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# A tale of two cytokines: IL-17 and IL-22 in asthma and infection

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## Abstract

The Th17 pathway has recently been shown to play a critical role in host defense, allergic responses and autoimmune inflammation. Th17 cells predominantly produce IL-17 and IL-22, which are two cytokines with broad effects in the lung and other tissues. This review summarizes not only what is currently known about the molecular regulation of this pathway and Th17-related cytokine signaling, but also the roles of these cytokines in pathogen immunity and asthma. In the last 5 years, the Th17 field has rapidly grown and research has revealed that the Th17 pathway is essential in lung pathogenesis in response to exogenous stimuli. As work in the field continues, it is expected that many exciting therapeutic advances will be made for a broad range of diseases.

### Keywords

allergy; cytokines; lung; pneumonia; T cells

$CD4^+$ T helper (Th) lymphocytes are essential regulators of immune responses and inflammatory diseases by facilitating B-cell responses, modulating innate immunity and regulating $CD8^+$ T-cell expansion [1-4]. When naïve $CD4^+$ Th cells encounter antigen, their response varies based on the site of interaction, antigen type and inflammatory milieu present. Further, this antigen-induced response influences Th cell differentiation into effector cells with specific functional characteristics. Th cells are subdivided into lineages on the basis of the cytokines that they secrete, the specific transcription factors they express and the immunological function that they meditate.

In the mid-1980s, Th cells were first characterized and divided into two distinct lineages: Th1 and Th2 [5-9]. Th1 cells are driven by IFN-γ and IL-12 to express the transcription factor T-box 21 (*tbx21*: T-bet) through STAT1 and STAT4 signaling [10-12]. These cells secrete IFN-γ and IL-12 and are known to protect the host against intracellular pathogens



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[13]. In contrast, Th2 cells, whose differentiation is driven by IL-4-induced STAT6 activation, express GATA-binding protein 3 (GATA-3) and secrete IL-4, IL-5 and IL-13 to mediate allergy, asthma and host defense against parasitic infections [14]. Th1 and Th2 cells are opposing cell types as the expression of IL-12, IFN-γ and T-bet, inhibits Th2 differentiation; and IL-4 and GATA3 expression antagonizes Th1 polarization [15-19]. More recently, Th17 cells producing IL-17A, IL-17F and IL-22 emerged as a distinct population of $CD4^+$ T cells [20-23]. These cells are characterized by high expression of the transcription factors retinoic acid (RA)-related orphan receptor γ thymus (RORγT) and RA-related orphan receptor α (RORα), that are critical for Th17 differentiation. Th17 cells are not only critical for host defense against extracellular pathogens, but have been implicated in the pathogenesis of a number of inflammatory diseases, including autoimmune disorders and allergic asthma [24-28].

## Regulation of Th17 differentiation

Antigen presenting cells drive $CD4^+$ T cell differentiation through cytokines and costimulation [29]. Specifically, IL-23 is comprised of the IL-23-specific p19 subunit and the IL-12 p40 subunit, and is mainly produced by myeloid cells, such as dendritic cells and macrophages [25,30]. Although IL-23 was initially thought to induce Th17 polarization, naïve Th cells do not express IL-23 receptor (IL-23R) and therefore IL-23 is not required for early Th17 differentiation [31,32]. During Th17 development, IL-6 and TGF-β1 activates IL-23R expression; and IL-23 induces STAT3 and Th17 proliferation and production of cytokines, such as IL-17 and IL-22 [27,28]. In addition to IL-17 and IL-22, Th17 cells produce IL-21 which promotes Th17 cell lineage differentiation and potentially acts as an auto feedback mechanism [33]. IL-23 is also capable of inducing production of IL-17 from Th17 cells which are independent of T-cell receptor (TCR) ligation [34]. Overall, IL-23 is not required for the initiation of Th17 polarization, but instead is thought to stabilize and expand these cells, perhaps directing IL-17 and IL-22 production.

IL-6 and TGF-β are cytokines that participate in the induction and expansion of Th17 cells. These cytokines are known to be critical regulators of Th17 differentiation via signaling through the STAT3 and similar to mothers against decapentaplegic (SMAD) pathways, respectively [35]. Activation of STAT3 also increases expression of hypoxia inducible factor (HIF) 1α, which inhibits FoxP3 expression and promotes Th17 polarization [36]. TGF-β signaling promotes Th17 differentiation by activating RORγT and RORα and limiting T-bet expression. At low concentrations, TGF-β1 synergizes with IL-6 to promote Th17 differentiation [37,38]. However at high levels, TGF-β can induce FoxP3 expression and inhibit T-bet to promote $T_{reg}$ development [37]. $Foxp3^+$ $T_{reg}$ cells are essential for maintaining immune homeostasis and play a critical role in limiting excessive immune and inflammatory responses. Although there are many types of $T_{reg}$ cells, naturally occurring $T_{reg}$ and inducible $T_{reg}$ cells are the best characterized. Specifically, the balance between Th17 and $T_{regs}$ is known to be crucial for immune homeostasis and several mechanisms have been found to control the balance between $T_{reg}$ and Th17 cells. As mentioned, TGF-β is required for both Th17 and $T_{reg}$ differentiation and it can induce both Foxp3 and RORγT expression in these cells [39]. Further, TGF-β in conjunction with RA and STAT5 activation via IL-2 can increase FoxP3 expression to promote $T_{reg}$ formation. Both FoxP3 and RORγT

form complexes with Runx1 transcription factor and therefore regulate each other [40]. Specifically, FoxP3 is able to associate with RORγT and inhibit its transcriptional activation [39]. However, in the presence of IL-6, FoxP3-mediated inhibition is abrogated and Th17 differentiation is initiated. The reciprocal relationship between these cells, both an excess in Th17 function or increased number of Th17 cells or a defect in $T_{reg}$ function or reduced numbers of $T_{reg}$, may promote inflammation and disease pathogenesis. Both TGF-β and IL-6 are capable of controlling the balance between Th17 and $T_{reg}$ differentiation; however, the regulation of Th17 and $T_{reg}$ polarization is multifactorial and is still emerging.

Many other cytokines and factors are known to influence $T_H17$ differentiation. IL-1β promotes $T_H17$ polarization through p38 MAPK and serine-threonine protein kinase AKT/mTOR pathway. IL-1β also induces interferon regulated factor (IRF)-4, which regulates the autocrine function of the IL-21 [41-43]. Aryl hydrocarbon receptors are cytosolic receptors with transcriptional activator activity that are known to promote Th17 polarization when stimulated with exogenous ligand [44]. High levels of aryl hydrocarbon receptors induce early Th17 expression and animals deficient in aryl hydrocarbon receptors are partly protected from experimental autoimmune encephalomyelitis, a Th17-cell mediated disease [45].

Several cytokines oppose Th17 polarization by inhibiting RORγT and RORα expression. For instance, Type 1 interferon, Type 2 interferon and IL-27, negatively regulate Th17 cell polarization and cytokine production and promote T-bet expression [46,47]. Similarly, IL-4 activates STAT6 to promote the transcription factor GATA3 expression that inhibits Th17 polarization. Further, IL-2 signaling via STAT5 attenuates Th17 differentiation and STAT5 is known to directly limit *IL-17A* gene expression [48,49]. Overall, the regulation of Th17 cell differentiation and proliferation is complex and requires multiple factors (Figure 1).

