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Directing traffic: IL-17 and IL-22 coordinate pulmonary immune defense

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Summary

Respiratory infections and diseases are among the leading causes of death worldwide, and effective treatments likely require manipulating the inflammatory response to pathogenic microbes or allergens. Here we review mechanisms controlling the production and functions of interleukin-17 (IL-17) and IL-22, cytokines that direct several aspects of lung immunity. Innate lymphocytes ($\gamma\delta$ T cells, natural killer cells, innate lymphoid cells) are the major source of IL-17 and IL-22 during acute infections, while CD4⁺ T-helper 17 (Th17) cells contribute to vaccine-induced immunity. The characterization of dendritic cell (DC) subsets has revealed their central roles in T-cell activation. CD11b⁺ DCs stimulated with bacteria or fungi secrete IL-1 β and IL-23, potent inducers of IL-17 and IL-22. On the other hand, recognition of viruses by plasmacytoid DCs inhibits IL-1 β and IL-23 release, increasing susceptibility to bacterial superinfections. IL-17 and IL-22 primarily act on the lung epithelium, inducing antimicrobial proteins and neutrophil chemoattractants. Recent studies found that stimulation of macrophages and DCs with IL-17 also contributes to anti-bacterial immunity, while IL-22 promotes epithelial proliferation and repair following injury. Chronic diseases such as asthma and chronic obstructive pulmonary disease have been associated with IL-17 and IL-22 responses directed against innocuous antigens. Future studies will evaluate the therapeutic efficacy of targeting the IL-17/IL-22 pathway in pulmonary inflammation.

Keywords

IL-17; IL-22; lung; T cell; immunity

Introduction

Aerosolization followed by inhalation is one of the most common routes for pathogen spread. The World Health Organization reported that lower respiratory tract infections, chronic obstructive pulmonary disease (COPD), and tuberculosis are the third, fourth, and seventh leading causes of death in the world, respectively (The Global Burden of Disease: 2004 Update). In the U.S., the economic cost of pneumonia was \$20 billion in 2008, while

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COPD and asthma were \$68 billion (Morbidity and Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, National Institutes of Health NHLBI). Therefore, vaccines that elicit immunological protection have potentially substantial economic value. Respiratory pathogens including bacteria, fungi, and viruses have evolved to live in specialized lung microenvironments or establish colonization when the opportunity arises in immunocompromised individuals. Each pathogen has its own growth and metabolic requirements and is faced with host defense strategies that restrict colonization. In addition, noninfectious antigens may cause chronic lung inflammation leading to asthma and COPD. This is generally associated with dysregulated tissue repair processes. Here, we highlight lung immune mechanisms, focusing on epithelial barriers, pathogen recognition, T-cell priming, and effector function with specific attention to the roles of IL-17 and IL-22. In addition, the impact of commensal microbiota on health and disease is discussed.

Pulmonary epithelial immune barriers

The airway epithelium provides a barrier to pathogen colonization while facilitating alveolar gas exchange. The lungs are a complex network of structural cells (ciliated, goblet, basal, secretory, alveolar), extracellular matrix (collagen, laminin), mucus, and leukocytes (1). Mucus secreted by goblet cells traps foreign particles, which are transported out of the lungs through the action of ciliated cells. Antimicrobial proteins such as β -defensins and lysozyme are secreted into the mucus and have broad-spectrum antimicrobial activity (2, 3). Microorganisms and debris that escape mucociliary clearance may reach the alveoli, where they are confronted with resident macrophages. The steady-state lung environment is generally anti-inflammatory, which is beneficial for efficient gas exchange through alveolar type I cells. Infections, oxidative damage, or proteolysis, may damage these cells, contributing to airway obstruction. Type I cells are replenished from the large pool of alveolar type II cells (4), which also secrete surfactants and antimicrobial factors to help maintain homeostasis (1). The cell types responsible for self-renewal in large airways are incompletely defined but include pulmonary neuroendocrine, basal and bronchoalveolar stem cells. Most of the time, these mechanisms eliminate microbes and repair damaged cells prior to any clinical signs of exposure/infection. Host genetics as well as changes in immune status or environment can sometimes lead to disease. Further, pathogens have adopted strategies to colonize lungs in the face of innate immune defense and adaptive immunity is required to eliminate them. As described throughout this review, IL-17 and IL-22 are cytokines that are primarily secreted by adaptive ($CD4^+$ T cells) or innate lymphocytes ($\gamma\delta^+$ T cells, NK cells, innate lymphoid cells) that influence the outcome of pulmonary infections, allergies, and injuries by acting on the epithelium.

Alveolar macrophages are among the first responders and directly kill extracellular bacteria through reactive nitrogen species. In addition, they secrete inflammatory cytokines that recruit neutrophils and lymphocytes to the site (1). The migration of neutrophils to infected areas is a multi-step process involving their transit through the endothelium, basement membrane and epithelial layer. This is in part accomplished by the release of proteolytic granules from neutrophils, which may cause collateral damage of parenchymal tissue (1). Transepithelial migration utilizes chemokine gradients, selectins, and integrins to provide directional cues and assist in paracellular transit to infected sites. Neutrophils are important

for killing extracellular bacteria and fungi through phagocytosis, release of reactive oxygen/nitrogen species and extracellular traps (1,5). Several models have demonstrated impaired neutrophil recruitment in the absence of IL-17 receptor signaling. These include bacterial and viral infections, asthma, and COPD (6–8). Human studies have supported these findings, as IL-17-induced neutrophil influx is linked to severe asthma (9). IL-17 mediates neutrophil recruitment to lungs by stimulating the secretion of G-CSF and CXC chemokines from respiratory epithelium (8). In the steady-state, very few IL-17-producing cells are present in the lungs; therefore, neutrophil recruitment is a multi-step process that requires pathogen detection, T-cell accumulation, and release of IL-17, which acts on respiratory epithelium to induce chemokine gradients.

Chronic exposure to irritants can result in dysregulated epithelial responses, leading to COPD or asthma. These are complex diseases driven by genetic factors, inflammation and epithelial repair. Moreover, the pathways leading to disease may be beneficial for the eradication of acute infections. For instance, cytokines (IL-1 β , IL-17, IL-13) and microbial products (LPS) induce mucus production, but excessive inflammation leads to goblet cell hyperplasia. In response to allergens and cigarette smoke, matrix metalloproteinases (MMPs) are upregulated and participate in airway remodeling by degrading the extracellular matrix and decreasing epithelial tight junction integrity (1,10). COPD and asthma are associated with increased numbers of airway macrophages, T cells and neutrophils. Corticosteroids are typically used to block inflammation, but severe asthmatics can be resistant to treatment (6). In these cases, IL-17 is linked to disease, and new therapies may be aimed at blocking the pathway upstream of IL-17 secretion.

