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Review

T_H17 cells in asthma and inflammation ☆

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ABSTRACT

Background: The chronic airway disease asthma causes significant burden to patients as well as the healthcare system with limited options for prevention or cure. Inadequate treatment strategies are most likely due to the complex heterogeneous nature of asthma. Furthermore, the severe asthma phenotype is characterized by the lack of a response to standard medication, namely, corticosteroids.
Scope of Review: In the last several years it has been shown that the eosinophilic/atopic phenotype of asthma driven by T_H2 mechanisms is not the only immunologic pathway contributing to disease. In fact, there has been evidence revealing that severe asthmatics in particular have neutrophilic inflammation, and this is associated with corticosteroid resistance. T_H17 cells, a recently discovered lineage of T helper cells, play an important role in lung host defense against multiple pathogens via production of the cytokine IL-17. IL-17 promotes neutrophil production and chemotaxis via multiple factors.
Major Conclusions: Mouse and human studies provide robust evidence that T_H17 cells and IL-17 play a role in severe asthma and may contribute to corticosteroid resistance.
General Significance: As we learn more about T_H17 cells in severe asthma, the goal is to potentially target this pathway for treatment in the hope of significantly improving the quality of life for those children and adults affected with this disease. This article is part of a Special Issue entitled: Biochemistry of Asthma.
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1. Introduction to asthma phenotypes

Asthma continues to be a significant public health problem affecting 300 million people worldwide and over 22 million people in the United States, over 6 million of which are children (http://www.nhlbi.nih.gov/guidelines/asthma/). Asthma is one of the most common chronic lung diseases in children and adults and yet it is a disease that we are currently unable to prevent or cure [1]. Certainly, steps have been made in asthma awareness and diagnosis and therefore appropriate treatment, including daily corticosteroid medications. Despite this, a large burden remains on children and families who suffer from the disease. This burden includes missed school and employment days as well as major healthcare costs [2]. Even children on the appropriate controller medications for asthma still develop asthma exacerbations which often result in hospitalizations. The key features of asthma include variable symptoms, bronchial hyperresponsiveness, reversible airway obstruction, and chronic underlying airway inflammation. Asthma is a complex syndrome, the etiology of which is multifactorial, including a combination of genetic factors and environmental exposures [3,4]. A major contributor to the difficulty in managing asthma is the vast heterogeneity present in the clinical spectrum, underlying pathogenesis, and even treatment response of this disease. The several phenotypes (both clinical and inflammatory) in asthma also vary based on age, therefore adults and children are not evaluated and managed in the same manner [5]. These immense phenotypic differences likely contribute to the large range of severity of asthma seen in patients.

Although mild to moderate asthma is the most common clinical presentation of the disease, severe or difficult asthma contributes to a disproportionate burden on morbidity and mortality even though it accounts for fewer than 10% of all patients with asthma [6]. Healthcare resource utilization is highest in those patients with severe asthma [7]. Research produced from the National Institute of Health, National Heart, Lung, and Blood Institute (NHLBI) driven Severe Asthma Research Program (SARP) has informed much of our current knowledge on severe asthma phenotypes and mechanisms. One of the goals of this network has been to define the clinical and underlying mechanistic features of severe asthma compared to mild–moderate asthma in adults and children. A consensus definition from the American Thoracic Society (ATS) and NHLBI centers on the point that severe asthmatics have inadequate control of their disease despite aggressive, high doses of corticosteroid therapy [7]. In both children and adults there are other minor criteria which focus on symptoms, exacerbations and lung function to classify severe asthma [8,9]. Severe asthmatics have persistent symptoms, frequent and more severe exacerbations (requiring hospitalization and intubation),

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and take multiple controller medications [6]. Fitzpatrick et al. studied school aged children with severe asthma and found that they had increased allergic sensitization, elevated nitric oxide, and more airway obstruction than those with mild–moderate asthma [8]. This was confirmed in a cross sectional study of children with difficult asthma by Bossley et al., in which patients were more commonly male and atopic [10]. The authors make note that this is in contrast to adults with severe asthma, in which females make up the majority of cases and atopy is not as common.

The SARP investigators recently published that five heterogeneous clusters exist within the SARP adult cohort [11]. Some of the clusters are composed of subjects with more atopy and earlier onset of the disease, whereas others appear to be of a non-allergic phenotype. Whether there was an allergic predisposition or not, the subjects with the longest duration of disease had the most severe asthma. All clusters contained severe asthmatic subjects and three of the five clusters were characterized as atopic. One particular cluster was made up mostly of women with the most reduced lung function who had later onset disease, less atopy, poor quality of life, and elevated sputum neutrophils. Eighty percent of these subjects met criteria for severe asthma. The authors point to the varying pathophysiologic mechanisms that establish these clusters, again providing more evidence for heterogeneity in asthma. Severe asthmatics are extremely challenging to treat, because despite high doses of systemic and inhaled corticosteroids, they continue to have significant disease burden [6]. The major hallmark differentiating severe from mild to moderate asthma is in fact the reduced responsiveness to corticosteroids.

For this reason, corticosteroid resistance in asthma has been of great interest. There has been a focus on a non-eosinophilic phenotype of asthma as being primarily corticosteroid resistant and that the mechanism behind steroid resistance is variable [5]. Berry et al. conducted a study looking at participants with eosinophilic and non-eosinophilic asthma compared with healthy controls [12]. Non-eosinophilic asthmatics had elevated sputum neutrophils, but interestingly lower levels of sputum IL-8, a neutrophil chemokine, compared with eosinophilic asthmatics. Subjects with non-eosinophilic asthma were mostly non-atopic middle aged women, and their lung function and methacholine response did not differ from those with eosinophilic asthma. However, after eight weeks of inhaled mometasone, subjects with non-eosinophilic asthma did not have improvement in their airway hyperresponsiveness (AHR) or asthma quality of life, whereas those with eosinophilic asthma did. Although this study included a small sample size of asthmatics, these findings point to non-eosinophilic asthma as being a distinct phenotype unresponsive to short term inhaled corticosteroids. One of the proposed mechanisms of corticosteroid resistance has been airway neutrophilia and the ability of the neutrophil to avoid glucocorticoid effects [13]. The glucocorticoid receptor (GR) exists in humans as two protein isoforms, GR-α and GR-β. It has been shown that neutrophils express higher levels of the GR-β form and that IL-8 exposure leads to an upregulation of GR-β [14]. GR-β binds glucocorticoids (GC), but cannot promote cellular signaling to turn on GC sensitive genes and therefore may be an inhibitor of GC action. Moreover, neutrophils have been implicated in playing a role in the pathogenesis and inflammation seen in severe asthma. In a study of bronchoalveolar lavage (BAL) and airway biopsies of severe asthmatics, it was found that there were significantly higher percentages of neutrophils compared to moderate asthmatics [15]. Similar results were seen in a study of sputum inflammatory cell profiles in severe asthmatics. Jatakanon et al. showed that there were increased neutrophils, IL-8, and neutrophil myeloperoxidase levels in sputum of severe asthmatics compared with those who had milder disease [16]. These earlier studies paved the way for the notion that the inflammatory state in asthma does not stem solely from eosinophilic pathways and cytokines.

2. T cells and asthma pathogenesis

The initial links between adaptive immunity and asthma focused on T helper (TH) 2 cells and their characteristic cytokines IL-4, IL-5, and IL-13. T_H2 cells were shown to play a key role in atopy and T_H2 cytokines directly induce airway eosinophilia. Early studies revealed that T_H2 cytokines IL-4 and IL-5 were present in the BAL fluid of subjects with atopic asthma, possibly explaining their inflammatory response [17]. Furthermore, the presence of increased $CD4^+$ T_H2 helper cells was found in asthmatic airways which secrete IL-4, IL-5 and IL-13. IL-4 and IL-13 lead to IgE production from B cells, whereas IL-5 contributes to eosinophilic inflammation by causing differentiation of these cells [18,19]. IL-4 plays an important role in driving T_H2 differentiation, whereas IL-13 acts on other airway cells to generate pro-inflammatory factors and mucus production [20]. There have been cytokine genetic polymorphisms in IL-4 and IL-13 that have been shown to increase asthma frequency and worsen asthma, respectively [21]. Cluster analysis of adult asthmatics enrolled in SARP did confirm the presence of an allergic asthma phenotype as several clusters were made up of atopic participants with childhood onset of their disease [11]. Furthermore, children with severe asthma appear to have more of a homogenous phenotype consisting of atopic predominance [5,22].