## Emerging influences on Th differentiation

Despite T cell fate determination, recent discoveries have emphasized that T cells are phenotypically unstable. For instance, it is apparent from both *in vitro* and *in vivo* studies that some T cells can produce both IFN-γ and IL-17 [50]. In addition, Th17 cells can produce IL-21 and/or IL-22 (proposed Th22 cells) in the absence of IL-17 [20,32,51]. It is also recognized that Th17 cells as well as other T cell subsets produce the immunosuppressive cytokine IL-10; thus, not all Th17 cells may be pathogenic [52]. The plasticity of T cell differentiation is thought to be cytokine-regulated and also is suggested to play a role in modulating inflammatory diseases [21]. This phenomenon is also thought to occur in humans. Human circulating memory Th cells co-expressing IL-17/IL-4 have been identified in asthmatics [53]. Further, circulating Th cells from healthy controls and asthmatics were found to express multiple transcription factors [54]. Together, these data support the concept that individual Th cells may have a flexible phenotype and multiple functions *in vivo*.

Aside from cytokine and immune cells influences, the host environment can also affect Th cell differentiation. The microbiome has recently been shown to influence various aspects of host innate and adaptive immunity, such as the development and differentiation of Th17

cells [55-57]. Intestinal lymphocytes are thought to be regulated by commensal microbiota [55]. Indeed, Th17 cells are present in the lamina propria of the small intestines and the number of Th17 cells is reduced in germ free or antibiotic-treated mice [58-60]. Atarashi and colleagues further elucidated this relationship as they found that extracellular adenosine 5′-triphosphate from microbiota activates dendritic cells in the lamina propria thereby inducing Th17 cells [60]. Mice housed in different facilities had different compositions of intestinal bacteria and were also found to have marked difference in the number of Th17 cells in their gastrointestinal tract [59]. Further, segmented filamentous bacteria (SFB) were identified as the first microbiota known to induce Th17 cell accumulation in the small intestines [61]. This induction of Th17 cells via mono-colonization of SFB in the gastrointestinal tract protected against the pathogenic bacterium, *Citrobacter rodentium* [61]. Although much is known about the influence of the microbiome on immunity in the gastrointestinal tract, the relationship between commensal microbiota and the host immune system in the lung is still poorly understood.

In addition to the microbiota, recent studies have shown that other environmental factors may affect Th17 responses, such as a high salt diet. Recent findings by Wu *et al.* and Kleinewietfeld *et al.* elucidate novel mechanisms by which sodium chloride (NaCl) induces pathogenic Th17 development and exacerbates Th17-mediated inflammatory and autoimmune disease [62,63]. Using transcriptional profiling, Wu and colleagues identified serum glucocorticoid kinase 1 (SGK1), a serine/threonine kinase known to influence cellular $Na^+$ transportation and NaCl homeostasis, as a downstream regulator of IL-23 signaling [62]. Further, they found that IL-23 signaling is critical to maintain SGK1 expression during Th17 cell differentiation and to stabilize Th17 cell phenotype by deactivating mouse Forkhead box protein O1 (FoxO1), a direct repressor of IL-23R expression [62]. Kleinewietfeld and colleagues also observed that high salt conditions activate SGK1, nuclear factor of activated T cells 5 and p38/MAPK during Th17 polarization [63]. Further, silencing these factors inhibited the high salt-induced Th17 cell development [63]. More significantly, both studies demonstrate via a mouse model of multiple sclerosis that a high-salt diet accelerates neuropathology in experimental autoimmune encephalomyelitis [62,63]. Other molecules related to sodium homeostasis, such as aldosterone and the mediators of the renin-angiotensin pathway are also known to influence Th17-mediated responses [64,65]. Further investigations are ultimately required to understand the role of these factors as well as other dietary and environmental factors in Th differentiation and the regulation of other immune cells and pathways influential in disease pathogenesis, completely.

## Th17 cytokines

The canonical Th17 cytokine, IL-17, is a proinflammatory cytokine that was originally identified as cytotoxic T lymphocyte antigen (CTLA)-8 [66]. IL-17 is now recognized as a family of cytokines including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F [67]. To date, IL-17A and IL-17F have been the most extensively studied and are localized to the same chromosome in both humans and mice (chromosomes 6 and 1, respectively) [68,69]. There is also a 62% sequence homology in IL-17A between mice and humans [68,69]. IL-17A is secreted as a disulfide-linked homodimeric glycoprotein [68]. IL-17A promotes inflammation through induction of cytokines and chemokines: CXCL1 (KC),

CXCL2 (MIP-2), CXCL5 (LIX), CXCL8 (IL-8), CXCL9 (MIG), CXCL10 (IP-10), G-CSF and GMCSF [68,70,71]. On the other hand, IL-17F has weaker biological activity than IL-17A [72,73]. Although IL-17F is known to be secreted at higher concentrations than IL-17A, it weakly associates the IL-17 receptor (IL-17R) [74]. IL-17F, like IL-17A, also forms a homodimer, but can also form a heterodimer with IL-17A. Functionally, both IL-17A and IL-17F are known to recruit, activate and regulate the migration of neutrophils [67]. Distinct actions of IL-17F have been described, but the precise function of this cytokine is yet to be determined [35]. In addition to IL-17, $T_H17$ cells also produce IL-22, a member of the IL-10 cytokine family, which is thought to play an influential role in inflammation and tissue homeostasis [75]. Although IL-10 and IL-22 have limited homology, IL-22 is structurally similar as it is composed of bundles of α-helices [76] and is located on chromosome 12q15 in humans [77]. The biological role of IL-22 is the subject of many current studies.

## Cellular sources of $T_H17$ cytokines

IL-17 and IL-22 were originally thought to be produced exclusively by αβ T lymphocytes, however many other immune cells are now known to secrete these cytokines. Other cellular sources of IL-17 include γδ T cells, cytotoxic T cells, invariant NK T cells, NK cells, innate lymphoid cells (ILCs) and lymphoid tissue inducer cells [78,79]. Recently, much work has focused on the identification and characterization of IL-17-producing γδ T cells and ILCs, which will be further discussed.

γδ T cells account for a small percentage of lymphocytes (<5% of total lymphocytes) and are most prevalent in mucosal and epithelial sites, such as in the gut and lung. Although these cells are not abundant, γδ T cells are known to be a more potent source of IL-17 than αβ T cells following *Myobacterium tuberculosis* infection [80]. Although γδ T cells are primarily activated through their TCR, activation of γδ T cells for the induction of IL-17 is known to involve various cytokines, chemokines and pattern recognition receptors. Indeed, IL-1, IL-6, IL-18, IL-23 and TGF-β1 expression as well as activation of Toll-like receptor 2, DC-associated C-type lectin 1 and aryl hydrocarbon receptor, have all been implicated with IL-17 production by γδ T cells [81]. Specifically, Lalor and colleagues found that IL-18 synergizes with IL-23 to promote IL-17 production by γδT cells [82]. Further, these authors also demonstrate that the processing of IL-1β and IL-18 via inflammasome-triggered pathways is important for the generation of IL-17-secreting γδ T cells [82]. Similar to αβ T cells, RORγT and STAT3 expression have also been associated with activated IL-17 producing γδ T cells [58]. However, γδ T cells are known to have the high constitute expression when compared to the other T lymphocytes [83].

