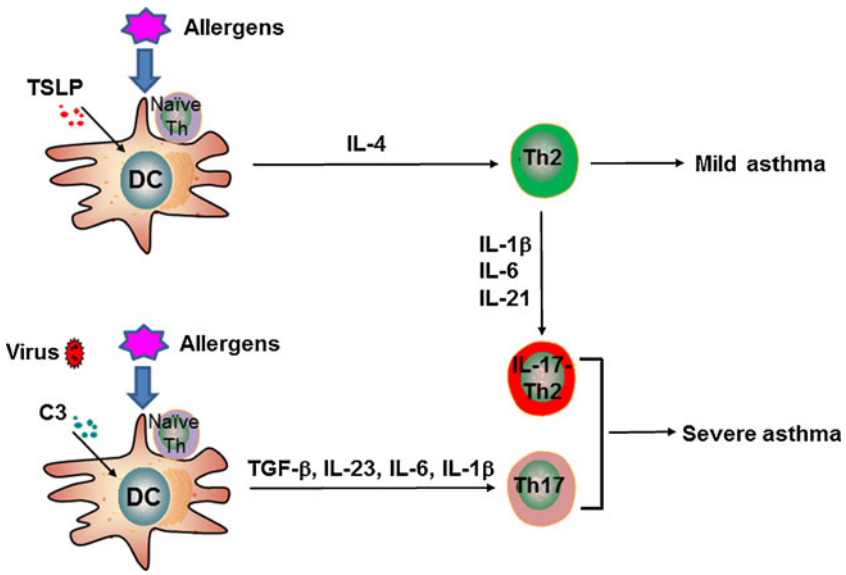


Fig. 1 The development of interleukin (IL)-17–producing T cells and the severity of asthma. Upon exposure to allergens and infectious agents, dendritic cells (DCs) activated by thymic stroma lymphopoietin (TSLP) or anaphylatoxin C3a can induce naïve T cells to differentiate into T-helper type 2 (Th2) or Th17 cells, respectively. Depending on the inflammatory signals in the microenvironment, local Th2 memory/effector cells may acquire distinct inflammatory properties to become IL-17–producing cells that promote severity of asthma. TGF—transforming growth factor

6. The cytokine IL-21 has pleiotropic effects on the proliferation, differentiation, and effector function of B, T, and natural killer cells [59]. Recent studies suggest that IL-21 secreted by Th17 or Th2 cells can also synergize with IL-1β and/or IL-6 to drive IL-17 production in an autocrine manner [48••, 60, 61]. Although the proinflammatory cytokines described above are now known to have the potential to induce IL-17 production, the factors that regulate their temporal and combinatorial expression during the course of allergic inflammation remain to be investigated.

Examples of an innate immune pathway shown to regulate the expression of proinflammatory cytokines, which in turn induce IL-17 production, are the anaphylatoxins C5a and C3a. A recent study designed to decipher the differences in susceptibility to severe asthma between strains of mice that are highly susceptible to the development of allergen-driven, severe airway hyperresponsiveness (A/J) and strains that are relatively resistant (C3H/HeJ) showed a role for the complement components C3a and C5a in regulating IL-17 production [62••, 63]. Using microarray analysis and single nucleotide polymorphism–based genotyping, a deletion in the coding sequence of the *C5* gene in A/J mice was identified and shown to be responsible for the susceptibility to severe AHR in a murine model of allergic asthma [63]. Furthermore, A/J mice that produced Th2 cytokines and elevated IL-17 cytokines developed more severe AHR than C3H/HeJ mice that produced only Th2 cytokines after intratracheal challenge with house dust mite (HDM) [62••]. Indeed, in vivo blockade of IL-17A in susceptible A/J mice reduced their airway responses to the level of the resistant C3H/HeJ mice. Taken together, these findings suggested that the lack of C5a in A/J mice might have contributed to their aberrant IL-17 production, leading to severe allergic asthma. The authors proceeded to show that the differences in IL-17A production were due to differences in bone marrow–derived dendritic cell (DC) cytokine production in that C5a-deficient A/J mice produced elevated levels of IL-23 compared with those from C5a-proficient C3H/HeJ mice; however, no differences were observed in their IL-1β or IL-6 production, suggesting that the presence of C5a signaling in C3H/HeJ mice controls IL-17 production by limiting IL-23 secretion from DCs during allergic inflammation. In addition to C5a, C3a also has an effect on regulating allergic inflammation [64]. Mice deficient in complement receptor C3a (C3aR) had less IL-23 production and fewer detectable IL-17–producing cells in the lung, and thus less AHR induction, after HDM challenge [62••]. HDM-treated, bone marrow–derived DCs from *C3ar1*-deficient mice produced less IL-23 compared with those from wild-type mice, suggesting that C3aR signaling promotes IL-23 production by DCs [62••]. Furthermore, HDM challenges induced enhanced C3a and C3aR mRNA expression, which mediates the elevated IL-23 production in A/J mice and to a lesser extent in C3H/HeJ mice. These interesting results show that C5a and C3a have reciprocal roles in the immunopathogenesis of allergic asthma by regulating the IL-23/IL-17 pathway and point to an additional layer of regulation of IL-17 production during allergic inflammation. As complement activation is important in the clearance of infections and has specifically been shown to play an important role in respiratory syncytial virus–induced pulmonary inflammation [65], these studies suggest that aberrant IL-17 production in the lungs of severe asthmatics may be driven by viral infection induction of complement and subsequent activation of the IL-23/IL-17 axis. Thus, understanding the involvement of anaphylatoxin control of the IL-23/IL-17 axis in virally induced exacerbations of asthma may be an important subject for future investigation (Fig. 1).