Although the T_H2 pathway likely plays an important role in childhood allergic asthma and in milder forms of adult allergic asthma, there are shortcomings to the notion that T_H2 inflammation is the only mechanism involved in asthma. There is now robust evidence sustaining the view that not all asthma can be explained by allergen-induced, T_H2 mechanisms, and this is supported by the presence of the different inflammatory profiles and cell types present in asthmatic [23]. This is true especially when considering the vast heterogeneity both in asthma clinical phenotypes and in response of asthmatics to treatments. Studies have not shown a clear connection between T_H2 eosinophilic inflammation and bronchial hyperresponsiveness when comparing asthma to allergic rhinitis/atopy [1]. Brown et al. found the presence of eosinophilic airway inflammation on bronchial biopsy in subjects with allergic rhinitis as well as asthmatics, indicating that there must be factors other than eosinophils alone to cause airway disease and asthma [24].

Molecular phenotyping has been utilized to explore specific T cell pathways in asthma. A recent study revealed that only half of adult asthmatic subjects had high expression of T_H2 cytokine stimulated genes and IL-5/IL-13 expression in bronchial biopsies, while the other half (termed "T_H2 low") were similar to healthy controls in these parameters [25]. The "T_H2 high" asthmatics had greater AHR, more atopy, and increased reticular basement membrane thickness. Interestingly, the "T_H2 low" asthmatics did not have improvement in forced expiratory volume (FEV) 1 after 8 weeks of inhaled corticosteroid, whereas the "T_H2 high" asthmatics did. This study provides further evidence of both T_H2 and non-T_H2 driven mechanisms in asthma, and cautions that therapies directed only at T_H2 inflammation would potentially benefit the "T_H2 high" group of asthmatics, but not the "T_H2 low" subgroup, which appear steroid resistant. The authors speculate that other mechanisms such as neutrophilic inflammation could be playing a role in the "T_H2 low" subgroup of asthma.

In a recent SARP sub-study of children with severe asthma, cytokine analysis in BAL fluid did not reveal a particular T_H1 or T_H2 molecular phenotype [22]. A combination of T_H1 (IFN-γ) and T_H2 (IL-13) factors as well as IL-8 was found in the BAL of severe asthmatics. BAL neutrophils and eosinophils were both elevated in this group of asthmatics, despite their being on corticosteroid treatment. T_H2 cell and eosinophil directed treatments have not had impressive clinical effectiveness although some of these therapies do show some promise in more recent trials. Studies in mild–moderate asthmatics and effects on airway eosinophils of anti-IL-5 antibody did not show significant clinical benefit [26–28]. However, in two recent

clinical trials of anti-IL-5 antibody targeted specifically to severe asthmatics with eosinophilic airway inflammation, there was improvement in asthma exacerbations but not in other asthma outcomes such as symptoms or FEV1 [29,30]. Further clinical trials are necessary in particular subgroups of severe asthma to investigate whether T_H2 targeted immune modulators are truly safe and effective [31].

Several other subsets of T cells have been suggested to play a role in asthma pathogenesis. Among these, T regulatory (T_{reg}) cells are $CD4^+$ T cells which express increased levels of CD25 as well as high levels of the transcription factor Foxp3 [32]. These T_{reg} cells have suppressive effects on cytokine production by other T cells and therefore play an important role in controlling the inflammatory response in atopy and asthma. Asthmatic children had reduced percentages of $CD4^+CD25^{high}$ T cells in BAL fluid compared to controls and those with chronic cough [33]. In addition, the BAL T_{reg} cells of asthmatic children had decreased capability to suppress effector T cell proliferation and cytokine production compared with T_{reg} cells from control subjects. Another study found that the adverse effects of air pollution on children in asthma may at least in part be regulated by epigenetic changes in T_{reg} cells, specifically the Foxp3 transcription factor [34]. Increased methylation of the Foxp3 locus in asthmatic children exposed to high levels of pollution led to decreased T_{reg} cell function. This could be a potential mechanism contributing to worsening asthma in children exposed to pollution. Yet another study found that compared to non-atopic controls, atopic asthmatic children had decreased Foxp3 expression and suppressor activity of T_{reg} cells [35]. All of these studies point to the role of T_{reg} cells in suppressing effector T cell responses and their inflammatory drive in asthma. An imbalance between T_H2 cells and T_{reg} cells appears to contribute towards the pathogenesis of asthma.

As noted earlier, several studies have shown that neutrophilic inflammation is present in severe and corticosteroid resistant asthma, pointing to a non-T_H2, non-eosinophilic mechanism in these patients. An early study by Jatakanon et al. found increased percentages of neutrophils and IL-8 levels in the sputum of severe compared to mild and moderate asthmatics [16]. The authors discussed that the neutrophilia may be regulated by IL-8 and that this pattern of inflammation was potentially corticosteroid resistant. A potential link between neutrophilic inflammation and severe asthma is the T_H17 lineage of $CD4^+$ T cells. These cells play an important part in several immune mediated diseases, and they induce proinflammatory cytokines from the airway epithelium, including several neutrophil chemoattractants. T_H17 also increase G-CSF production which increases neutrophil production from the bone marrow. The focus of the following sections will be on regulation of T_H17 development, T_H17 function and cellular signaling, and the proposed role of this pathway in allergic airway disease and asthma.

3. Regulation of T_H17 differentiation

The immune response to inhaled antigen is intricately controlled by T helper cell mediated processes. In the mid-1980s, T helper cells were divided into two distinct lineages T_H1 and T_H2 [36,37]. T_H1 cells, driven by IFN-γ and IL-12 stimulation of the transcription factors STAT1 and STAT4 resulting in T-bet activation, were shown to be critical for cell-mediated immunity against intracellular pathogens. T_H2 cells, promoted by IL-4 induced STAT6 activation and GATA3 expression resulting in production of IL-4, IL-5, and IL-13, were implicated in allergic responses, such as asthma. Cross-regulation of T_H1 and T_H2 cells resulted in a paradigm of two opposing cell types in immunity. Recently, our understanding of T_H immunity has expanded to include a third distinct lineage, termed T_H17 after its signature cytokine product, IL-17 [38,39]. T_H17 cells were initially identified as promoting host defense against extracellular pathogens, as well as playing a role in autoimmune responses. Regulation of T_H17 differentiation and proliferation is complex and multi-factorial (Fig. 1).