ILCs are a heterogeneous population of innate effector cells that originate from hematopoietic progenitors in the bone marrow. ILCs lack expression of specific antigen receptors but are further divided into three functional groups based on the transcription factors they express and the cytokines they secrete [84]. Although some types of ILCs are known to have a protective role in inflammatory disease and infection [85], recent studies suggest that some Group 3 ILCs (ILC3), which produce the cytokines IL-17A or IL-22, promote infection, inflammation and autoimmune disease [86]. One of the main challenges

in understanding the role of ILCs in disease pathogenesis is that different nomenclature used to describe these populations. However, these main subsets of ILCs and their expression profiles, functional characteristics and disease roles have been recently extensively reviewed elsewhere [84,87]. Other than Th17 cells [88], many cell types can produce IL-22, including but not limited to activated Th1 and $CD8^+$ T cells [76,89,90], NK cells [90-92], $CD11c^+$ myeloid cells [76,93], IL-22-producing CD4+ T cells (Th22) [94], lymphoid tissue inducer-like cells [91] and IL-22 producing ILC3s [95]. Overall, the discovery of these novel sources of IL-17 and IL-22 have led to the re-examination of Th17-related diseases, where these cytokines, such as infection, autoimmune disease, allergic airway disease and other inflammatory conditions.

## Th17 cytokine signaling

IL-17 signaling pathways are implicated in the pathogenesis of a number of autoimmune and inflammatory diseases. IL-17 induces inflammation through binding to the IL-17 receptor (IL-17R) family, which includes IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE [96]. IL-17R is widely expressed by T and B lymphocytes, neutrophils, epithelial, endothelial, fibroblast, monocytes and mesenchymal stromal cells as well as keratinocytes [97]. Although IL-17R is ubiquitously expressed, the majority of its effects in the lung are thought to be on epithelial, endothelial and fibroblast cells [78].

IL-17RA and IL-17RC bind both IL-17A and IL-17F [97]. In fact, IL-17RA binds to IL-17A with a higher affinity than IL-17F in humans, while IL-17F has a higher affinity for IL-17RC than IL-17A [98]. In mice, IL-17RA can bind both IL-17A and IL-17F but murine IL-17RC may only bind IL-17F [98]. IL-17RA complexes with IL-17RB to form the IL-25 receptor and thus IL-17 and IL-25 share the IL-17RA subunit. IL-17RB is also known to be a receptor for IL-17B [97]. The orphan receptor IL-17RD can also differentially regulate IL-17A-dependent pathways [99]. Lastly, recent studies reveal IL-17RE can form a receptor complex with IL-17RA to bind IL-17C and may have a role in intestinal immunity [72,100]. Additional studies are required to clarify the roles of IL-17RD and IL-17RE along with the functions of IL-17B, IL-17C and IL-17D in the lung.

Members of the IL-17R family possess an intracellular SEF/IL-17R (SEFIR) domain that is important for triggering down-stream signaling [101]. IL-17 signaling results in regulation of gene expression by activating the transcription factor NF-κB and MAPK pathways (Figure 2) [102]. Stimulation of IL-17RA leads to an association with the adaptor protein Act1, via SEFIR-SEFIR interactions, followed by recruitment and polyubiquitination of the scaffold protein TRAF6, thus initiating downstream activation of NF-κB and MAPKs [103,104]. Specifically, IL-17A and IL-17F have also been shown to activate MAPK, extracellular signal-regulated kinase (ERK), p38 and c-Jun N-terminal kinase (JNK) [105]. Recently, JNK signaling was shown to be required for IL-17 driven inflammatory cytokine and antimicrobial peptide production in epithelial cells and the lung [106]. IL-17 may also impact mRNA stability pathways downstream of Act1 that are independent of TRAF6 [107]. In addition, IL-17RD deficiency results in enhanced IL-17A-induced activation of NF-κB and IL-6 and keratinocyte chemoattractant (KC) expression [99]. IL-17RD disrupts the interaction of Act1 and TRAF6 causing differential regulation of NF-κB and p38 mitogen-

activated protein kinase signaling pathways [99]. Deletion of the IL-17R SEFIR domain or Act1 results in impaired IL-17 signaling and activation of NF-κB [108]. Many IL-17 target genes contain AP-1 DNA binding motifs that may be sites for direct regulation of transcription [109]. 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 [110].

To activate target cells, IL-22 signals through a heterodimeric receptor complex comprised of IL-22R1 and IL-10R2. Although IL-10R2 is present on the many immune cells, IL-22R1 is expressed predominantly on endothelial and epithelial cells [111]. Savan *et al.* demonstrated that the restriction of IL-22R1 to non-hematopoietic cells is biologically significant as transgenic mice that artificially expressed IL-22R1 on lymphocytes developed normally, but acquired lethal multi-organ inflammation 2-3 months after birth [112]. Similar to IL-10, IL-22 signaling activates STAT3 [90,113], that induces STAT3 signaling and the suppressor of the cytokine signaling (SOCS)-3 [114-116]. Upon binding of IL-22 to its receptor tyrosine kinases Jak1 and Tyk2 are phosphorylated, which in turn activates STAT1, STAT3 and STAT5 [111,117]. Similar to IL-17, IL-22 also activates the JAK/STAT, ERK, JNK and p38 MAPK pathways [117]. An endogenous antagonist of IL-22, IL-22 binding protein (IL-22BP), regulates the bioavailability of IL-22 thereby inhibiting IL-22-driven STAT3 activation [118]. The immune role of IL-22BP in the lung is currently unclear.

## Role of IL-17 in asthma

Asthma is a common respiratory disease affecting approximately 300 million people worldwide with no broadly effective preventions or cures. Atopic asthma is driven by the development and recruitment of $CD4^+$ T lymphocytes to the lungs and is characterized by pulmonary inflammation, mucus hypersecretion and airway hyperresponsiveness (AHR). Asthma is traditionally viewed as an eosinophilic airway disorder and a great deal of research has focused on the role of Th 2 cells and cytokines (IL-4, IL-5 and IL-13) in promoting disease pathogenesis. However, Th17 cells, which mediate neutrophil recruitment, are known to play an influential role in asthma pathogenesis, especially in asthmatics who have severe disease and fail to respond to glucocorticoid therapy. Studies have also indicated IL-23-induced Th17 cell effector function, which was impaired in gene variant carriers of the protective allele *IL-23R R381Q* resulting in significantly reduced IL-17A production and STAT3 phosphorylation, which supports a critical role for the IL-23/IL-23R signaling in generating pathogenic Th17 responses [119].

IL-17 is known to be strongly upregulated in asthma [120] as serum and airway IL-17 mRNA and protein levels are found to be elevated in asthmatics [121-124]. The increased level of IL-17A and IL-17F in the lung directly correlates with disease severity (i.e., increased AHR to methacholine) [125,126]. In addition, Zhao *et al.* showed that the percentage of Th17 cells and the IL-17 and IL-22 levels correlated with increased disease severity [127]. The antigenic drivers of the IL-17 response in asthma are currently unclear. A recent study suggests that IL-17 levels are higher in asthmatics with elevated IgE compared to asthmatics with low IgE [128]. Another study showed that IL-17 production by T cells in response to *Dermatophagoides farinae* extract was significantly induced in atopic

asthmatics when compared to nonatopic asthmatics and normal controls [120]. Together, these results suggest that IL-17 may play a larger role in atopic asthma. The association of an IL-17F polymorphism (His161Arg) with asthma suggests that IL-17F plays an important role in asthma pathogenesis [129]. Further, IL-17F was also reported in cells from the bronchoalveolar lavage following antigen stimulation in patients with asthma [130].