IL-22 is another T cell-derived cytokine and has pro- or anti-inflammatory functions depending on the environment. In the presence of IL-17, IL-22 promotes lung inflammation (11). The same study found that IL-22 protects against pathology in the absence of IL-17, suggesting the IL-17R and IL-22R signaling pathways synergize to promote inflammation and some IL-22-inducible genes are IL-17-independent. Protective functions of IL-22 are linked to increasing airway epithelial cell proliferation (12), which is essential for repair following injury. Another study found IL-22 promotes the initiation of asthma in an animal model, but has anti-inflammatory functions during antigen challenge/exacerbation (13). The dual role of IL-22 in airway inflammation may be determined by whether or not effector T cells co-express IL-17. Thus, regulating IL-17 production without affecting IL-22 levels might improve lung function in subsets of patients with asthma or COPD.

In cystic fibrosis (CF), a dysfunctional CFTR on epithelium enhances and thickens airway mucus, resulting in impaired mucociliary clearance and chronic bacterial colonization. The most common pathogens isolated from CF patients include *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Cystic fibrosis foundation patient registry: Annual data report 2010). IL-17 is increased in the sputum of CF patients compared to controls (14), and therapy against *P. aeruginosa* during pulmonary exacerbations decreases IL-17 production (15). Further, lymph nodes of CF patients contain CD4⁺ IL-17⁺ IL-22⁺ T cells specific for *P. aeruginosa* antigens (16). This suggests a direct correlation between bacteria burden and IL-17 production. Acidification of the airways in CF patients decreases anti-microbial protein function (17), providing an explanation for increased colonization by opportunistic

pathogens. High bacteria burdens coupled with impaired anti-microbial activity may contribute to the pathologic effects associated with IL-17 in CF (reviewed in 18).

Pathogen recognition in lungs

Germline-encoded innate immune receptors detect the presence of microorganisms in lungs and other tissues. In general, conserved microbial structures such as lipoproteins or nucleic acids trigger pattern recognition receptors (PRRs), initiating inflammatory responses. Dendritic cells (DCs) activated through PRRs migrate to lymph nodes and present antigen to T cells, resulting in the generation of effector and memory T cells that target the specific infection. In this way, PRRs help to eliminate pathogens that evaded innate immunity. The characterization of PRRs and their signaling pathways in the last decade has broadened our understanding of host defense, and human studies have confirmed experimental data from animal models on the essential functions of PRRs.

Perhaps the best characterized immunomodulatory molecule is lipopolysaccharide (LPS), or endotoxin, on the cell wall of Gram-negative bacteria. This lipoprotein stimulates Toll-like receptor 4 (TLR4) (19). A prototypical member of the TLR family, TLR4 is a type I transmembrane protein with extracellular leucine-rich repeats for ligand recognition and an intracellular TIR domain for signaling (20). Upon LPS stimulation, TLR4 forms homodimers and recruits the signaling adapters MyD88 and TRIF to its TIR domain. MyD88 rapidly activates NF- κ B and mitogen-activated protein kinases (MAPKs), resulting in the expression of pro-inflammatory genes including *Tnf*, *Il6* and *Il1 β* (21). The TRIF signaling pathway activates IRF3, resulting in the production of type I IFNs which induce a plethora of interferon-stimulated genes (20,22). The MyD88 and TRIF signaling pathways are thought to fully account for LPS responsiveness.

The TLR family comprises 10 members in humans and 13 members in mice (23). In addition to TLR4, other cell surface TLRs also recognize structural components of microbes including bacterial peptidoglycan (TLR2), flagellin (TLR5), and protozoan profilin (TLR11). On the other hand, TLRs localized to endocytic compartments recognize nucleic acids including viral double-stranded RNA (TLR3), single-stranded RNA (TLR7, TLR8), or bacterial DNA (TLR9) (20). The expression of TLRs is also compartmentalized at the cellular level. For instance, the expression of TLR7 and TLR9 by plasmacytoid DCs is required for the type I IFN response during viral infections (24). Some of the genes induced by TLRs will inactivate NF- κ B, preventing excessive inflammation. Negative regulation of TLR signaling occurs through the dissociation of adaptor complexes, degradation of signaling proteins and transcriptional downregulation (25). For instance, Toll IL-1R8 reduces inflammatory pathology and IL-17 levels following pulmonary fungal infection by inhibiting IL-1R signaling (26). Some pathogens, including Vaccinia virus and *Mycobacterium tuberculosis*, produce proteins that negatively regulate TLR signaling in order to evade host immunity. Several cells in the lung express TLRs, including airway epithelial cells, alveolar macrophages and pulmonary dendritic cells (DCs) (2). The contribution of TLR expression by airway epithelial cells to host defense is much less studied than TLR expression on DCs. Of note, parenchymal MyD88 expression restricts the

early growth of *P. aeruginosa* following infection and augments CXC chemokine release (27), suggesting that TLR signaling in epithelium contributes to phagocyte recruitment.

Mice that are defective in TLR4 signaling are susceptible to pulmonary infections with *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *M. tuberculosis* (28,29). The inability of *Tlr4*-deficient mice to control bacterial growth is due to impaired production of inflammatory cytokines. *Klebsiella pneumoniae* induces several genes required for neutrophil activation/recruitment, growth factors and adhesion molecules in a *Tlr4*-dependent manner (30). MyD88 and TRIF signaling pathways both contribute to host defense against *K. pneumoniae*, with MyD88 having a more integral role (31). Humans with the TLR4 alleles Asp299Gly and Thr399Ile have an increased prevalence of septic shock and infections, respectively, caused by Gram-negative bacteria (32). Functionally, the Asp299Gly mutation inhibits MyD88 and TRIF recruitment to the TLR4 intracellular domain, resulting in decreased cytokine production following LPS stimulation (33, 34). This mutation is associated with an increased prevalence of severe pulmonary tuberculosis (35), although it is not clear if direct recognition of mycobacteria by TLR4 contributes to the phenotype or if basal TLR4 stimulation conditions the immune system non-specifically to resist infection. During chronic viral infections including SARS and influenza, activation of the TLR4/TRIF pathway in alveolar macrophages has a pathogenic role via recognition of oxidized phospholipids (36). The dual role of TLR4 in providing immunity to bacterial infections and inducing acute lung injury demonstrates the challenge the lung faces when responding to multiple insults, and also the therapeutic potential of TLR negative regulators.