Initial studies have identified TGF-β and IL-6 as critical regulators of T_H17 cell differentiation [40,41]. These observations were somewhat confounding as TGF-β is known to also promote development of T_{reg} cells through induction of the transcription factor Foxp3 [40]. In that study, it was suggested that the dose of TGF-β may be critical to determining its effects on naïve T cell polarization. Low dose TGF-β synergizes with IL-6 to promote T_H17 differentiation, whereas, high dose TGF-β preferentially induces Foxp3 and T_{reg} development [40]. The molecular mechanisms by which TGF-β induce T_H17 cells are currently unclear. TGF-β canonically signals through the Smad 2/3/4

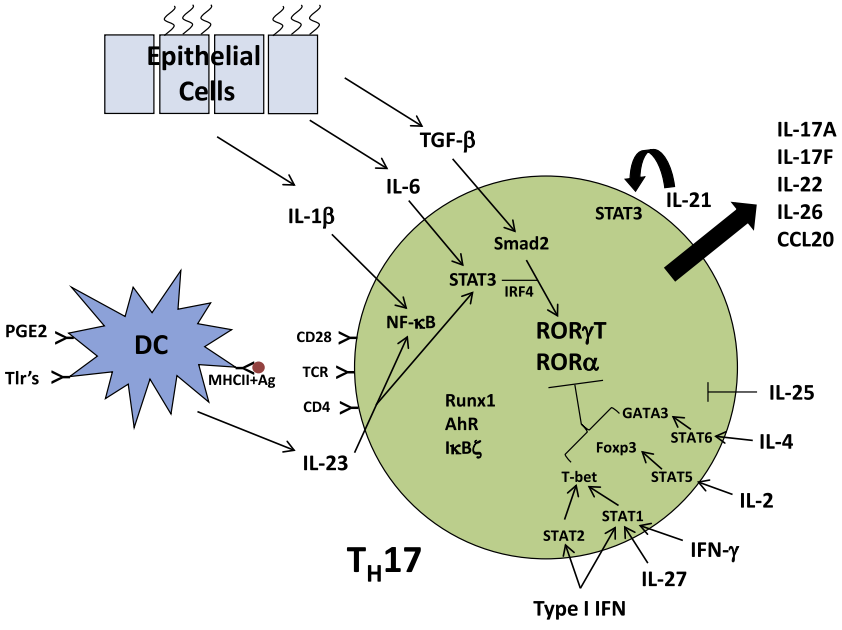


Fig. 1. Regulation of T_H17 cell polarization. Diverse cytokine signaling pathways initiate T_H17 differentiation in conjunction with T cell receptor (TCR) ligation with presented antigen. The T_H17 lineage is characterized by the transcription factors RORγt and RORα. Several cytokines that promote T_H1 and T_H2 immunity oppose T_H17 polarization by inhibiting RORγt expression. Arrows indicate activation or production. Squared lines indicate inhibition. Ribbon arrow indicates autocrine or paracrine effects. Ag, antigen; DC, dendritic cell; Tlr, toll-like receptor.

proteins to alter transcription. Conflicting reports exist regarding the requirement for Smad proteins in T_H17 polarization [42,43]. Recently, Martinez et al. suggested that Smad2 is required for TGF-β induction of T_H17 cells, whereas Smad3/4 are required for T_{reg} development, suggesting a molecular pathway by which TGF-β can promote each cell type [44]. At this time there are no known Smad DNA-binding sites in the T_H17 related genes IL-17A, RORγt (RORc), IL-21, or IL-23. Despite many studies regarding the role of TGF-β in T_H17 cells, a few studies of human T cells have shown that TGF-β may be dispensable for T_H17 polarization [45,46]. In these studies, IL-6, along with IL-1β and IL-21, may be sufficient to promote T_H17. However, TGF-β has been shown to directly induce RORγt in human T cells enhancing T_H17 differentiation [47]. The reasons for these discrepancies remain unclear.

The mechanisms by which IL-6 promotes T_H17 cell development are better defined. IL-6 is known to activate the transcription factor STAT3 which is critical for T_H17 differentiation. STAT3 deficient T cells fail to sufficiently polarize to T_H17 cells, whereas STAT3 overexpression results in increased IL-17 production by T cells [48,49]. Microarray analysis of T_H17 cells demonstrated that nearly 50% of the differentially induced genes are STAT3 regulated, further confirming a role for STAT3 [50]. Furthermore, deletion of the STAT3 inhibitor SOCS3 results in increased IL-17 production [51,52]. These data demonstrate a clear function of STAT3 as a critical regulator of T_H17 cells. IL-6 is thought of as a key factor in directing the naïve T cell response to TGF-β away from T_{reg} differentiation and toward T_H17 via STAT3 dependent inhibition of Foxp3 expression [40,53]. In addition, IL-6 also potently stimulates production of IL-21 by T_H17 cells, another T_H17 promoting cytokine, via STAT3 [54,55]. IL-21, like IL-6, activates STAT3 and can inhibit Foxp3 expression and T_{reg} development [54,56]. In these studies, deletion of IL-21 *in vivo* results in defective T_H17 differentiation. Taken together these findings implicate TGF-β, IL-6, IL-1β and IL-21 as the primary cytokines which promote T_H17 lineage differentiation (Fig. 1).

T_H17 cells are further regulated by the cytokine IL-23 which promotes T_H17 proliferation and cytokine production. IL-23 is a heterodimeric protein made up of the IL-12p40 subunit and IL-23p19. Due to this shared usage of IL-12p40, many early studies in IL-12p40 knockout mice produced confusing results often attributing host defense functions to T_H1 cells that have been later described as T_H17 dependent. IL-23 is mainly expressed by myeloid cells, such as dendritic cells and macrophages [57]. Naïve T cells do not express IL-23R, explaining why IL-23 is not required for early T_H17 differentiation, however during T_H17 development, IL-23R expression is activated by IL-6 [49,55]. After binding its receptor, IL-23 signals through STAT3 to enhance many T_H17 characteristic genes. IL-23 is capable of inducing T_H17 cell production of IL-17 independent of T-cell receptor ligation [58]. In addition, IL-23 results in expansion of T_H17 cell populations and deficiency of IL-23 attenuates T_H17 driven inflammation in a number of models [59–61]. IL-23 promotes sustained differentiation of T_H17 cells and prolongs IL-17 production [60]. Further, prostaglandin E2 promotes IL-23 production by dendritic cells and promotes expansion of IL-17 producing cells [62,63]. Additionally, several members of the Toll-like receptor family, including Tlr2, Tlr4, Tlr6, and Tlr9 have been shown to promote T_H17 development, perhaps through regulation of IL-23 production [64–67]. These data indicate a critical role for IL-23 in promoting T_H17 immunity.

Stimulation of naïve T cell polarization with these T_H17 inducing cytokines results in upregulation of the steroid nuclear receptors RORγt and RORα. A characteristic of this receptor family is that there are currently no known receptor-binding ligands. RORγt is a splice variant of the RORc gene restricted to T cells. It is not known whether STAT3 activation directly induces RORγt expression in T_H17 cells. However, STAT3 is required for IL-6 induction of RORγt. Functionally, RORγt is known to directly bind to the IL-17A gene and stimulate transcription [68]. The transcription factor IRF4 may regulate RORγt expression in T_H17 cells, as stimulation of RORγt by TGF-β and IL-6 is greatly reduced in IRF4 knockout cells [69]. IRF4 may function along with STAT3 to promote RORγt expression, but the molecular pathway involved in unknown. RORα has also been shown to regulate IL-17A production, although to a lesser extent than RORγt [70]. IL-6 and TGF-β induced RORα in a STAT3 dependent manner. It is likely that RORγt and RORα synergize to promote T_H17 differentiation, but no known molecular interactions have been identified. In addition to ROR, T_H17 cells have been shown to upregulate aryl hydrocarbon receptors and when stimulated with endogenous ligand, T_H17 cells produce elevated IL-17 [71]. Aryl hydrocarbon receptor may negatively regulate both STAT1 and STAT5 to enhance T_H17 differentiation [72]. Runx transcription factors have also been implicated in T_H17 regulation. Runx1 interacts with RORγt to promote T_H17 differentiation [73]. Recently, the NF-κB family gene, IκBζ has been shown to cooperate with ROR to drive T_H17 polarization [74]. IκBζ was shown to directly bind to the IL-17A promoter region. The contributions of these newly described pathways to T_H17 immunity are rapidly emerging (Fig. 1).