IL-17 plays a critical role in driving neutrophil influx into the airways [122]. Specifically, IL-17A drives the production of neutrophil growth factors and chemokines, such as IL-6, granulocyte-colony stimulating factor (G-CSF), KC and macrophage inflammatory protein (MIP)-2/IL-8 that are known to be elevated in some asthmatics [131]. Overexpression of IL-17F in the lung also results in increased neutrophilic inflammation in the airspaces [132]. Further, IL-17A and IL-17F induce human fibroblasts to produce IL-6 and IL-8, which serve to activate and promote the expansion of these cells [74]. Several studies have shown that the extent of airway neutrophilia correlates to asthma severity [133-135]. Indeed, asthmatics with neutrophilic inflammation exhibit decreased improvement in forced expiratory volume in one second ($FEV_1$) and airway responsiveness following glucocorticoid treatment [136]. Furthermore, neutrophils are known to be largely steroid-insensitive and glucocorticoids are known to inhibit neutrophil apoptosis [137,138], which may account for the increase in neutrophils observed in the lungs.

Animal models of the allergic airway disease have also established a causative link between Th17 cells and glucocorticoid-insensitive allergic airway disease in mice [139]. The model described by McKinley *et al.*, is characterized by elevated neutrophil chemokines, growth factors and neutrophilic inflammation in the lung. Transfer of ovalbumin (OVA)-specific Th17 cells to donor mice resulted in neutrophilic inflammation, AHR and mucus metaplasia following OVA challenge, which could not be attenuated by glucocorticoid treatment [139]. This study showed that Th17 cells are sufficient to promote many of the hallmark characteristics of asthma *in vivo* and that this response was steroid insensitive, unlike many Th2-dependent models utilized in asthma research.

IL-17 has been shown to play a regulatory role in allergic airway disease in animal models, although many findings are somewhat contradictory. IL-17 was shown to synergize with IL-4 and IL-13 to enhance Th2 cytokines and CCL11 in a murine OVA model [140,141]. However, neutralization of IL-17A prior to OVA challenge increased airway eosinophilia and Th2 cytokines levels in the lungs, while decreasing neutrophilia [142,143]. IL-17R−/− mice displayed decreased eosinophilia in the airways, IgE, and Th2 cytokines following OVA [144]. Consistent with this, studies have shown that IL-17 neutralization or downregulation inhibit $T_H2$-driven disease [145,146]. Although, anti-IL-17 monoclonal antibodies (mAb), given repeatedly after OVA challenge in OVA-sensitized mice, reduced bronchial neutrophilic influx but aggravated allergen-induced bronchial eosinophilia [143]. Exogenous IL-17A treatment also decreased eosinophil recruitment and bronchial hyperreactivity in mice [144]. Overall, these studies suggest that IL-17 may both promote and inhibit Th2 driven airway inflammation and AHR depending on the context and conditions of the study. Additional work is necessary to define the role of IL-17 in asthma and will require distinct modeling of asthma phenotypes.

Besides its role in inflammation, IL-17 is implicated in airway remodeling, which is more prominent in chronic steroid-resistant disease [125,143]. Indeed, IL-17 induces gene expression of mucins (Muc5ac and Muc5b) in human bronchial and murine epithelial cells [147]. Oda *et al.* found that overexpression of IL-17F increased goblet cell hyperplasia and mucin expression in mice [132]. Further, IL-17A was reported to increase IL-6 and IL-11 production in human bronchial fibroblasts and thus may promote remodeling [148]. IL-17 can directly induce steroid insensitivity in bronchial epithelial cells [149]. In murine models of the allergic airway disease, IL-17 has been shown to control bronchial hyperresponsiveness and airway remodeling. Further, IL-17A has been shown to have direct effects on bronchial smooth muscle cell contractility [150]. Together, these findings show that IL-17 may contribute to asthma pathogenesis by inducing airway remodeling in addition to inflammatory effects.

IL-23 is also thought to have an important role in severe asthma as it is a key molecule for Th17 cell propagation. In a murine asthma model, IL-23 levels were elevated in lung homogenates and IL-23p19 mRNA was induced upon antigen inhalation in the lung of antigen-sensitized mice [151]. In this study, IL-23 also enhanced antigen-induced activation of both Th17 and Th2 cells and administration of anti-IL-23p19 antibodies lessened airway inflammation and Th2 cytokine production [151]. Specific roles for IL-23 in asthma are currently emerging.

## IL-22 in asthma

IL-22 is thought to play a dual role in the allergic airway disease, as recent studies have shown that this Th17-related cytokine exhibits both pro-inflammatory and anti-inflammatory properties. The pro-inflammatory properties of IL-22 are demonstrated as IL-22 is detected at the sites of allergic airway inflammation [152]. In fact, it was reported that serum levels of IL-22 are higher in patients with severe asthma than those seen in patients with mild asthma and healthy control subjects [127]. In addition, blocking IL-22 during Th2 sensitization significantly decreased eosinophilic inflammation, Th2 cytokine production, AHR and mucus hyperplasia in a mouse model of asthma. On the other hand, studies showed that IL-22 neutralization during allergen challenge increased airway inflammation and Th2 cytokine production and that treatment with recombinant IL-22 during allergen challenge attenuated it [153,154]. These somewhat contradictory data illustrate the critical importance of study design when modeling human asthma. IL-22 is also thought to promote epithelial repairs through the production of antimicrobial peptides (AMP) and by suppressing production of pro-inflammatory cytokines and chemokines. These findings suggest that the functions of IL-22 are influenced by the inflammatory milieu present in the lung. Indeed, IL-17A influences the proinflammatory and pathological versus protective role of IL-22 in the lung [155]. Sonnenberg and colleagues found that in the absence of IL-17A, IL-22 serves a tissue-protective role, while when IL-17A is present IL-22 contributes to the disease pathogenesis in a model of airway inflammation [155].

## Role of IL-17 in host defense

In addition to its role in asthma, IL-17 plays a key role in pulmonary host defense by inducing chemokine production for neutrophil emigration into infected tissues and regulating the production of AMPs (Table 1). It protects against pathogenic microorganisms at the mucosa, although may contribute to tissue injury in chronic biofilm infections that occur in patients with cystic fibrosis and bronchiectasis [156].