Another family of proteins involved in lung immunity are NOD-like receptors (NLRs), containing a cytosolic C-terminal leucine-rich repeat domain, central NOD domain, and N-terminal effector domain (37). This family is expressed both in the epithelium and leukocytes. NLRC family members contain an effector caspase recruitment domain that activates NF- κ B, while NLRP family members contain a pyrin domain that activates the inflammasome. The NLRC members NOD1 and NOD2 recognize peptidoglycan structures, contribute to protection against several bacteria and increase susceptibility to sarcoidosis and asthma (37). Inflammasomes consist of an NLRP protein, ASC, and pro-caspase-1. Activation of caspase-1 then results in the processing of pro-IL-1 β and IL-18 into active cytokines. Inflammasomes are activated by a variety of stimuli including microbial products, molecules released from dying cells and reactive oxygen species that are induced from a disruption of host cell physiology (37). Acute lung injury can lead to fibrosis through NLRP3, and the caspase-1/IL-1 β pathways are implicated in COPD, demonstrating that chronic inflammasome activation has detrimental effects on lung physiology. Inflammasome-dependent IL-17 production has been implicated in the pathogenesis of asthma and fibrosis (38,39), but protects from bacterial and fungal infections (40). Future studies may determine specific cell populations that must express NLRs for their biological effects.

The RIG-I-like receptor (RLR) family consists of the cytoplasmic RNA sensors named RIG-I, MDA5, LGP2, that induce type I IFNs through IRF3 and IRF7 (41). These proteins protect against virus infections but inhibit IL-17 release, increasing susceptibility to bacterial pneumonia after viral infection (42). IRF3 binds to the *Il12b* promoter, blocking TLR-

dependent induction of IL-12/23p40 and subsequent release of IFN- γ and IL-17 from effector CD4⁺ T cells (43). Signaling through the type I IFN receptor also directly inhibits the release of neutrophil chemoattractants from macrophages (44), and IFN- γ produced in response to influenza inhibits macrophage phagocytic activity and expression of the scavenger receptor MARCO (45). This demonstrates that co-infections can result from immune suppression induced by viruses. Interestingly, CD8⁺ T cells that produce IL-17 are protective against influenza independently of perforin and granzyme (46), demonstrating that heterogeneity within T-cell populations can compensate for immune suppression induced by pathogens.

Pulmonary DCs and Th17 immunity

DCs are CD11c⁺ MHC II^{high} cells that present antigens on MHC class II molecules to CD4⁺ T cells. CD11c is an α integrin that pairs with CD18 to form complement receptor 4 and also functions as an adhesion molecule. In the steady-state, CD11c is primarily expressed on myeloid cells but its expression is inducible on activated lymphocytes (47) (Fig. 1). The three major DC subsets in lungs are CD103⁺ CD8 α ⁺, CD11b⁺, and plasmacytoid (48). CD103⁺ and plasmacytoid DCs are found in the conducting airways in contact with epithelium, whereas CD11b⁺ DCs reside in parenchymal tissue. It is important to distinguish lung DCs from alveolar macrophages which also express CD11c. Alveolar macrophages are identified as F4/80⁺ MHC II^{low} and are autofluorescent (48). Although macrophages phagocytose microbes and secrete cytokines that recruit leukocytes, DCs initiate adaptive immune responses by activating CD4⁺ T cells. Specifically, CD103⁺ CD8 α ⁺ DCs cross-present viral antigens to CD8⁺ T cells (49), and CD11b⁺ DCs present fungal antigens to CD4⁺ T cells (50). The DC subset that primes protective CD4⁺ T-cell immunity may be pathogen-dependent. Another distinct subset of CD11b⁺ MAR-1⁺ monocyte-derived DCs is recruited to lungs during inflammation and may play a role in the reactivation of memory T cells rather than inducing primary responses (48).

IL-17 was identified in 1995 as a T cell-derived cytokine with similarity to a gene encoded by herpesvirus Saimiri (51, 52). Stimulating memory but not naive CD4⁺ T cells with IL-23 induces IL-17 secretion (53), suggesting the potential to release IL-17 is regulated through antigen-dependent interactions with DCs. Naive CD4⁺ T cells interact with DCs in lymph nodes through T-cell receptor:antigen:MHC class II complexes. This interaction is insufficient for T-cell activation and can lead to tolerance or non-responsiveness (54). T-cell activation also requires the binding of CD28 to its ligands CD80 and CD86 expressed on DCs. Together, these signals will activate NFAT and NF- κ B transcription factors in antigen-specific T cells. The effector function of CD4⁺ T cells is determined by the cytokine milieu provided by DCs. The combination of TGF- β plus IL-6 induces a Th17 differentiation program mediated by the transcription factors ROR γ t and ROR α (55). Expression of integrin α v β 8 on DCs is required for activation of TGF- β and Th17 differentiation (56, 57). Effector Th17 cells are heterogeneous but typically produce IL-17A (IL-17), IL-17F, IL-21, and IL-22 among other cytokines. IL-21 is an autocrine cytokine that potentiates Th17 differentiation, while IL-17, IL-17F, and IL-22 are effector cytokines that stimulate mucosal epithelium. In the absence of IL-6, TGF- β will promote regulatory T-cell (Treg) differentiation through the induction of Foxp3 (55). IL-23 is important for the terminal

differentiation and clonal expansion of effector Th17 cells *in vivo* (58). Another subset, termed Th22, is induced by IL-6 and IL-23 in the absence of TGF- β (59). This population is IL-22⁺IL-17⁻ and contributes to intestinal immunity but their role in lung host defense is undefined. Finally, a subset of Th17 cells has been found to develop in the thymus rather than periphery. These natural Th17 cells require MHC class II expression on thymic medullary epithelium and preferentially express TCR V β 3 (60). Although natural Th17 cells can traffic to the lungs (61), their role in lung inflammation has not been examined.

During fungal infection, CD11b⁺ DCs are required for optimal Th17 differentiation (50, 62). This is attributed to their expression of the transcription factor IRF4, leading to increased production of IL-6 and IL-23 from CD11b⁺ DCs relative to CD103⁺ DCs (50). Dectin-1 signaling, possibly in DCs, promotes Th17 differentiation by inhibiting the expression of T-bet and upregulating ROR γ t in T cells (62). In humans, myeloid DCs analogous to the murine CD11b⁺ subset have been implicated in driving pathogenic Th17 responses during emphysema (63). Although CD11b⁺ DCs induce Th17 differentiation *in vivo*, *in vitro* experiments revealed that CD103⁺ DCs are capable of supporting IL-17 production (64). This finding suggests that functional specialization of DC subsets *in vivo* may be determined by their anatomical localization, type of infection, and cytokine environment rather than intrinsic qualities. CD11b⁺ DCs are infected by *Mycobacterium tuberculosis*, leading to antigen presentation in lymph nodes and protective Th1 differentiation; however, *M. tuberculosis* induces anti-inflammatory Tregs early following infection, inhibiting the recruitment of effector T cells (65). This demonstrates that pathogens can modulate DC functions to promote tissue colonization. Developing a vaccine that generates Th17 cells instead of Tregs could have therapeutic value for *M. tuberculosis* and other pathogens.