The pathways outlined above function to promote T_H17 development, however there are many inhibitory modulators of T_H17 cells. Early reports describing the T_H17 lineage identified the T_H1 cytokine IFNγ and the T_H2 cytokine IL-4 as negative regulators of TH17 differentiation, suggesting that T_H17 cells are opposed by the other two major T_H lineages. IL-2 is known as a key T cell proliferative signal; however IL-2 inhibits T_H17 development via induction of STAT5a/b [75]. STAT5a/b activation results in Foxp3 expression which promotes T_{reg} development. IL-27 is a member of the IL-12 cytokine family and activates STAT1 in T cells similar to IFN-γ. STAT1 activation promotes T-bet expression which inhibits T_H17 development and favors T_H1 [76,77]. IL-27 inhibits IL-17 production directly via suppression of RORγt expression in T cells [78]. In addition to IL-27, type I interferons, which activate STAT1 and STAT2, inhibit dendritic cell production of IL-23 and IL-1, while promoting IL-12 production [79]. This results in a pro-T_H1 cytokine environment opposing T_H17. The pro-T_H1 cytokine IL-12 also directly inhibits dendritic cell production of IL-23 to attenuate T_H17 development [80]. In addition to T_H1 pathways, the T_H2 cytokine IL-25 also opposes T_H17 development [81,82]. Emerging evidence suggests that T_{reg} derived IL-10 may also inhibit T_H17, although the mechanisms are unclear [80]. These data demonstrate that T_H1, T_H2, and T_{reg} cells can regulate T_H17 through the suppressive actions of their characteristic cytokines (Fig. 1).

Finally, T_H17 lineage commitment may not be as terminal as has been described for T_H1 and T_H2 cells. It has recently been suggested that T_H17 and T_{reg} expression of Foxp3 may be highly flexible resulting in significant plasticity of these cells [83,84]. Mukasa et al. recently showed that chromatin instability in T_H17 cells results in plasticity at the IL-17 and IFN-γ loci [85]. In this study, IL-12 induced IFN-γ locus remodeling and permits STAT4 and T-bet inhibition of RORγt. On the other hand, TGF-β induced modifications to the IL-17A gene to promote expression. These types of epigenetic regulation are supported by studies of the IL-17A and IL-17F loci in T_H17 cells that show H3 histone acetylation and H4 histone trimethylation [86]. These modifications promote expression of IL-17 genes in T_H17 cells. Furthermore, the miRNA miR-326 is highly upregulated in T_H17 cells [87]. miR-326 inhibits the activity of the transcription factor ETS-1, which is known to oppose T_H17 development. ETS-1 knockout T cells have enhanced T_H17 differentiation and increased IL-17 production and ETS-1 is required for IL-2 inhibition of T_H17 cells [87,88]. The role of epigenetic regulation of T_H17 cells requires future investigation and will likely reveal many novel mechanisms of T_H17 control.

4. T_H17 cytokine functions

The canonical T_H17 cytokine, IL-17 (IL-17A) was originally identified in 1993 as cytotoxic T lymphocyte antigen (CTLA)-8 [89]. The IL-17A gene maps to human chromosome 6p12 and has 62%

sequence homology to mouse IL-17A [90,91]. Subsequently, additional cytokines with similar homology to IL-17A have been identified and comprise the IL-17 family; IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. IL-17A and IL-17F share the greatest homology of the family and have been shown to have somewhat overlapping functions. IL-17E (IL-25) is the most divergent member and is not produced by T_H17 cells and does not share functional similarity with IL-17A. IL-17 family members are characterized by 4 conserved carboxy-terminal cysteine residues involved in dimerization. The primary identified function of IL-17A is to promote inflammation through induction of macrophage and neutrophil chemokines and growth factors including CXCL1 (KC), CXCL2 (MIP-2), CXCL5 (LIX), CXCL8 (IL-8), CXCL9 (MIG), CXCL10 (IP-10), CCL-2 (MCP-1), G-CSF, and GM-CSF [90,92–94]. Increased production of IL-17A has been linked to many human inflammatory disorders including asthma, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, hyper IgE syndrome, and allograft rejection [39,95,96]. In addition, the role of IL-17A has been demonstrated in mouse models of experimental autoimmune encephalitis (EAE) [97]. IL-17A has also been shown to induce production of antimicrobial peptides including serum amyloid A, lipocalin-2, β-defensins, S100 proteins, and C-reactive protein [98–102]. These data suggest the IL-17A plays a critical role in host defense. Furthermore, IL-17A promotes inflammation through its known synergy with TNF-α [103,104]. The combination of these cytokines has been shown to result in increased mRNA stability of the inflammatory genes IL-6, IL-8, CXCL1, CXCL2, and IκBζ [104–106]. Recently, T_H17 cells and IL-17A have been implicated in promoting B cell immunoglobulin class switch and germinal center formation [107]. The functional roles of IL-17A are diverse and continuously expanding.

IL-17A has been shown to be sufficient to induce neutrophilic inflammation in the lung [92,108]. Consequently, IL-17A or IL-17R deletion or IL-17A neutralization results in impaired host defense to a variety of pathogens. Mice deficient in IL-17A signaling display attenuated clearance of Gram-negative and Gram-positive bacteria [109,110]. This defect in immunity correlates with decreased neutrophil chemokines and recruitment to the lung. IL-17A has also been shown to promote host defense against the intracellular pathogen *Francisella tularensis* via induction of IL-12 production and promotion of T_H1 mediated host defense [111]. IL-17A is not required for clearance of *Mycobacterium tuberculosis*, although IL-17A may promote the development of T_H1 immunity in vaccine approaches to TB control [112]. Recently, IL-17A has been linked to viral immunity. IL-17A was shown to be protective against lethal influenza A challenge and IL-17R knockout mice display reduced neutrophil recruitment and decreased morbidity compared to control mice following influenza A infection [113,114]. Additionally, IL-17A promotes neutrophil recruitment in response to human rhinovirus and respiratory syncytial virus induces IL-17A in the absence of STAT1 signaling [115,116]. IL-17A also plays a key role in protection against fungal pathogens promoting clearance of *Pneumocystis carinii*, *Candida albicans*, and *Cryptococcus neoformans* [117–120]. These data further illustrate the broad effects of IL-17A in host defense.

T_H17 cells also produce IL-17F, whose gene is located in a similar chromosomal localization as IL-17A. IL-17F, while often secreted at higher concentrations than IL-17A, has weaker biologic activity than IL-17A [121,122]. IL-17F only weakly associates with the IL-17R compared to the affinity for IL-17A [123]. IL-17F, like IL-17A, forms a homodimer and has similar pro-neutrophilic functions as IL-17A. In addition, IL-17F can form a heterodimer with IL-17A; however the molecular consequences of this interaction are not well defined. Subsets of T_H17 cells that produce only IL-17A or IL-17F have also been described [124]. The specific effect of IL-17F in host defense is an active area of research and differential roles for IL-17A and IL-17F in immunity are likely to emerge.

In addition to IL-17 family members, T_H17 cells produce the IL-10 family cytokine IL-22. IL-22 was first identified as a gene product induced by IL-9 stimulation of T lymphoma cells and was originally labeled IL-10-related T-cell-derived inducible factor (IL-TIF) [125]. The human IL-22 gene is located on chromosome 12q15 in proximity to IFN-γ and IL-26 [126]. Similar to IL-17A, deletion of IL-22 results in impaired host defense against Gram-negative bacteria [98]. IL-22 stimulates production of antimicrobial peptides in synergy with IL-17A suggesting a key mechanism of promoting bacterial clearance [98,101]. IL-22 likely has many distinct roles from those of IL-17A. IL-22 promotes keratinocyte differentiation and wound healing processes in the skin and the intestinal epithelium [127–130]. Furthermore, IL-22 promotes epithelial cell homeostasis, protects against injury, and increases hepatocyte survival [131,132]. IL-22 was also shown to protect against bleomycin induced epithelial apoptosis and lung injury and inflammation [133]. These functions suggest a tissue protective role for IL-22 during inflammation. Systemic administration of IL-22 mimics the acute phase response upregulating fibrinogen, platelets, serum proteins, and wasting [134]. Additional studies are required to fully elucidate the function of IL-22 in immunity and asthma. Recently, the existence of a separate T_H22 lineage of T cells has been proposed [128] that express IL-22, but not IL-17. The role of these cells in immunity is yet to be fully determined.