IL-17 is protective in several models of gram-negative bacterial infection including extracellular *Klebsiella pneumoniae* [157,158]. Mice with homozygous deletion of IL-17RA have increased mortality and bacterial dissemination compared to wild-type controls following challenge with *K. pneumoniae*. They have reduced production of G-CSF and MIP-2 with a delay in neutrophil recruitment to the alveolar space [158]. Mice that receive exogenous IL-17A prior to *K. pneumoniae* have increased production of G-CSF and MIP-2 with improved survival and bacterial clearance [157]. Mice that produce decreased amounts of IL-17A and IL-17F due to a homozygous deletion in IL-23p19 have increased mortality from *K. pneumoniae* [159]. Recently, a role for IL-17 in promoting serotype-independent antibody immunity against *K. pneumoniae* has been demonstrated [160]. It has also been shown that mice infected with the intracellular pathogen, *Francisella tularensis*, have increased numbers of IL-17 producing cells in the lung and increased IL-17 in the bronchoalveolar lavage fluid [161]. IL-17 is critical to the clearance of *F. tularensis* and helps mediate the Th1 response against tularemia [162]. IL-17 is elevated in response to *Bordatella pertussis* infection and IL-17 helps mediate vaccine-induced cellular immunity protection against *B. pertussis* [163-166]. In acute *Pseudomonas aeruginosa* infection, IL-17 levels are increased and the late recruitment of neutrophils is dependent on IL-17 [167,168]. Vaccine induced protection against acute *P. aeruginosa* pneumonia is thought to be IL-17 dependent [169].

In addition to gram-negative bacteria, IL-17 is protective in several models of gram-positive infection. Multiple cells make IL-17 in response to *Staphylococcus aureus* pneumonia, including Th17 and γδ T cells [170]. IL-17R−/− challenged with *S. aureus* have decreased bacterial clearance, decreased G-CSF and decreased IL-6 production compared to wild-type controls [170]. Mice that have a homozygous deletion for the T cell receptor δ chain and lack γδT cell receptor expression have decreased production of KC, MIP-2, GM-CSF, IL-6 and TNF-α in response to *S. aureus* pneumonia. As expected, they have decreased neutrophil recruitment and increased bacterial burden of *S. aureus* in the lung [171]. Studies have also shown that IL-17 is required for the recruitment of neutrophils that facilitate the clearance of colonized *S. pneumoniae* from the mucosa of the nasopharynx [172]. In addition, IL-17 levels are increased in mice during acute S. pneumoniae pneumonia [173]. In the murine model of chlamydial pneumonia, IL-17 was critical for preventing bacterial clearance and dissemination as well as decreasing mortality [174]. Interestingly, the intracellular bacterium *Mycobacterium tuberculosis* and *Mycobacterium bovis* do not require IL-17 for clearance, although IL-17−/− mice have an altered inflammatory response to mycobacterial challenge [175-177]. Studies show that IL-17 plays a role in vaccine-induced immunity against *M. tuberculosis* by prompting the release of chemokines that recruit IFN-γ producing T cells [178].

IL-17 also plays a key role in host defense against viral and fungal pathogens. Crowe and colleagues found that IL-17R−/− mice had decreased lung inflammation, weight loss and mortality without attenuation of viral clearance from the lungs compared to wild-type mice after lethal influenza A infection [179]. These data show that IL-17 is required for acute lung injury during influenza A infection. However, others have shown that IL-17 deletion of neutralization resulted in worsened influenza-induced weight loss and mortality [180,181]. In humans, rhinovirus synergizes with IL-17 to enhance IL-8 production by epithelial cells, which may help to promote the recruitment of immune cells to the airway [182]. Although these data suggest that neutralization of IL-17 may be beneficial in viral pneumonia, bacterial pneumonia following viral infection is associated with increased mortality. Mice that are co-infected with influenza and *S. aureus* have decreased levels of IL-17, decreased chemokines G-SCF and KC, and increased bacterial burden compared to mice that receive *S. aureus* alone [170]. Similarly, mice infected with influenza followed by *S. pneumoniae* have decreased levels of IL-17, increase bacterial burden and increased mortality compared to mice that received *S. pneumoniae* alone [183]. In both studies, it is suggested that Type 1 IFN induction by influenza results in suppression of IL-17 and IL-22 production in the lung. These data suggest a mechanism by which influenza may promote subsequent bacterial infection. Regarding fungal pathogens, IL-17 neutralization in mice leads to impaired fungal clearance in both *Pneumocystis carinii* and *Aspergillus fumigatus* models [184,185]. Authors have also suggested that IL-17 interferes with antifungal immunity against *A. fumigatus* [186]. Interestingly, IL-17 has been found to play an integral part in vaccine induced immunity against multiple fungal pathogens that cause disease in North America including *Blastomyces dermatitidis, Coccidioides posadasii* and *Histoplasma capsulatum* [187].

Cystic fibrosis (CF) is a disorder caused by abnormalities in the CF transmembrane conductance regulator protein, which results in failure of transcellular chloride absorption and subsequent elevation of sodium and chloride in the airway surface liquid. Patients with CF have chronic airway infection and inflammation, which leads to a progressive decline in lung function. Common infectious pathogens in CF patients include *P. aeruginosa* and *A. fumigatus*. *P. aeruginosa* most often becomes a chronic biofilm infection in patients with CF and those colonized with *P. aeruginosa* have a more rapid decline in lung function compared to others. IL-17 has been linked to CF: patients colonized with P. aeruginosa have elevated levels of IL-17 and IL-23 in sputum during a pulmonary exacerbation [188]. Analysis of the airway submucosa has revealed that IL-17 producing cells are present [189]. In a recent study by Chan *et al.*, explanted lungs from patients with CF undergoing transplantation were found to have antigen (*P. aeruginosa* and *A. fumigatus*)-responsive IL-17 and IL-22 positive cells [190]. Further, Tiringer and colleagues found that elevated IL-17 levels negatively correlated with $FEV_1$ in patients with CF, proposing that IL-17 may contribute to a decline in the lung function. Elevated IL-17 levels were also predictive of future *P. aeruginosa* acquisition in this study [191]. In a murine model of mucoid *P. aeruginosa*, mice with a homozygous deletion in IL-23p19 produce decreased amounts of IL-17. They have similar bacterial burden but reduced airway inflammation compared to controls [156]. In a murine pulmonary aspergillosis model, IL-17−/− mice had improved fungal clearance and reduced airway inflammation compared to controls [192]. Although the

specific role of IL-17 in CF remains unclear, the IL-23/Th17 axis has proved important. IL-17 may promote tissue injury and even make patients more susceptible to primary acquisition of chronic biofilm infections. Further, recent studies have shown that salt promotes the differentiation of CD4+ T lymphocytes to Th17 cells [62,63]. The role of environmental factors on this axis is still largely unexplored, but these findings suggest that high-salt concentration of the airway surface liquid of CF patients may contribute to disease by promoting tissue inflammation and Th17-mediated disease.

## IL-22 & host defense

IL-22 is critical for maintaining the integrity of the epithelium in the lung upon exposure to injurious and infectious agents and is believed to be mainly protective and regenerative [75,193,194]. IL-22 also acts synergistically with IL-17 to induce the production of multiple AMPs, including but not limited to β-defensins, S100 proteins, regenerating islet-derived protein (Reg) 3 β and γ and lipocalin 2, suggesting a role in bacterial clearance [20,175]. Similar to IL-17, deletion of IL-22 results in impaired host defense against gram-negative bacteria. IL-22 levels are increased during infection with *K. pneumonia* and the neutralization of IL-22 results in increased morbidity and mortality [175]. In a model of gram-positive *S. aureus* pneumonia, the deletion of IL-22 results in decreased bacterial clearance [170]. IL-22 protein levels are increased in human bronchoalveolar lavage fluid from patients with *M. tuberculosis* disease and peripheral blood from healthy adults that have been exposed to *M. tuberculosis* have IL-22 producing $CD4^+$ T cells [195]. Dectin-1-dependent interleukin-22 production contributes to early innate lung defense against *A. fumigatus* and lung inflammation and immunopathology associated with persistent fungal exposure [196,197].