Interactions between DCs and CD4⁺ T cells also contribute to DC activation. Notably, CD40L on the surface of T cells stimulates CD40 on DCs, increasing their surface expression of costimulatory molecules and secretion of cytokines including IL-12 (66). IL-17 also enhances IL-12p70 secretion from DCs, supporting Th1 responses (67). Further, macrophages stimulated with IL-17 produce IL-12, IFN- γ , CCL20, and MMP12 and have increased bactericidal activity (63, 67). This mechanism of DC activation may contribute to protective effects of vaccine-induced Th17 cells against *M. tuberculosis* (68). A similar finding was reported for fungal infection in which IL-17 augmented the accumulation of IFN- γ -producing Th1 cells in lungs (69). This was associated with increased expression of MHC class II and CD80/86 on CD11c⁺ CD11b⁺ cells. These findings revealed a novel role for IL-17 in promoting Th1 immunity to intracellular bacteria and fungi.

Innate cellular sources of IL-17 and IL-22

$\gamma\delta$ T cells are the major IL-17-producing population in naive animals (70). These cells develop in the thymus, where TGF- β and Notch signaling induces IL-17-producing potential (71,72). Interestingly, naive $\gamma\delta$ T cells make IL-17, whereas the presence of antigen induces IFN- γ production (71). CD27 expression may be a marker for antigenic stimulation, as $\gamma\delta$ T-cell subsets were characterized as exclusive CD27⁺ IFN- γ ⁺ or CD27⁻ IL-17⁺ populations (73). Thymic epithelial cells can control $\gamma\delta$ T-cell fate, as Skint-1⁺ epithelium inhibits IL-17 production (74). The mechanism by which this occurs is through inhibition of Sox13, a

transcription factor upstream of ROR γ t. In the periphery, IL-1 β or IL-18 synergizes with IL-23 to induce IL-17 secretion from $\gamma\delta$ T cells, demonstrating that inflammasome activation is necessary for optimal IL-17 production (75).

Innate lymphoid cells (ILCs) have lymphoid morphology but lack antigen receptors and myeloid/DC markers (76). This broad category includes NK cells and lymphoid tissue-inducer cells. ILCs are important for immunity at barrier surfaces including the lungs. The common cytokine receptor γ chain (IL-2R γ), ID2, and IL-7R α are required for ILC development, although NK cells use IL-15R α instead of IL-7R α (76). ILCs are analogous to CD4⁺ T-helper subsets and have been named according to their cytokine profile. ILC1 cells express T-bet and produce IFN- γ , ILC2 cells express GATA3 and produce IL-5/IL-13, and ILC3 cells express ROR γ t and secrete IL-17 and/or IL-22. ILC phenotypes are also plastic, as NKp46⁺ ILC3s convert into ILC1s when stimulated with IL-12 and IL-18, resulting in their downregulation of ROR γ t and upregulation of T-bet (76). Coexpression of GATA3 and ROR α has been observed in ILC2 cells, suggesting possible functional similarities with ILC3s. Specific functions for ILC subsets have been identified, as ILC2 cells expressing GATA3 and IL-33R are pathogenic in allergen-induced asthma (77, 78), while ILC3 cells contribute to obesity-induced asthma (79). Consuming a high-fat diet results in NLRP3-dependent IL-1 β production from macrophages, triggering IL-17 release from CCR6⁺ ILC3 cells and airway hyperreactivity. Further, severe asthma patients have an increased prevalence of ILC3-like cells residing in airways with IL-17-producing potential (79). These data demonstrate the pathologic potential of antigen-independent IL-17 release from ILC3 cells, and that targeting this pathway with IL-1 receptor antagonism may alleviate symptoms during exacerbations.

IL-22 is controlled by similar factors that influence IL-17 production. Although Th17 cells co-produce IL-17 and IL-22, $\gamma\delta$ T cells and ILCs are known to produce IL-22 independently of IL-17. The cytokines IL-1 β , IL-6, and TGF- β stimulate IL-22 production from $\gamma\delta$ T cells in non-human primates (80). These cells migrate to lungs during *M. tuberculosis* infection and reside in granulomas, although antigen stimulation decreases IL-22 and upregulates IFN- γ production. The aryl hydrocarbon receptor (AhR) is required for IL-22 production in $\gamma\delta$ T cells (81). AhR is pleiotropic and has ligand-dependent effects on Th17- and Treg-differentiation, suggesting it may act *in trans* with other transcription factors or its biological effects are determined by T-cell epigenetics. Recently, lactobacilli were shown to produce the AhR agonist indole-3-aldehyde in the stomach, inducing IL-22 production from NKp46⁺ ILCs (82). This enhances resistance to *Candida albicans* infection, demonstrating that metabolic products of commensal metabolism support host defense. Additional AhR ligands that influence IL-22 production *in vivo* are being studied. Interleukin-23 is another factor that stimulates ROR γ t⁺ NK cells to secrete IL-22 (76). Future studies are needed to understand the regulation of ILC development *in vivo*, the plasticity of ILC subsets, and their roles in specific diseases.

IL-17 and IL-22 receptor signaling

The IL-17 receptor (IL-17R) family comprises five members that function as heteromeric complexes (83). The subunits are single transmembrane proteins with extracellular

fibronectin III domains and intracellular SEFIR domains that recruit the signaling adaptor Act1. Their expression is prominent on mucosal epithelium, endothelium and fibroblasts but is also detected on leukocytes. IL-17A and the closely related cytokine IL-17F signal through IL-17RA/RC, activating the MAPK, canonical NF- κ B and C/EBP β pathways (83). In addition, Act1 signaling increases the stability of mRNAs such as *CSF3* or *CXCL1* that are induced by IL-17 (84,85). Although they stimulate the same receptor, IL-17A induces a more potent response than IL-17F, and the influence of IL-17A/F heterodimers on host defense and inflammation is largely unknown. IL-17RA expression is ubiquitous while IL-17RC is primarily limited to non-immune cells including epithelium (83). In addition to its essential role in IL-17A- and IL-17F-responsiveness, IL-17RA couples with IL-17RB to detect IL-17E, or IL-25.