Human T_H17 cells also produce the IL-10 family member IL-26, which does not exist in mice [46]. Elevated IL-26 has been linked to Crohn's disease and induces intestinal epithelial cell proliferation and inflammation [135]. The role of IL-26 in the lung is currently unknown. In addition, T_H17 cells produce the chemokine CCL20 (MIP3α). T_H17 cells characteristically express the CCL20 receptor, CCR6, suggesting that T_H17 cells may in fact regulate their own chemotaxis [46]. CCL20 also promotes dendritic cell migration to inflammatory sites which may facilitate T_H17 cell differentiation and proliferation. CCR6 deficiency has been shown to be protective in EAE and T_H17 driven arthritis models [136,137]. Besides T_H17 derived CCL20, IL-17 has been shown to drive tissue production of CCL20 likely further amplifying T_H17 recruitment [39]. Future investigation is likely to identify additional T_H17 products and further clarify TH17 function in immunity.

5. T_H17 cytokine signaling

IL-17 induces inflammation through binding to the IL-17R family, composed of five members A through E. The IL-17R genes are clustered on human chromosome 3 and all encode single transmembrane spanning receptors. IL-17R is expressed ubiquitously in mouse and man, although the majority of IL-17 effects occur on epithelial, endothelial, and fibroblast cells. IL-17RA was the first identified IL-17 receptor, however regulation of its expression is poorly defined. IL-15 and IL-21 have been implicated as upregulating IL-17RA expression [138]. IL-17RA transduces IL-17A and IL-17F signals through interaction with IL-17RC. IL-17A signaling requires both IL-17RA and IL-17RC, whereas IL-17F signaling is largely only dependent upon IL-17RC [139,140]. IL-17RA also complexes with IL-17RB to form the receptor for IL-25, thus IL-17RA is involved in signaling for both IL-17 and IL-25 which often have opposing immunologic function. IL-17RB is also the receptor for IL-17B, whose function is largely unknown, although it likely promotes inflammation. IL-17RD has no known ligand and may associate with FGFR, however very little is known about its function. The final IL-17R family member, IL-17RE, is very poorly understood and it appears to bind IL-17C with unknown function. The receptor for IL-17D is currently unidentified. Further investigation is warranted to clarify the roles of these IL-17R and their ligands.

Members of the IL-17R family contain a conserved extracellular fibronectin III-like domain and a SEFIR (similar expression to FGF receptor/IL-17R) domain [141]. The SEFIR domain is a cytoplasmic region with homology to a TIR (Toll/IL-1R) domain. TIR domains allow for interactions with adapter proteins, such as MyD88, although the SEFIR domain lacks the ability to associate with Toll/IL-1R adapter

proteins. IL-17RA in particular also contains a TIR-like loop domain (TILL) which likely interacts with yet to be identified adapter proteins and is required for signal transduction [142]. The SEFIR domain of IL-17R interacts with the signaling adaptor Act1 to initiate NF-κB activation [143,144]. Act1 contains a TRAF6 binding domain which allows interaction with TRAF6, TRAF3, and TAK1 [145]. Deletion of the IL-17R SEFIR domain or Act1 results in impaired IL-17 signaling and activation of NF-κB [146]. IL-17 results in stimulation of the classical NF-κB pathway, p50 and p65 (Rel A), and has not been shown to activate alternative NF-κB pathways. In addition to the NF-κB signaling cascade, IL-17 has been shown to activate MAPK signaling, particularly the ERK pathway. The role of MAPK activation by IL-17 appears to be largely directed at increasing mRNA stability of pro-inflammatory genes [141]. However, many IL-17 target genes contain AP-1 DNA binding motifs that may be sites for direct regulation of transcription [147]. IL-17 also activates the CCAAT/enhancer binding protein (C/EBP) transcription factors. The IL-17 target genes IL-6 and lipocalin-2 both require C/EBP activation for transcription [148]. It is likely that IL-17 induced signal transduction requires these and other components to regulate inflammatory gene expression (Fig. 2).

IL-22 initiates a different signaling cascade compared to IL-17 through binding to its heteromeric receptor made up of IL-22R1 and IL-10R2 [149]. The pattern of IL-22R expression in tissues is largely unknown, however our laboratory has shown high levels of IL-22R expression on both ciliated and non-ciliated epithelial cells in the airway (unpublished observation). Further study has identified another IL-22 receptor with 33% homology to IL-22R1, which lacks a transmembrane domain [150]. This molecule, termed IL-22BP (binding protein) binds to IL-22 with high affinity and neutralizes its activity [151,152]. Thus, IL-22BP likely regulates IL-22 function *in vivo*. Upon receptor binding, IL-22 triggers phosphorylation of Jak1 and Tyk2 tyrosine kinases, which in turn lead to activation of STAT3 [153,154]. STAT3 activation is required for IL-22 induction of antimicrobial peptides [155]. In addition to STAT3, IL-22 also induces phosphorylation of all three MAPK pathways, ERK, p38, and JNK [153]. A recent study has shown that IL-22 drives both STAT3 and MAPK activities through interaction of Shp2, a protein tyrosine phosphatase, with IL-22R1 [156]. IL-22 signaling interactions require additional studies to determine the key molecular pathways involved (Fig. 2).

6. Additional cellular sources of IL-17 and IL-22

T_H17 cells are not the only known source for IL-17 and IL-22 in the immune response (Fig. 3). Initial support for this derived from the observation that IL-23 stimulated IL-17 production in recombination-activating gene (RAG)-deficient mice, which lack B and T cells [157]. The best characterized non-$CD4^+$ T cell source of IL-17 and IL-22 are γδT cells that are found in the periphery and play a role in mucosal immunity. γδT cells, unlike $CD4^+$ T cells that experience antigen in the periphery, can engage antigen in the thymus and undergo polarization, thus emerging primed for rapid antigenic responses. Although, it may indeed be antigen naïve γδT cells that are the significant producers of IL-17 during inflammation [158]. γδT cells are divided into two major subgroups, $CD27^+$ and $CD27^-$ populations [159]. $CD27^-$ γδT cells express RORγt and Runx1, similar to T_H17 cells, and produce IL-17. $CD27^+$ γδT cells express T-bet and make IFN-γ, similar to T_H1 cells. IL-17 producing γδT cells also express CD25/IL-2Rα, which may allow for IL-2 regulation of IL-17 induction [160]. In addition, IL-17 secreting γδT cells express CCR6 similar to T_H17 cells. These findings suggest that γδT cells serve as first responders at mucosal surfaces to pathogenic stimuli by initiating an early IL-17 and IL-22 response.

Identification of additional subsets of RORγt expressing cells revealed lymphoid tissue inducer (LTi) cells, which are $CD3^-$ cells, as potential sources of IL-17 and IL-22. LTi cells are characterized by the transcription factor ID2, common gamma chain signaling, and IL-7R expression [161]. This cell type is required for lymph node development, although perhaps not for organogenesis. LTi cells in mice are $CD4^+CD127^+$, and express the chemokine receptors CCR7 and CXCR5 [162]. Interestingly, human LTi cells are generally $CD4^-$ and express distinct surface markers from mouse cells [163]. LTi cells express IL-17