The role of IL-22 in anti-viral host defense and virus-associated inflammation has also been studied. Although neutralization of IL-22 in mice does not affect disease mortality resulting from H1N1 influenza A infection [198,199], IL-22 has been shown to protect bronchial epithelial cells against damage cause by influenza A virus [200] and thought to participate in airway epithelial cell regeneration 7–18 days after H1N1 influenza A virus infection [201]. Recently, IL-22 was observed to play a critical role in lung repair following H1N1 influenza A infection in mice. At 21st day following infection, IL-22 null mice (compared to wild-type) had increased lung injury, decreased lung function, decreased epithelial metaplasia and altered gene expression of genes known to be involved in epithelial repair [202]. In addition, during sublethal H3N2 influenza A infection, IL-22 functions to protect against respiratory tissue damage and decreases susceptibility to secondary bacterial infections [203]. In influenza, *S. aureus* co-infection models that display severe lung injury, IL-22 levels are suppressed (similar to IL-17) compared to *S. aureus* alone [170]. These data suggest that a primary role of IL-22 during lung injury is maintenance of epithelial integrity and promotion of repair.

## Conclusion

In this review, the primary pathways that regulate Th17 immunity in disease have been discussed. Many discoveries have been made regarding the molecular regulation of this

subset of T cells. The primary secretory cytokines, IL-17 and IL-22, have been the focus of many recent studies in both mouse and man. Herein, the current role of these cytokines in asthma and host defense was described (Figure 3). It is now clear that these pathways are critical immune regulators in many diseases ranging from infectious to allergic to autoimmune disorders.

## Expert commentary

Th17 immunity encompasses a broad range of functions and roles in the lung. In addition to these, Th17 cells regulate autoimmunity in many organ systems, which has been reviewed elsewhere [28]. Th17 cells and IL-17 and IL-22 also play critical host defense roles in the intestine and other mucosal sites. The pharmaceutical potential in the Th17 pathway has been targeted in diseases such as psoriasis, Crohn's disease and rheumatoid arthritis. Antibodies against IL-17 and IL-23 are the subject of several completed and ongoing clinical trials. Recently, anti-IL-17 therapy has begun to be tested in asthma. Data that show that the Th17 pathway may be critical in steroid insensitive, refractory asthma is enticing. Disease processes that are predominantly characterized by inflammatory (neutrophilic) pathologies present the highest probability of efficacy for drugs against the Th17 pathway. The therapeutic potential of targeting IL-17, IL-22 and/or IL-23 in acute lung injury is largely unknown. Data from several animal models suggest that lung injury can be alleviated by blocking Th17-driven inflammation. Further, it may be possible to separate the inflammatory damage induced by Th17 cytokine activation from the host defense mechanisms in order to preserve pathogen clearance and lung integrity. Due the fact that the Th17 pathway has broad action in many disease states, it will likely be difficult to target the detrimental roles of these cytokines without attenuating the beneficial functions. Therapeutic design will have to show great care to achieve improved patient outcome. As we have seen thus far, blocking the autoimmune inflammation promoting activity of IL-17 has not resulted in serious host defense side effects however, diligence is necessary as we move forward.

## Five-year view

The Th17 lineage of T cells has yet to see its 10th birthday, however much has been discovered. Despite this, there are many critical issues to be resolved as the field moves forward. It is now clear that many immune cell types produce IL-17 and IL-22 in disease models. Over the next few years, the field must define which cell types are critical in each circumstance. This information is essential to understand the mechanisms of immunity, allergy and autoimmunity. Much of the literature is well stocked with contradictory findings regarding cellular sources and even IL-17 and IL-22 function. It is a significant challenge to design better animal models and to translate current findings into human disease to better resolve these uncertainties. While the pro-inflammatory functions of IL-17 are fairly well known, additional roles of IL-17 are rapidly emerging. It is likely that neutrophil recruitment will only comprise one area of IL-17 biology. For IL-22, the epithelial protective/repair role has just recently been described. IL-22 may very well represent the yin to IL-17's yang during the normal host defense response. To better understand these cytokines' action, the field will need to better resolve which lung cells are responding to the stimuli and the downstream networks that are essential to pathogen clearance. In the last 5 years, our

understanding about Th17 cells, IL-17 and IL-22 has moved forward tremendously. The field has grown substantially in terms of publications and focused research grants. If the current pace is maintained, we should expect to have better answers to many of these questions when the calendar turns to 2018.

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**Key issues**

- The Th17 lineage of T cells was first described in 2006 and is characterized by expression of retinoic acid-related orphan receptor α (RORα), retinoic acid-related orphan receptor γ thymus (RORγT) and STAT3.
- Several cytokines, such as IL-6, IL-1β, TGF-β, IL-21 and IL-23 positively regulate Th17 polarization and function.
- Th17 cells are opposed by the functions of Type 1 and 2 interferons, IL-27 and IL-4.
- Segmented filamentous bacteria in the gut microbiome regulate Th17 (and $T_{reg}$) priming and likely impact lung immunity.
- Th17 cells (and several additional lymphocytes) secrete IL-17 and IL-22 as effector cytokines.
- IL-17 primarily enhances inflammation by inducing chemokine and growth factor production by the lung epithelium. IL-17 and IL-22 stimulate antimicrobial peptide production and IL-22 regulates epithelial repair.
- IL-17, IL-22 and IL-23 all play emerging roles in asthma and allergy which may be both beneficial and detrimental depending on context.
- In host defense, IL-17, IL-22 and IL-23 promote pathogen clearance, drive inflammation and orchestrate epithelial repair.