IL-17 stimulates the basolateral surface of human respiratory epithelium and synergizes with TNF to induce GRO- α and G-CSF secretion (15). During *Klebsiella pneumoniae* infection, IL-17RA is required for the induction of G-CSF and neutrophil recruitment (8). By enhancing bicarbonate secretion in a CFTR-dependent manner, IL-17 contributes to alkalization of airway surface liquid (86). This process may be abnormal in CF, resulting in acidic airways with impaired microbicidal activity (17). IL-17 also stimulates mucous cell metaplasia (87). Thus, IL-17 has multiple effects on lung epithelial cell function.

IL-22 is an IL-10 family member, and its receptor is a heterodimer of IL-22R1 and IL-10R2 (88). IL-22R1 is expressed on non-immune cells in outer body barriers such as the skin, digestive tract, and respiratory tract (88, 89). In addition, IL-22R1 has been found on pancreas, liver, joints, and thymic epithelium and functions as a receptor for the related cytokines IL-20 and IL-24. The binding of IL-22 to IL-22R1 recruits IL-10R2 to the complex and primarily stimulates the STAT3, MAPK, and PI3K pathways, although activation of STAT1 and STAT5 has also been observed (88). Negative regulation of IL-22 bioactivity occurs through the secretion of IL-22-binding protein (IL-22BP) by immature DCs. This is a secreted receptor that binds to soluble IL-22 with higher affinity than IL-22R1 and functions as an antagonist (88). Although intestinal CD103⁺ CD11b⁺ DCs were found to secrete IL-22BP (90), the role of endogenous IL-22BP in pulmonary host defense has not been characterized. In airway epithelium, IL-22 induces the secretion of antibacterial proteins and chemokines, and also augments cell proliferation and repair following injury. Synergism with IL-17 has been demonstrated, as the IL-17 plus IL-22 combination induces the expression of MMP members that may contribute to emphysema (10). As described below, pro- versus anti-inflammatory functions of IL-22 may be determined by the lung microenvironment.

IL-17 in lung immunity

The roles of Th17 effector cytokines in host defense have been extensively reviewed. Here we discuss key findings with model pathogens that highlight their primary functions in lung inflammation. IL-17RA^{-/-} mice are highly susceptible to pulmonary infection with *Klebsiella pneumoniae* (8). This extracellular Gram-negative bacterium causes nosocomial infections including pneumonia in immunocompromised individuals (91). The TLR4 pathway induces IL-23 which triggers IL-17 release early following infection (92),

suggesting a protective role for innate lymphocytes or pre-formed memory T cells. The related cytokines IL-12 and IL-23 contribute to immunity by augmenting Th1 and Th17 cell responses, respectively (93). Detection of bacterial products by TLR4 and TLR9 are required for optimal production of both IFN- γ and IL-17, demonstrating cooperative effects between cell surface and intracellular TLRs (94). IL-17 stimulates the epithelium to release chemokines that augment neutrophil recruitment, preventing bacterial dissemination (8). Alcoholism is linked to bacterial pneumonia, and alcohol inhibits the production of IL-23 and IL-17 following infection (95, 96). Adenoviral delivery of IL-17 restores survival of ethanol-treated mice during *K. pneumoniae* challenge (96), demonstrating that immune pathways downstream of IL-17R signaling are intact following ethanol consumption. Dissecting the role of TLR expression by individual DC subsets can help us to understand the mechanisms of innate IL-17 release during acute bacterial infections.

During primary *M. tuberculosis* infection, IL-23 drives Th17 cell accumulation but is not required for controlling bacterial burden (97). Another study found that IL-17RA contributes to long-term control of *M. tuberculosis* infection (98), suggesting an important role for Th17 cells in memory or secondary immune responses. In mice and humans, $\gamma\delta$ T cells are the main source of IL-17 following *M. tuberculosis* infection (99, 100). PRRs that are implicated in *M. tuberculosis* recognition and contribute to IL-17 induction include Dectin-1 and TLR4 (101), while TLR2 signaling helps to maintain Th17 cells at the site of infection (102). IL-17 is important for early neutrophil recruitment, granuloma formation and Th1 cell accumulation following infection (103). Patients with active tuberculosis have elevated frequencies of Th17 cells in peripheral blood that respond to mycobacterial antigens (104,105). While these data demonstrate potent induction of IL-17 following *M. tuberculosis* infection, the IFN- γ response is essential for limiting bacterial growth and dissemination. As described below, IL-17 is critical for vaccine-induced immunity by augmenting Th1 responses.

Influenza viruses are segmented negative stranded RNA viruses that target airway epithelial cells (106). Antibodies are protective against reinfections with the same serotype; however, they do not provide heterosubtypic immunity to serologically distinct viruses. CD8⁺ T cells recognize influenza antigens from internal conserved proteins and help to clear infections through perforin or Fas-dependent mechanisms (106). During heterosubtypic challenges, IL-17⁺ IFN- γ ⁺ CD8⁺ T cells protect against weightloss and mortality (46). Another study identified a pathogenic role for IL-17RA signaling during primary influenza infections, increasing weight loss, myeloperoxidase activity, and oxidized phospholipids in lung tissue, with no effect on viral clearance (7). Further, IL-17 drives acute lung injury during experimental infection with the 2009 H1N1 pandemic virus (107). These data demonstrate that mechanisms contributing to anti-bacterial immunity have potential to cause pathology when directed against virus-infected cells. Although influenza induces anti-viral IL-17 production, it potently inhibits Th17 immunity towards secondary bacterial infections. Specifically, type I IFNs produced in response to the virus increases susceptibility to the Gram-positive pathogens *Streptococcus pneumoniae* and *S. aureus* and blocks neutrophil recruitment (42, 44, 108). The mechanism by which type I IFNs downregulate Th17-type immunity appears to be through TLR desensitization in alveolar macrophages or DCs (109),

inhibiting their release of IL-23 and IL-1 β in response to bacteria (42, 110). Therefore, modulation of Th17 immunity by influenza viruses enhances lung pathology and susceptibility to secondary bacterial pneumonia.