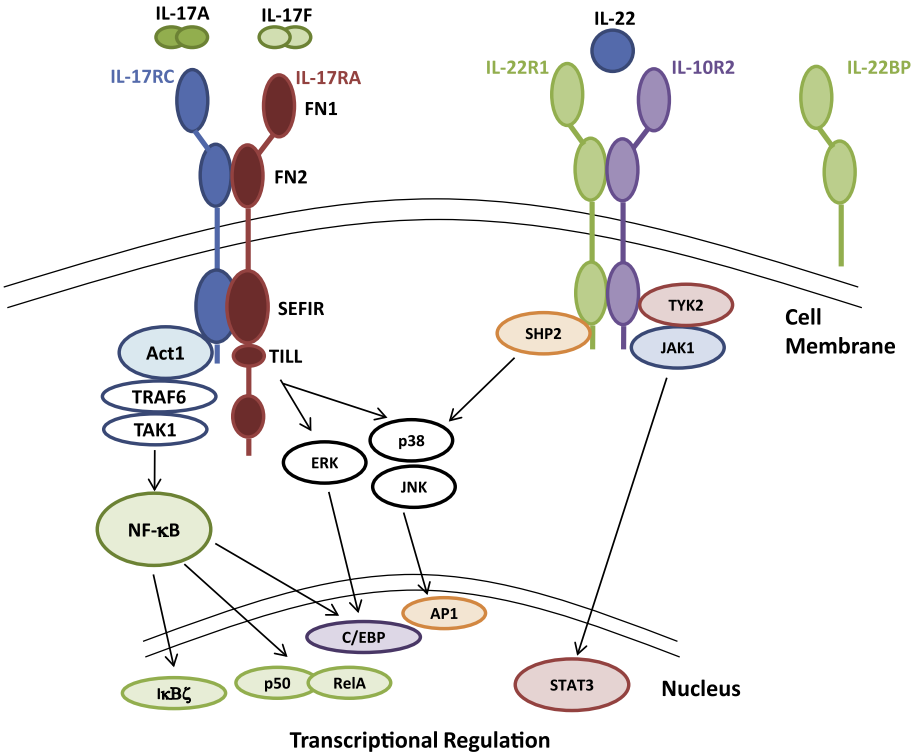


Fig. 2. T_H17 cytokine signaling networks. IL-17 and IL-22 bind to single transmembrane heteromeric cell surface receptors to induce a variety of cellular pathways. IL-17 and IL-22 stimulation result in transcriptional regulation through direct activation of transcription factors.

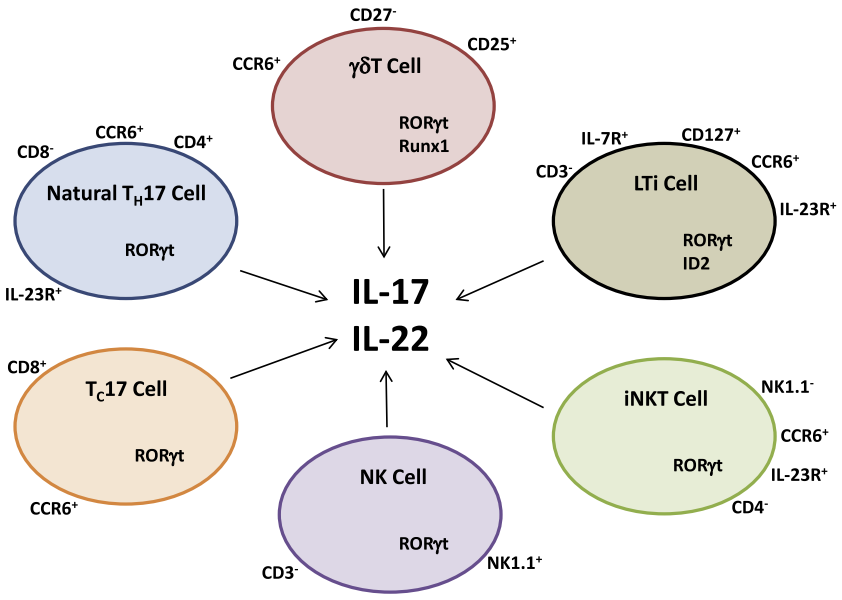


Fig. 3. IL-17 and IL-22 producing cell types. Several lymphocyte lineages have been shown to produce IL-17 and IL-22 in addition to canonical T_H17 cells. IL-17 producing cells express the characteristic T_H17 transcription factor RORγt. LTi, lymphoid tissue inducer; iNKT, invariant natural killer T; NK, natural killer; T_C, cytotoxic T.

or IL-22 when stimulated with either IL-23 or Tlr2 ligand, or PMA/ionomycin, respectively [163]. IL-17 producing LTi cells were shown to express IL-23R, aryl hydrocarbon receptor, and CCR6 and were only partially inhibited by STAT3 deletion [164]. The role of LTi cells in host defense or allergic responses is currently unclear.

Invariant natural killer T (iNKT) cells have also been shown to produce IL-17 [165]. iNKT cells are activated through their T cell receptor by antigen presenting cells expressing the non-variant MHC I-like molecule CD1d on their cell surface, which presents foreign or self glycolipids, such as α-galactosylceramide (GalCer). α-GalCer treatment of $NK1.1^{-}CD4^{-}$ iNKT cells results in rapid IL-17 production [165]. These cells may also express CCR6 similar to T_H17 cells. IL-17 producing iNKT cells express RORγt and IL-23R, but not T-bet, in contrast to $NK1.1^{+}$ iNKT cells that express T-bet and produce IFN-γ [166]. Interestingly, iNKT cells do not require IL-6 for IL-17 production unlike T_H17 cells [167]. The specific contributions of iNKT derived IL-17 and IL-22 are yet to be fully understood.

Natural killer (NK) $NK1.1^{+}$ cells have been shown to be capable of producing IL-17 in response to *Toxoplasma gondii* [168]. In addition, $NK1.1^{+}$ NK cells have also been shown to make IL-22 as well as IFN-γ following influenza infection [169]. However, it has been suggested that IL-17 producing NK cells may be a separate lineage related to LTi cells. $CD3^{-}NKp46^{+}$ cells express IL-22 dependent upon ID2 and RORγt expression [170]. NK cells may play a role in rapid production of IL-17 and IL-22 following injury or infection, although the exact role is undetermined. Additional subsets of lymphocytes have been characterized as IL-17 producers. In influenza A infection $CD8^{+}$ cytotoxic T cells were shown to produce IL-17 and were termed T_C17 cells [114]. T_C17 cells have since been identified in several models [171,172]. Recently, a population of $CD4^{+}CD8^{-}$ "natural" T_H17 cells that develop in the thymus, as opposed to the periphery like T_H17 cells, has been suggested as being capable of rapid IL-17 and IL-22 production in response to self antigens [173]. In addition, Wang et al. reported a $CD4^{+}$ T_H2 cell subset, expressing both GATA3 and RORγt, capable of producing both IL-17 and T_H2 cytokines [174]. These findings remain to be further elucidated and the role of other IL-17 producing cells in allergic inflammation is largely uncharacterized.

Finally, myeloid cells have been suggested as being capable of producing IL-17 in some models. Alveolar macrophages were shown to express IL-17 mRNA in an allergic challenge model [175]. In a kidney ischemia–reperfusion injury model, early IL-17 production was mediated by $CD11b^{+}GR1^{+}$ cells perhaps indicating a neutrophil source of IL-17 [176]. Another study in rheumatoid arthritis showed IL-17 mRNA in purified neutrophils [177]. In addition to myeloid cells, intestinal Paneth cells, a specialized type of epithelial cell, were shown to secrete IL-17 following TNF-α stimulation [178]. These limited studies indicate the potential for non-lymphoid IL-17 production which may also regulate immune function, although evidence for non-leukocyte derived IL-17 in asthma is lacking.