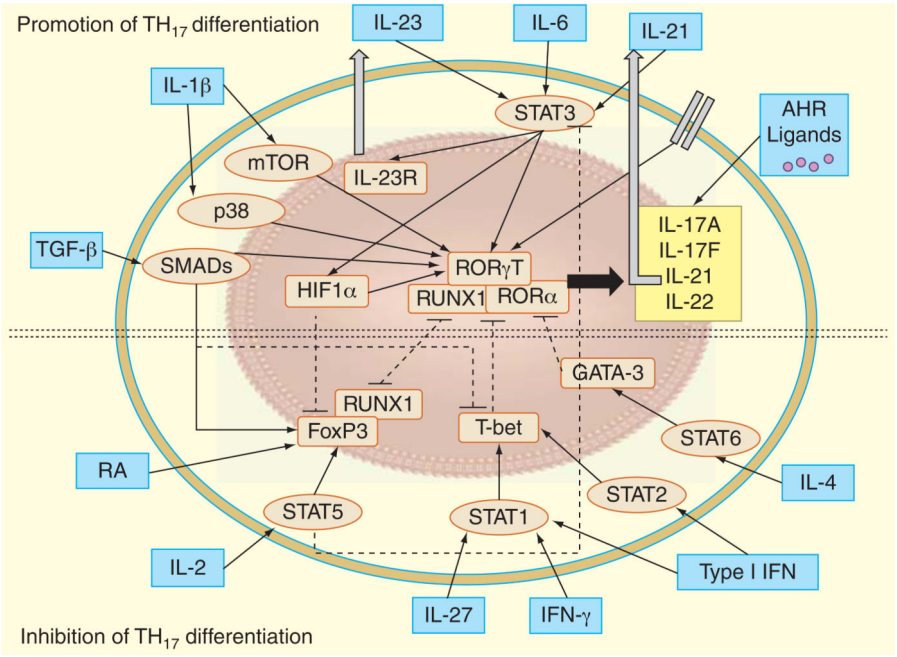


**Figure 1. Regulation of Th17 differentiation**

Th17 cells are induced upon TCR ligation with presented antigen from dendritic cells in the presence of the cytokines, IL-6, IL-23 and IL-21, which activate signal STAT3. The transcription factors RORγT and RORα activate expression of gene encoding Th17-related cytokine, IL-17A, IL-17F, IL-21 and IL-22. Once secreted, IL-21 acts in an autocrine fashion to further promote Th17 differentiation and proliferation. Further, STAT3 activation *via* IL-6 increases the expression of IL-23R, thus causing the Th cell to be more sensitive to the polarizing effects of IL-23. Activation of STAT3 also increases expression of HIF1α, which inhibits FoxP3 expression and promotes Th17 polarization. IL-1β promotes Th17 differentiation by activating the AKT/ mTOR and p38 MAPK. TGF-β signals through SMADs to promote Th17 differentiation by activating RORγT and RORα and limiting T-box transcription factor TBX21 (T-bet) expression. Further, TGF-β in conjunction with RA and STAT5 activation via IL-2 can increase FoxP3 expression to promote $T_{reg}$ formation. When stimulated with exogenous ligand, aryl hydrocarbon receptors in the cytosol cause Th17 cells to produce IL-17 and also may negatively regulate STAT1 and STAT5 to enhance Th17 differentiation (not shown). Several cytokines that promote Th1 and Th2 cell polarization oppose Th17 polarization by inhibiting RORγT and RORα expression. For instance, Type 1 interferon signals through STAT1 and 2 signaling and IFN-γ and IL-27 *via* STAT1 to promote T-bet expression, which inhibits Th17 differentiation. Similarly, IL-4 activates STAT6 to promote the transcription factor GATA-3 expression that inhibits Th17 polarization. Both FoxP3 and RORγT form complexes with Runx1 and therefore regulate each other. RA is known to limit Th17 polarization. Arrowed lines (solid) indicate activation or production, while square lines (dotted) illustrate inhibition. IL-23R: IL-23 receptor; RA: Retinoic acid; RORα: RA-related orphan receptor α; RORγT: RA-related orphan receptor γ thymus; TCR: T-cell receptor; Th: T helper.

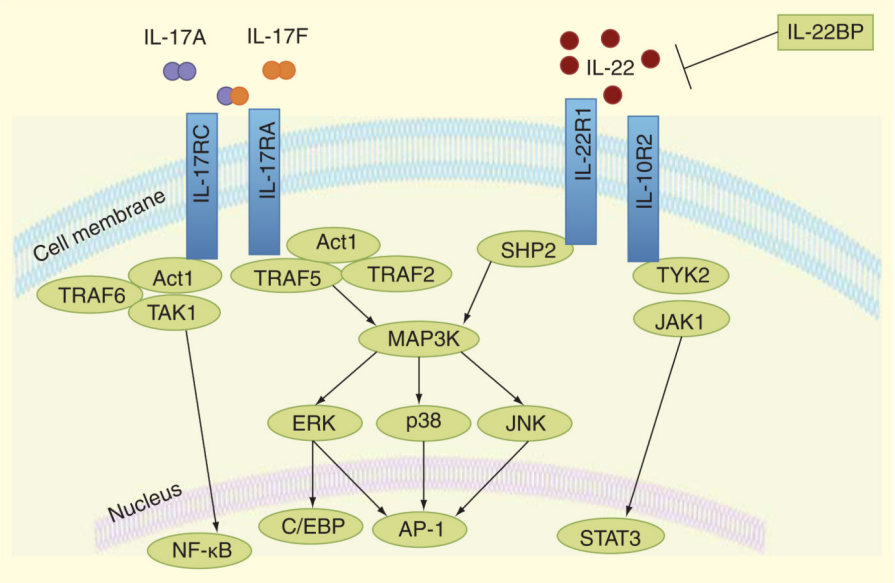


**Figure 2. IL-17 and IL-22 signaling pathways**

IL-17 and IL-22 bind to transmembrane heterodimeric cell surface receptors to induce cellular signaling pathways. Specifically, IL-17A or IL-17F binds to the IL-17RA and IL-17RC, respectively as homodimers or heterodimers. The binding of IL-17 to its receptor leads to the recruitment of adaptor protein and E3 ligase, Act1. Scaffold proteins TRAF6 and TAK1 interact with Act1 to activate NF-κB expression, which leads to subsequent induction of proinflammatory genes. IL-17 signaling through its receptor also induces ERK, p38, and JNK activation via Act1 binding with TRAF2 and TRAF5. Further, this MAP kinase activation can induce downstream signaling to activate AP-1 and CCAAT/enhancer binding protein (C/EBP). Receptor signaling of IL-22 through its heterodimer receptor of IL-10R2 and IL-22R1 induces phosphorylation of tyrosine kinases Jak1 and Tyk2, which activate the transcription factor STATs. In some cases, MAP kinases (ERK, p38, and JNK) are also activated through a distinct pathway following IL-22R activation. IL-22 binding protein (IL-22BP) acts as a soluble antagonist.