Aspergillus fumigatus is an opportunistic fungal pathogen that infects immunocompromised hosts (111). Normally, *A. fumigatus* is rapidly cleared by alveolar macrophages and neutrophils. IFN- γ -producing Th1 cells are protective against invasive aspergillosis, preventing dissemination from the lungs (112). Since *A. fumigatus* is a ubiquitous soil fungus, pre-formed memory Th1 cells may contribute to natural resistance. The IL-23/IL-17 pathway is a negative regulator of protective Th1 responses against *A. fumigatus* and causes lung pathology through neutrophil recruitment (113). Perhaps Dectin-1 stimulation of DCs induces IL-23, subverting a protective Th1 response in favor of IL-17. Factors that determine the balance of IL-12 versus IL-23 following conidia exposure may include fungal load or immune status of the host. In a model of chronic granulomatous disease with defective neutrophil function, $\gamma\delta$ T cells are the source of IL-17 that causes acute lung injury (114). Production of IL-17 is inhibited by the tryptophan metabolite L-kynurenine, which depends on NADPH oxidase activity. The lack of L-kynurenine in *p47^{phox}-deficient* mice leads to unrestrained IL-17 production (114). In immunocompetent hosts, Dectin-1-mediated induction of IL-17 is protective, augmenting anti-fungal responses from alveolar macrophages and neutrophils (115). The related receptor Dectin-2 is required for Th17 differentiation following systemic fungal infection (116,117), but its role in lung immunity is not fully characterized. Other PRRs involved in fungal recognition include Mincle, DC-SIGN, and CD206 (118). As described below, IL-17 also contributes to fungal allergies. Overall, the role of IL-17 in pulmonary anti-fungal immunity is complex and may be determined by the local inflammatory milieu.

IL-22 in lung immunity

IL-22 protects against bacterial pneumonia through multiple mechanisms. Stimulating bronchial epithelial cells with the combination of IL-17 and IL-22 induces the expression of antimicrobial genes including *Lcn2* (encoding lipocalin-2) and *DEFB4* (β -defensin 2) (12). IL-22 also increases lung epithelial cell proliferation and repair following injury. In these ways, IL-22 helps to maintain the lung epithelial barrier. Although IL-22 by itself has minimal effects on G-CSF and IL-6 secretion, it synergizes with IL-17 to stimulate large amounts of these cytokines (12). These defense pathways cooperate to limit *K. pneumoniae* growth in the lungs and dissemination. During acute infections with *K. pneumoniae*, IL-22 is produced by multiple cell types including CD4⁺ T cells, $\gamma\delta$ T cells, and NK cells. A recent study found that NK cells are sufficient for IL-22 production and have protective functions in normal mice and mice lacking T cells (119). Although the innate IL-22 response to *K. pneumoniae* contributes to host defense, stimulating adaptive immunity through vaccination is necessary to prevent mortality, as described below.

Following *A. fumigatus* infection, the Dectin-1/IL-23 pathway induces IL-22 production, enhancing fungal clearance (120). The increased fungal burdens in *Il22*^{-/-} mice are associated with increased IL-17 levels. It appears that rather than regulating IL-17 directly, IL-22 augments airway anti-fungal activity (120), which could indirectly lower local IL-17

production. CD4⁺ T cells are the major IL-22 producing subset in human PBMCs stimulated with *A. fumigatus* (121). Although memory T-cell markers and the role of T-cell receptor signaling were not assessed, IL-22 production was dependent on IL-1 receptor signaling. Following *Candida albicans* infection, production of IL-22 by ILCs protects against *P. aeruginosa*-induced lung injury (122). This protection may be associated with epithelial repair that has been observed during *K. pneumoniae* infection. Therefore, IL-22 reduces airway fungal burden and release of IL-22 by ILCs provides cross-protection against bacteria.

During influenza infection, IL-22 produced by NK or iNKT cells contributes to the regeneration of damaged tracheal epithelial cells (123, 124). Similar to other lymphocytes, NK and iNKT cells secrete IL-22 in response to the DC products IL-23 and IL-1 β (124, 125). Although the IL-22R is localized to airway epithelium prior to infection, it is upregulated at parenchymal sites of lung remodeling induced by influenza (89). The defective epithelial regeneration observed in *Il22*^{-/-} mice correlates with increased collagen deposition, consistent with development of a fibrotic phenotype. Conventional $\alpha\beta$ T cells and $\gamma\delta$ T cells are also sources of IL-22 in response to influenza, and survival following a superinfection with *Streptococcus pneumoniae* requires IL-22 (126). This was attributed to protective effects of IL-22 on pulmonary epithelium. Overall, the role of IL-22 in host defense complements that of IL-17, with synergistic effects (cytokine and anti-microbial protein release) and non-redundant functions (epithelial repair/regeneration).

IL-17 and IL-22 in asthma and inflammation

Severe asthma is linked to increased levels of IL-17, IL-17F, and neutrophils in lung tissue (9, 127). IL-17 contributes to airway remodeling and hyperresponsiveness through goblet cell hyperplasia and smooth muscle contraction, respectively (9, 57). While airway hyperresponsiveness induced by Th2 cells is treatable with dexamethasone, Th17 cell-induced pathology and neutrophilic inflammation were found to be steroid-resistant (128). In contrast to dexamethasone, vitamin D potently suppresses IL-17 production in T cells cultured from severe asthmatics (129). Further, patients with allergic bronchopulmonary aspergillosis have decreased serum vitamin D levels compared to control patients (130). Although vitamin D directly inhibits T-cell function (129), it also blocks OX40L expression in DCs, inhibiting Th2 cell differentiation (130, 131). During *A. fumigatus*-induced allergy, fungal recognition by TLR6 augments production of IL-23 and IL-17, but also protects against airway hyperresponsiveness and inflammation (132). This suggests that IL-17 is not sufficient to cause allergic disease and that other cytokines might modulate events downstream of IL-17R signaling.

The role of IL-22 in allergic responses is also complex. During chronic exposure to *A. fumigatus*, Dectin-1-mediated induction of IL-22 contributes to lung pathology and impaired function (133). IL-22 is capable of inducing airway smooth muscle cell proliferation, which may contribute to airway remodeling (134). In a model of Th2-induced lung inflammation, IL-22 was protective and reduced levels of IL-13 and IL-25, resulting in decreased eosinophil recruitment and goblet cell hyperplasia (135). Antibody-mediated depletion was used to more carefully examine the dual role of IL-22 in allergic airway inflammation (13).