Interleukin-17 and Severity of Asthma

Although asthma symptoms in most patients with mild asthma are well-controlled with current therapies, the disease in approximately 10% of the asthmatic population with severe asthma remains poorly controlled despite high-dose inhaled therapy [66•]. Those individuals in this subpopulation of asthma patients were found to express elevated IL-17 protein in their airways, which correlated with increased neutrophil infiltration, chemokine IL-8 production, and the degree of AHR [6•, 32, 67]. Using an immunohistochemical approach, a recent study further demonstrated that the number of detected IL-17–producing cells in lung tissue of patients with severe asthma is significantly higher compared with other groups of asthma patients [6•]. Notably, these immunoreactive IL-17$^+$ cells were exclusively mononuclear cells and located within clusters of inflammatory cells in the subepithelial tissues [6•]. These studies provide evidence that the presence of IL-17A$^+$ cells is positively correlated with the severity of human asthma. However, it remains to be determined which IL-17–producing cell type contributes to acute exacerbation asthma in response to various airway insults in humans.

The direct role of IL-17 in contributing to the severity of asthma was further substantiated in murine studies. Mice deficient in IL-17RA or IL-17A had markedly diminished recruitment of neutrophils into the lung in response to challenge with gram-negative bacteria or allergens [37, 38]. The identification of a novel IL-17–producing Th2 memory cell type may provide a plausible explanation for the cause of severe asthma with a mixed airway inflammation during the chronic phase [48••]. IL-17–producing Th2 cells secrete both Th2 and Th17 cytokines that have profound synergis-

tic effects on the induction of various chemokine genes in primary human lung bronchial epithelial cells, including *MIP-1β*, *MCP-1, Gro-α*, *IL-8*, and particularly *eotaxin-3*, thereby promoting the recruitment of a heterogeneous pattern of inflammatory leukocytes [48••]. In animal models of asthma, transfer of antigen-specific, IL-17–producing Th2 cells triggered an influx of heterogeneous leukocytes, including neutrophils, eosinophils, macrophages, and lymphocytes, resulting in distinct pathophysiologic features of severe asthma [48] similar to those of the combined Th2 and Th17 cells [48••, 68, 69]. Importantly, IL-17–producing Th2 cells may represent the key pathogenic Th2 cell that may have additional inflammatory properties capable of promoting exacerbations of allergic asthma (Fig. 1). To examine whether increased IL-17 contributes directly to the severity of AHR in response to allergen, several studies utilized intranasal IL-17 administration or neutralization in murine models of allergic lung disease. Treatment of A/J mice that have aberrant IL-17 production with IL-17–specific antibody resulted in significantly less AHR and fewer neutrophils in the BALF [62••]. Conversely, administration of recombinant IL-17 to C3H/HeJ mice that had little IL-17 production during allergen challenge increased their susceptibility to AHR [62]. In another study, a causative link between Th17 cells and glucocorticoid-insensitive allergic airway disease in mice was demonstrated [70]. Glucocorticoid treatments did not abrogate IL-17 and IL-22 production by Th17 cells in vitro and Th17-induced neutrophilic inflammation in airways by transferred Th17 cells in vivo, whereas glucocorticoid treatment was effective in inhibiting Th2-driven diseases [70]. Whereas most studies provided similar findings, one study suggested that IL-17 may act as a negative regulator during the effector phase of the allergic response [71]. These discrepancies may be due to differences in the experimental design (eg, timing of IL-17 administrations/neutralizations and allergen challenges) or the experimental system used to assess AHR. Overall, the findings of most of these human and murine studies provide direct evidence to suggest a causative role of IL-17 in inducing severe asthma (Fig. 1).

Conclusions

In summary, emerging evidence suggests that activation of the IL-17–producing cells may be associated with the neutrophilic inflammatory response and the development of severe forms of asthma. In response to exposure to irritants, infectious agents (or allergens), injured airway epithelial cells, and altered innate immune responses initiate distinct inflammatory processes that may determine the identity of the initial IL-17–producing cells during the acute phase of asthma. The inflammatory response may be propagated in the airway and regulate the maintenance of Th2- and Th17-cell subsets during the chronic phase. The interplay between innate and adaptive immunity thus may have an important role in the induction and maintenance of IL-17 production. Environmental insults and intrinsic genetic factors, such as complement genes, also may be involved in the development of IL-17–producing cells during allergic inflammation. Future studies to explore further the factors that regulate IL-17 induction and the generation of IL-17–producing cells in the context of allergic inflammation will provide the basis to elucidate the distinct pathophysiologic mechanisms that mediate the severity of asthma. As severe forms of asthma have proven difficult to treat with existing therapies, modulation of this pathway may hold promise for the treatment of this disease that is ever increasing in prevalence.

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- • Of importance
- •• Of major importance

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