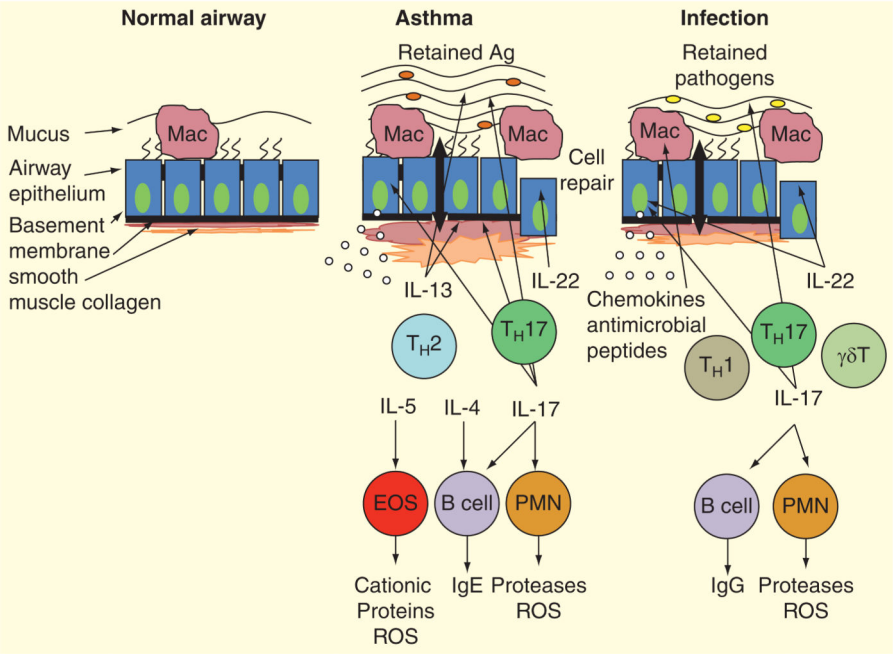


**Figure 3. The role of Th17 cytokines in asthma and infection**

The normal airway (left panel) is characterized by low or undetectable levels of Th17 cytokines. In the context of allergy (center panel), Th17 and Th2 cells likely interact to drive the airway changes characteristic of disease; mucus metaplasia, smooth muscle hypertrophy, airway wall thickening, and inflammation. IL-17 orchestrates neutrophilic inflammation via the airway epithelium production of chemokines and growth factors. IL-22 functions to regulate epithelial injury. The precise mechanisms by which Th17 cytokines interact with Th2 pathways remain unclear. During infection (right panel) Th17 cells and other sources of IL-17 and IL-22 drive inflammation and pathogen clearance. Many of these functions involve activation of the airway epithelium to produce chemokines and AMPs. It is likely that there is additional crosstalk with Th1 and IFN-γ regulated pathways in many contexts. Ag: Antigen; AMPs: Antimicrobial peptides; EOS: Eosinophils; Ig: Immunoglobulin; Mac: Alveolar macrophage; PMN: Polymorphonuclear cells; ROS: Reactive oxygen species.

**Table 1**

**The role of IL- 17 and IL- 22 in host defense**

| Pathogen | Overall | Experimental approaches | Ref. |
|---|---|---|---|
| ***Gram-negative bacteria*** | | | |
| *Klebsiella pneumoniae* | Protective | IL17RA−/− mice have increased mortality and bacterial dissemination | [158] |
| | | IL17RA−/− mice have reduced production of G-CSF and MIP- 2 and delayed neutrophil recruitment | [158] |
| | | Exogenous IL- 17 improves clearance | [157] |
| | | IL- 23p19−/− mice have increased mortality | [159] |
| | | IL- 17 induces heterologous antibody immunity | [160] |
| | | WT mice in which IL- 22 is neutralized have increased morbidity | [175] |
| *Francisella tularensis* | Protective | WT mice have increased IL- 17 producing cells in the lung and bronchoalveolar lavage fluid | [161] |
| | | IL17RA−/− and IL- 23a−/− mice have increased bacterial burden | [162] |
| *Bordatella pertussis* | Protective Vaccine response | *B. pertussis* drives Th17 polarization in human epithelial kidney cells | [164] |
| | | WT mice in which IL- 17 is neutralized have higher bacterial burden | [165] |
| | | Baboons with *B. pertussis* infection have higher levels of Th17 axis cytokines | [166] |
| | | Baboons following *B. pertussis* infection have circulating *B. pertussis*-specific Th17 cells 2 years post infection | [166] |
| *Pseudomonas aeruginosa* | Protective | WT mice have increased IL- 17 levels in response to acute *P. aeruginosa* infection | [167] |
| | | WT mice in which IL- 17 is neutralized have higher bacterial burden | [168] |
| | | IL- 23p19−/− mice similar bacterial burden, reduced airway inflammation | [156] |
| ***Gram-positive bacteria*** | | | |
| *Staphylococcal aureus* | Protective | IL17R−/− mice have decreased bacterial clearance and decreased G-CSF | [170] |
| | | γδTCR−/− mice have decreased IL- 17 associated chemokine production and decreased neutrophil recruitment | [171] |
| | | IL- 22 mice have decreased bacterial clearance | [170] |
| *Streptococcus pneumoniae* | Protective | WT mice in which IL- 17 is neutralized have decreased bacterial clearance and macrophage recruitment | [172] |
| | | WT mice have increased levels of IL- 17 during infection and γδTCR−/− mice have decreased levels of IL- 17 during infection | [173] |
| *Listeria monocytogenes* | ? | IL- 17R−/− mice have normal host defense | [175] |

| Pathogen | Overall | Experimental approaches | Ref. |
|---|---|---|---|
| *Chlamydia muridarum* | Protective | WT mice in which IL- 17 is neutralized have increased bacterial growth, dissemination and mortality | [174] |
| ***Acid-fast bacteria*** | | | |
| *Mycobacterium tuberculosis* | Vaccine response | IL17R−/− mice have no change in bacterial growth | [175] |
| | | IL- 23p19−/− mice have no change in bacterial growth although there are decreased CD4+ IL- 17-producing cells | [176] |
| | | Vaccinated WT mice in which IL- 17 is neutralized produce less antigen-specific IFN- γ-producing T cells | [178] |
| | | IL- 22 is produced in humans exposed to *M. tuberculosis* | [195] |
| *Mycobacterium bovis* | ? | IL- 17−/− mice have no change in bacterial growth but decreased granuloma formation | [177] |
| *Viruses* | | | |
| Influenza | ? | WT mice in which IL- 17 is neutralized have increased weight loss and increased mortality (H1N1) | [180] |
| | | IL- 17−/− mice have increased weight loss and increased mortality (H5N1) | [181] |
| | | IL- 17R−/− mice have decreased weight loss and increased survival (H1N1) | [179,198] |
| | | WT mice in which IL- 22 is neutralized have no change in morbidity, mortality (H1N1 and H3N2) | [200] |
| | | IL- 22 from iNKT cells prevents lung epithelial injury (H3N2) | [201] |
| | | IL- 22 from conventional NK cells promotes epithelial repair (H1N1) | [202] |
| | | IL- 22−/− mice have increased lung epithelial injury and decreased lung function (H1N1) | |
| Rhinovirus | ? | IL- 17 syngergizes with HRV in epithelial cells to induce IL- 8 | [182] |
| Viral/bacterial co-infection | Protective | WT mice co-infected with influenza AIS. aureus have increased bacterial burden, but decreased levels of IL- 17 and associated chemokines | [170] |
| | | WT mice co-infected with influenza AIS. pneumoniae have increased mortality and bacterial burden, but decreased levels of IL- 17 | [183] |
| | | IL- 22−/− mice co-infected with influenza AIS. pneumoniae have increased bacterial burden following sublethal influenza infection | [203] |
| *Fungi* | | | |
| *Pneumocystis carinii* | Protective | WT mice in which IL- 17 is neutralized have increased fungal burden | [185] |
| *Aspergillus fumigatus* | ? | WT mice in which IL- 17 is neutralized have increased fungal burden | [184] |
| | | IL- 17−/− mice have improved fungal clearance | [192] |
| | | IL- 17 promotes lung pathology and impedes clearance | [186] |

| Pathogen | Overall | Experimental approaches | Ref. |
|---|---|---|---|
| | | WT mice in which IL- 22 is neutralized have improved lung function | [196] |
| | | WT mice in which IL- 22 is neutralized have increased fungal burden | [197] |
| | | IL- 22−/− mice have increased fungal burden | [197] |
| *Blastomyces dermatitidis* | *Vaccine response* | Vaccinated WT mice in which IL- 17 is neutralized have increased fungal burden | [187] |
| | | Vaccinated IL- 17RA−/− mice have increased fungal burden | [187] |
| *Coccidioides posadasii* | Vaccine response | Vaccinated IL- 17RA−/− mice have increased fungal burden | [187] |
| *Histoplasma capsu latum* | Vaccine response | Vaccinated IL- 17RA−/− mice have increased fungal burden | [187] |

G-CSF: Granulocyte colony stimulating factor; MIP: Macrophage inflammatory protein; TCR: T cell receptor; WT: Wild-type.