Depleting IL-22 during allergen sensitization resulted in decreased levels of IL-5, eosinophils and lung pathology. During antigen challenge, IL-22 neutralization significantly increased these inflammatory markers (13). The authors concluded that IL-22 contributes to the onset of asthma but negatively regulates established allergic inflammation. In this model, CD4⁺ T cells are the major IL-17 producers and increase following IL-22 depletion (13). Further, IL-17 promoted allergic lung inflammation in normal mice but was anti-inflammatory in *Il22*^{-/-} mice. This suggests that pro- versus anti-inflammatory effects of IL-17 are determined by IL-22. The converse is also true, as a model of bleomycin-induced inflammation found that IL-22 is tissue protective in the absence of IL-17 but pathogenic in its presence (11). Overall, understanding the cross-regulation between IL-17 and IL-22 effector responses will have therapeutic implications for treating allergic diseases such as asthma.

IL-17 and vaccine-induced immunity

Innate immunity is essential for detecting the presence of infections and initiating the inflammatory cascade that results in phagocyte recruitment and pathogen containment. When the innate immune system is not sufficient to combat infections, effector CD4 T cells play instrumental roles in pathogen clearance (136). During the weeks and months following infection, a pool of Ag-specific memory T cells persists in the host, capable of mounting a rapid recall response to a secondary encounter with the same pathogen. The benefits of memory T-cell responses include (i) antigen specificity that can limit bystander damage to the host, (ii) increased precursor cell numbers capable of controlling high inoculums of the pathogen, and (iii) rapid effector cytokine responses that proceed within hours rather than days following infection. A major goal of vaccine development is to generate memory CD4⁺ T cells and Th17 cells have recently emerged as important players in vaccine-induced protection (137).

Pretreating mice with an adenovirus construct expressing IL-17 protects against subsequent *K. pneumoniae* infection (138), suggesting that memory Th17 cells could help to prevent Gram-negative pneumonia. Indeed, vaccinating mice with *K. pneumoniae* extract induces Th17 cells specific for conserved outer membrane proteins that mediate bacterial clearance through neutrophils (139). This is a model of heterologous immunity, in which protection is conferred against multiple serotypes of bacteria that express clade-specific antigens. A similar finding was reported for *Pseudomonas aeruginosa*, in which a live attenuated vaccine protected against challenges with LPS heterologous strains (140). IL-17 was detected in bronchoalveolar lavage fluid as early as 6 h following challenge, contributing to lung neutrophil recruitment. Although vaccination with the non-related organism *Escherichia coli* also increased neutrophils following challenge, this was not sufficient to decrease bacterial burdens (140), suggesting a non-redundant role for antigen-specific Th17 cells. The TLR4 pathway is required for vaccine induced immunity to *Bordetella pertussis* (141). In this study, production of IL-23 and IL-1 β by DCs contributed to Th17 cell differentiation, and IL-17 increased bacterial clearance and enhanced macrophage bactericidal activity in a dose-dependent fashion. Likewise, the Gram-positive pathogen *S. pneumoniae* has several capsular polysaccharide serotypes, and serotype-independent vaccine efficacy depends on IL-17-mediated neutrophil recruitment (142–144). Therefore,

vaccine-induced Th17 cells provide serotype-independent immunity to Gram-positive and Gram-negative pathogens by enhancing neutrophil- and macrophage-mediated clearance.

Resistance to *M. tuberculosis* is mediated by IFN- γ and BCG vaccination accelerates pulmonary Th1 immunity following challenge (68). Protection was dependent on IL-23 and IL-17, leading to increased production of CXCR3 ligands required for Th1 cell recruitment. Further, IL-17 indirectly augments Th1 cell accumulation by inhibiting vaccine-induced IL-10 production (145). Mucosally delivered vaccines for *M. tuberculosis* preferentially induce Th17 cells and provide Th1-independent immunity (146). IL-17 contributes to granuloma formation and *Cxcl13* expression, increasing the localization of CXCR5⁺ T cells to lymphoid structures. In this model, Th17 and CXCR5⁺ cells protect by enhancing macrophage bactericidal activity (146). In addition to protective effects of Th17 cells, NK cells producing IL-22 are required for BCG vaccine efficacy (147). NK cell depletion at the time of vaccination increases regulatory T-cell accumulation and bacillary burden. Exogenous IL-22 rescued the effect of NK cell depletion, enhancing memory CD4⁺ T-cell accumulation in the lungs (147). Finally, antigen load and immunization timing are important factors to consider, as repeated BCG vaccinations after *M. tuberculosis* infection causes lung damage in an IL-23 and IL-17-dependent manner (148). These data demonstrate non-redundant functions for IL-17 and IL-22 in vaccine-induced protection from chronic bacterial infections.

Th17 cells also provide vaccine-induced immunity against fungi. Specifically, IL-17 protects against *Blastomyces dermatitidis* by enhancing phagocyte recruitment and function (149). Vaccine-induced resistance required MyD88 signaling but not Dectin-1, suggesting a dominant role for TLR signaling. In the absence of CD4⁺ T cells, CD8⁺ T cells compensate and produce IL-17 following vaccination (150). Effective vaccination against *Coccidioides posadasii* requires IL-17R signaling but not IL-17A (151), suggesting that other IL-17 family members such as IL-17F contribute to immunity. Future studies should examine the impact of vaccine-induced Th17 responses on superinfections, as IL-17-inducing adjuvants exacerbate lung pathology during influenza challenges (152).

Microbiota and lung inflammation

The immune system is in constant contact with microbes and must be fully developed to control pathogenic infections. Many of the innate immune signals required for lymphoid tissue maturation are provided by commensal microbiota (153). Germ-free animals have decreased germinal centers and antibody responses in the gut. Commensals also provide nutrients to the host and competitively inhibit pathogen colonization. Overall, having a diverse microbiota primes the immune system to initiate robust responses to infections. Many studies have evaluated intestinal microbiota, but relatively few have examined lungs. This is important given the prevalence of microbes that are transmitted through aerosol. Technical advances and a developing appreciation have resulted in lung microbiota becoming an emerging area of research (154).

To characterize entire populations of microbes, unbiased culture-independent strategies are necessary. Gel electrophoresis methods such as terminal restriction fragment length

polymorphism or denaturing gradient gel electrophoresis of a biomarker gene provide a fingerprint of the most highly abundant members, and can identify shifts in dominant community members (155). A more sensitive technique is to PCR amplify conserved ribosomal RNA regions in bacteria or fungi, followed by sequencing to reveal microbial diversity at the phylogenetic and family levels. Although ribosomal sequencing is useful for studying the impact of disease on diversity, changes in microbial metabolism independent of species prevalence will go unnoticed with this technique. One challenge in studying metabolism is to purify sufficient quantities of microbial RNA from mammalian tissues. An advantage of metabolic profiling is that it can reveal novel competitive interactions among organisms which can be studied using animal models. As described below, most studies in humans have measured lung species diversity using 16S rRNA sequencing.