7. T_H17 regulation of allergic airway disease in mouse models

The role of T_H17 cytokines in allergic airway disease has been examined by numerous investigators of the last few years. Several studies have utilized the ovalbumin (OVA) sensitization and challenge model to study the T_H17 pathway. This model recapitulates several of the hallmarks of allergic asthma; eosinophilia, mucus metaplasia, IgE production, collagen deposition, and AHR. In the OVA model increased IL-17A, IL-17F, and IL-22 mRNA and protein have been observed [179–182]. Initial studies of IL-17RA knockout mice revealed decreased OVA induced airway eosinophilia, OVA specific-IgE, and T_H2 cytokines [181]. These data suggest that IL-17 drives the allergic T_H2 response, however, recent identification of IL-17RA as a component of the IL-25 receptor confounds these data. IL-25 is known to promote T_H2 immunity and allergic airway disease [183,184]. Despite this caveat, other studies have suggested that IL-17 promotes OVA induced T_H2 responses by synergizing with IL-4 and IL-13 to further increase T_H2 cytokine production and CCL11 (eotaxin) secretion [175,185–187]. In support of these findings, PPARγ agonists and NF-κB inhibitors reduced IL-17 production in the OVA model alleviating inflammation [186,188]. Additional transgenic mouse models suggest a pro-inflammatory role for the T_H17 pathway in the OVA model. CCSP-IL-23 overexpressing mice had increased IL-17, eosinophilia, and T_H2 cytokines following OVA, whereas IL-23 knockout mice showed reduced eosinophilia [189,190]. Inhibition of T_H1, by T-bet knockout, or T_H2, by IL-4/IL-13 double knockout, signaling in the OVA model resulted in increased IL-17 production and airway neutrophilia [191,192]. In T-bet knockout mice, the increase in inflammation driven by IL-17 could be attenuated with IL-17 antibody neutralization or exogenous IL-12 driven IL-10 production [80,191]. In addition to driving inflammation, IL-17 may induce airway remodeling. In a model of prolonged OVA challenge, elevated IL-17 production was observed along with increased collagen

deposition, airway smooth muscle mass, and mucus hypertrophy [193]. IL-17 has been shown to be directly capable of inducing mucin (MUC5B and MUC5AC) production by airway epithelial cells via NF-κB activation [194,195]. These data suggest that T_H17 cells may promote T_H2 allergic immune responses in the context of the mouse OVA model.

Contrary to these reports, other studies have shown that T_H17 cytokines oppose T_H2 immunity in the OVA model. In these studies, IL-17A neutralization prior to OVA challenge resulted in exacerbated airway eosinophilia and T_H2 cytokine production, as well as decreased neutrophil recruitment [179,196]. In agreement with these findings, exogenous IL-17A decreased eosinophil recruitment to the lung [180,181]. The reasons for these discrepancies are unclear, however the strategy utilized for IL-17 intervention may be responsible for some of the differences observed. The exact methodology utilized in the OVA model may also be critical to the immune outcome. Wilson et al. demonstrated that airway OVA sensitization resulted in robust T_H17 polarization, whereas intraperitoneal OVA sensitization led to mainly T_H2 generation [197]. In addition, TNF-α activity during antigen sensitization was shown to be critical to directing IL-17 production [198]. These and other studies indicate that the route of antigen sensitization, cytokine milieu, and adjuvant usage all impact the relative degree of T_H17 polarization. The precise role of T_H17 cytokines in the mouse asthma model is complicated by many factors, however it appears likely that IL-17 acts in a pro-inflammatory role in allergic airway disease. Interestingly, IL-22 appears to oppose T_H2 mediated inflammation [180]. In the OVA model, antibody against IL-22 increased airway eosinophilia, whereas exogenous IL-22 suppressed eosinophil recruitment. These data further support the concept that IL-22 may have anti-inflammatory properties in certain contexts.

The impact of T_H17 cytokines on AHR is also unclear with some studies reporting enhanced AHR, other showing reduced AHR, and yet others indicating no effect. Initial studies utilizing whole body plethysmography produced conflicting results. Exogenous IL-17A reduced AHR and IL-17A antibody neutralization led to increased AHR [181]. However, elevated IL-17A levels or IL-17F overexpression by gene transfer led to either no change in AHR or elevated AHR despite both studies showing increased neutrophilia [192,199]. Interpretation of these data is challenging due to limitations of Penh as a measure of AHR in mice [200]. Using the forced oscillation technique several groups have reported a causative role for IL-17 in promoting AHR. OVA induced elevation of IL-17 and the T_H17 pathway resulted in increased AHR and antibody neutralization of IL-17A attenuated AHR [188,191,197]. Furthermore, adenoviral expression of IL-17A was sufficient to induced AHR in the absence of antigen [201]. In an ozone injury model, IL-17A production by iNKT cells was required for AHR [202]. These studies indicate that IL-17A, and perhaps T_H17 cells, induce AHR and may exacerbate lung responsiveness in the mixed T_H2/T_H17 OVA model. However, Murdoch et al. recently reported that IL-17 derived from γδT cells may promote resolution of allergic inflammation and AHR [203]. The precise mechanism of T_H17 cells in regulating AHR remain to be further elucidated.

The role of T_H17 cells in allergic airway disease has been examined in several other mouse models. In the keyhole limpet hemocyanin (KLH) antigen sensitization and challenge model IL-17A and IL-17F knockout mice displayed differing phenotypes [124]. IL-17A knockout mice had attenuated airway eosinophilia and neutrophilia, whereas IL-17F knockout mice were characterized by increased eosinophil recruitment and diminished neutrophil numbers. These data suggest a differential role for IL-17A and IL-17F in allergic responses. Several recent studies have also examined the T_H17 pathway in the house dust mite (HDM) model. HDM sensitization and challenge result in increased IL-17 and neutrophil recruitment in a MyD88 dependent manner [204]. In the HDM model, an AHR sensitive mouse strain was shown to have predominant myeloid dendritic cell production of IL-23, which drove T_H17 activation and AHR, whereas an AHR insensitive mouse strain was characterized by antigen presenting plasmacytoid dendritic cells and did not develop T_H17 or AHR responses [205]. In addition, the ability of anaphylatoxins to modulate T_H17 responses through complement activation in the HDM model was demonstrated [206]. Complement receptor C3aR was shown to induce IL-23 production, whereas C5aR led to elevated IL-10 production and inhibited IL-23 synthesis. These data provide greater insights into the role of T_H17 cells in response to authentic allergens.

Work in our laboratory and others have led to the development of a T cell adoptive transfer model of allergic airway disease. In this model, OVA specific T_H2 or T_H17 cells are differentiated *in vitro* and are transferred intravenously to T cell deficient mice. Mice are then challenged in the airways with OVA and the effector T cell response is assessed. The adoptive transfer model allows for the separation of antigen sensitization events from the effector functions of polarized T_H2 and T_H17 cells. T_H2 cell transfer results in increased IL-5, IL-13, airway eosinophilia, mucus metaplasia, and AHR. T_H17 cell transfer induces IL-17A, airway neutrophil recruitment, mucus metaplasia, and AHR [201]. Interestingly, T_H2 driven allergic airway disease was largely attenuated by GC treatment, however T_H17 mediated inflammation, mucus hypersecretion, and AHR were GC insensitive. Furthermore, T_H2 cell production of IL-5 and IL-13 was inhibited by GC *in vitro*, while T_H17 secretion of IL-17A and IL-22 were not affected by GC treatment. These data suggest a potential role for T_H17 cells in steroid resistant asthma. However, *in vitro* studies of epithelial cells and fibroblasts have shown that IL-17 stimulated production of chemokines is steroid sensitive [207,208]. In further support of a role for T_H17 cells in promoting allergic airway disease, adoptive transfer of both T_H17 and T_H2 cells resulted in worsened airway eosinophilia and AHR compared to T_H2 cells alone [190]. The findings in the T cell adoptive transfer model indicate that T_H17 cells are sufficient to drive many of the hallmarks of allergic airway disease. In addition, T_H17 driven neutrophilia may play a key role in steroid resistant or severe forms of asthma.

8. T_H17 cells in asthma

The role of IL-17 and T_H17 cells in human asthma is still being elucidated; however there is strong evidence supporting their involvement in the disease. Zhao et al. investigated T_H1, T_H2, and T_H17 cell subsets by flow cytometry as well as cytokines from peripheral blood mononuclear cells (PBMC) from allergic asthmatics and controls [209]. In this study, there was a significant increase of IL-17A$^+$ T cells in PBMC in the asthmatics compared with healthy controls. Furthermore, the IL-17A$^+$ cells increased in proportion to the severity of asthma. Moreover, IL-17 (as well as other T_H17 cytokines) was increased in the plasma and culture supernatants of activated PBMC in the asthmatics over controls. IL-17A levels also were increased in severe asthmatics compared to mild and moderate asthmatics. In support of this finding, two recent studies demonstrated an increase in CCR6$^+$CD4$^+$ cells in the peripheral blood of asthmatics versus controls [210,211]. These cells produced elevated IL-17A, IL-21, and IL-22, characteristic T_H17 cytokines. Elevated IL-17A mRNA and protein in asthmatics has been reported by several groups and it was shown to induce inflammatory mediators from fibroblasts isolated from asthmatic bronchial biopsies [207,212–214]. In one study Bullens et al. examined IL-17A mRNA in sputum of asthmatics and normal controls [212]. Both IL-17A and IL-8 mRNAs were significantly increased in sputum of asthmatics compared to controls. Sputum neutrophils were highest in moderate–severe asthmatics compared with mild asthmatics. All moderate–severe asthmatics had elevated sputum IL-17A and IL-8 mRNA, whereas this was only found in approximately half of mild asthmatics. The authors suggest that T_H17 cells and IL-17A lead to neutrophilic inflammation in asthma, via IL-8. This was supported in a later study in which there was increased IL-17A mRNA expression and IL-17A$^+$ cells in bronchial biopsies of

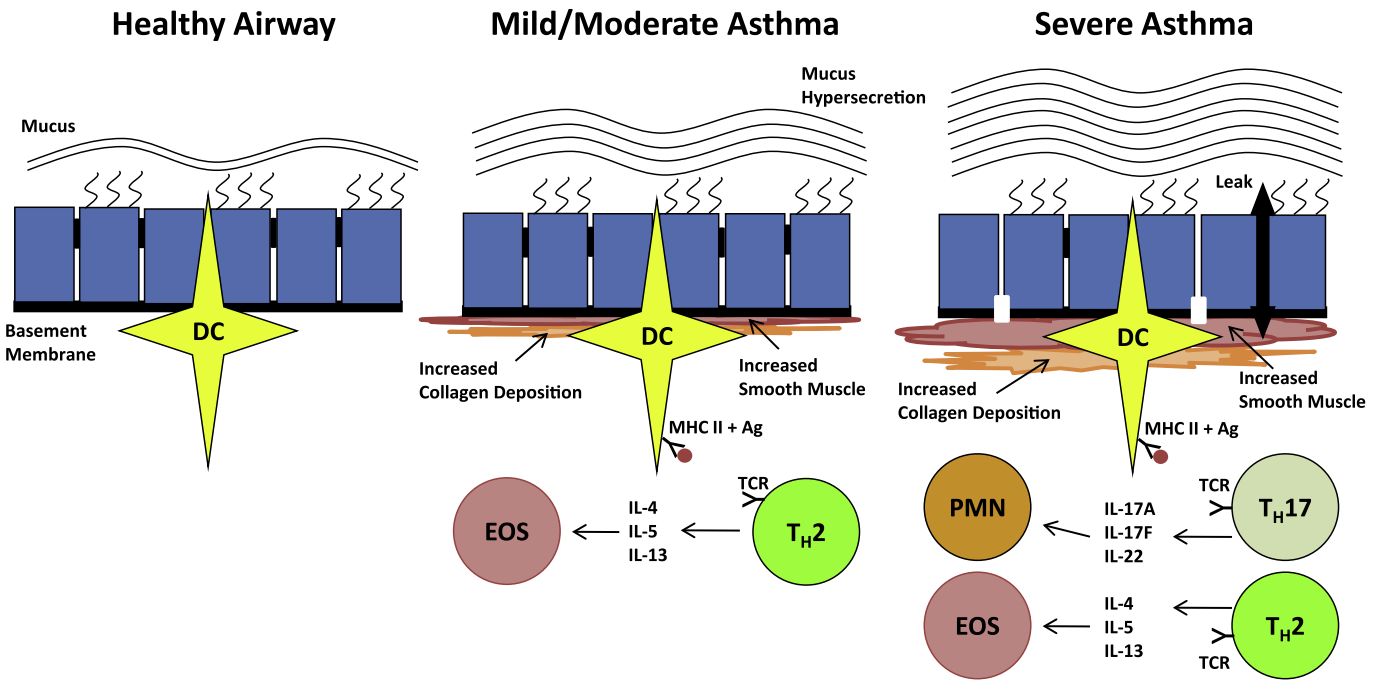


Fig. 4. Model for T cell mediated inflammation and lung remodeling in asthma. In mild/moderate asthma, T_H2 driven processes predominate along with eosinophilic inflammation. In severe asthma, both T_H2 and T_H17 induced inflammation occur and airway damage and remodeling are worsened. DC, dendritic cell; Ag, antigen; EOS, eosinophil; PMN, polymorphonuclear cell.

asthmatics [215]. The presence of increased IL-17A$^+$CD4$^+$ cells in the tissue of asthmatics has been recently been reported by several groups, suggesting a T_H17 cell population [216–218]. Elevated sputum IL-17A has also been associated with bronchial hyperresponsiveness to methacholine in asthmatics [219]. Investigators have also found that elevated serum IL-17A is an independent risk factor for severe asthma [220]. In conjunction with elevated IL-17A, Roussel et al. have shown that IL-17RA and IL-17RC mRNA are increased in asthmatic epithelial and endothelial cells versus normal controls [221]. This finding suggests that IL-17A signaling and downstream transcriptional regulation are enhanced in asthmatic tissues. Taken together, the studies outlined above indicate that IL-17A, likely produced by T_H17 cells, may play a key role in asthma pathogenesis, perhaps particularly in more severe types of asthma.

Several of the above summarized studies included some asthmatic participants taking maintenance inhaled corticosteroids, but who still had severe disease and increased expression of IL-17A. The potential connection between T_H17 cells and corticosteroid resistance was studied by Vazquez-Tello and colleagues [222]. In this study, both IL-17A and IL-17F upregulated GR-β mRNA expression in bronchial epithelial cells from mild asthmatics. As discussed previously, the GR-β isoform of the glucocorticoid receptor acts as an inhibitor to GC signaling and therefore leads to decreased action of corticosteroids. The authors also found that dexamethasone did not suppress IL-17A induced IL-6 mRNA production in bronchial epithelial cells of asthmatics, as it did in normal controls. Of note, asthmatic bronchial epithelial cells did express higher GR-β protein levels than normal cells, which could explain why there was a lower response to dexamethasone in asthmatic cells. These data further implicate IL-17 and T_H17 cells in steroid resistant asthma.

IL-17F has also been suggested to play a role in modulating the inflammation of asthma. One study has found that an IL-17F polymorphism (His161Arg) was protective against the development of asthma and *in vitro* experiments revealed that this variant was unable to induce proinflammatory cytokine production in bronchial epithelial cells [223]. Polymorphisms in the IL-17A gene related to asthma risk have also recently been described [224,225]. However, the mechanistic links between these changes and disease progression were not identified. Additional studies are required to fully characterize T_H17 pathway genetics in asthma.

9. Summary and future directions

The studies summarized above provide robust evidence that asthma, especially severe disease, does not only stem from T_H2 driven inflammation, as was previously thought. There is clinical data showing that T_H17 inflammation appears to contribute a large role in those asthmatics with more severe disease and neutrophilic inflammation, including steroid resistant patients (Fig. 4). T_H17 cells already have been shown to play a role in several immune mediated diseases as outlined herein. Of course, researchers should not ignore the complex heterogeneity of asthma and the vast array of molecular mechanisms and pathways contributing to the pathogenesis of the disease [11]. Caution has to be taken in targeting T_H17 cells or IL-17 as treatments for asthma. The T_H17 lineage of cells provides us with critical host defense against extracellular and intracellular pathogens as has been discussed. Therefore, any treatment involving blockade of T_H17 cells or IL-17 may increase vulnerability to infection [226]. Further studies are needed to discover whether IL-17 can safely be a therapeutic target for asthma, as several children and adult asthmatics alike continue to struggle with severe disease that is not responsive to current available therapies.

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