The lung microbiome is variable between individuals and throughout the bronchopulmonary tree. The nostrils and oropharynx primarily contain *Firmicutes/Actinobacteria* and *Firmicutes/Proteobacteria/Bacteroidetes*, respectively (156). The lung microbiome is similar to that in upper airways but has less biomass by a factor of 2–4 logs (157). Some species, including *Enterobacteriaceae*, *Haemophilus*, *Methylobacterium*, and *Ralstonia*, are more highly represented in the lower respiratory tract than the mouth, suggesting the lung microbiome does not entirely derive from the mouth (158). One question that remains is the stability of lung microbiota throughout life. In CF patients, *S. aureus* is the number one pathogen isolated until the age range 18–24, when *P. aeruginosa* becomes the most prevalent (Cystic fibrosis foundation patient registry: Annual data report 2010). This suggests developmental and environmental factors influence the lung microbiome. Further, smoking was found to affect bacteria species recovered from the mouth but not lungs (158). Future studies may examine microbial metabolism in lungs of patients with chronic inflammatory diseases. This information could reveal potential causes or effects of disease. The oral fungal ‘mycobiome’ also has extensive diversity. One study identified 85 fungal genera, with significant variation among people (159). The most prevalent genera include *Candida* and *Cladosporium*. There is a paucity of studies on lung-resident viruses, although a model of AIDS found that pathogenic enteric infections are capable of expanding the enteric virome (160). This suggests a potential role for T cells in limiting commensal virus replication. Due to the degree of variation observed in lung microbiota, epidemiological and longitudinal studies will be helpful to grasp the factors that control colonization.

Loss of microbiota diversity is a hallmark of chronic inflammatory disease, correlating with FEV1 measurements (155,161,162). In CF, depletion of the airway surface liquid layer generates a permissive environment for colonization through impaired mucociliary clearance. This may be one reason why *P. aeruginosa* and *Stenotrophomonas maltophilia* are abundant (161, 163). Further, exacerbations are associated with increased abundance of *Gemella* species (164). This does not prove a causal relationship but suggests it may be a biomarker of CF exacerbations. In contrast, anaerobic bacteria were associated with less inflammation and higher FEV1 levels (165). Patients with COPD, but not healthy controls, experienced an outgrowth of *Proteobacteria* including *Haemophilus influenzae* after rhinovirus infection (166). This suggests that changes to the immune tone of the lungs caused by long-term smoking significantly impacts bacterial colonization. *Proteobacteria*

were also more prevalent in the lower airways of patients with asthma, while *Bacteroidetes* were increased in healthy controls (167). In summary, several studies have analyzed the effects of disease on lung microbial composition (reviewed in 154, 168), and animal models will be useful for understanding their immunological roles.

The influence of intestinal commensals on systemic immunity is another burgeoning area of research. Animal models incorporate antibiotics to decrease species diversity or use germ-free facilities to control the environment. Neomycin-sensitive bacteria in the gut have a protective effect against influenza challenge (169). Commensal-driven inflammasome activation enhances DC migration to lung draining lymph nodes and subsequent T-cell priming. Further, macrophages from antibiotic-treated mice are hyporesponsive to influenza infection (170). This is due antibiotics decreasing tonic signaling through the type I IFN receptor, resulting in defective induction of an IFN gene program following infection. The authors concluded that commensal-derived signals calibrate the activation threshold of innate anti-viral immune responses (170). The PRRs required for tonic signaling in the steady-state are unknown but may include TLRs or NLRs. On the other hand, microbiota have anti-inflammatory functions during experimental asthma. Allergic airway inflammation was increased in germ-free mice relative to controls, marked by increased eosinophilia and lymphocytes (171). Another study identified vancomycin-sensitive bacteria in the gut, i.e. Gram-positive, as protective against experimental neonatal asthma (172). Studying the mechanisms of how intestinal microbiota influence pulmonary host defense will provide insight into immune surveillance and cross-talk between organs.

Conclusions

The last decade of research in pulmonary immunology identified key molecules required for pathogen detection and clearance, with IL-17 and IL-22 emerging as major effector cytokines. Recent studies have focused on the cellular mechanisms mediating inflammation (Fig. 2). Although PRRs for many pathogens have been delineated, their functional significance in distinct cell types such as the pulmonary epithelium, alveolar macrophages, DCs, and lymphocytes has not been examined. The degree to which DC subsets have overlapping versus non-redundant functions in T-cell priming is another interesting avenue (Fig. 1). Cytokine responses from DCs depend on their developmental history, anatomical residence, and basal stimulation in the steady-state. Thus, DC adoptive immunotherapy may be an effective strategy to regulate T-cell-mediated inflammation. DC immunotherapy is currently being explored as a treatment for cancer (173) and may benefit chronic infections as well. Innate lymphocyte-derived IL-17 is not always sufficient for pathogen clearance, demonstrating that memory CD4⁺ T cells are required to produce large quantities of IL-17 and to direct the IL-17 response towards specific antigens. A major challenge in vaccine design is to identify serotype-independent antigens in pathogens that elicit protection. Basic research has also revealed mechanisms through which some pathogens can immunosuppress their hosts, increasing susceptibility to superinfections. This exemplifies the cross-talk occurring among cytokine signaling pathways that the immune system must interpret on a daily basis. Of note, the abundance and diversity of our lung microbiota suggests it may condition our innate immune system in a similar manner as has been described for gut

commensals (170,174). Overall, understanding how IL-17 and IL-22 effects are regulated will benefit vaccine research and therapies for chronic inflammatory diseases.

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References

1. Tam A, Wadsworth S, Dorscheid D, Man SF, Sin DD. *Ther Adv Respir Dis.* 2011; 5:255–273. [PubMed: 21372121]
2. Bals R, Hiemstra PS. *Eur Respir J.* 2004; 23:327–333. [PubMed: 14979512]
3. Parker D, Prince A. *Am J Respir Cell Mol Biol.* 2011; 45:189–201. [PubMed: 21330463]
4. Barkauskas CE, Crouce MJ, Rackley CR, Bowie EJ, Keene DR, Stripp BR, Randell SH, Noble PW, Hogan BL. *J Clin Invest.* 2013; 123:3025–3036. [PubMed: 23921127]
5. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A. *Science.* 2004; 303:1532–1535. [PubMed: 15001782]
6. Alcorn JF, Crowe CR, Kolls JK. *Annu Rev Physiol.* 2010; 72:495–516. [PubMed: 20148686]
7. Crowe CR, Chen K, Pociask DA, Alcorn JF, Krivich C, Enelow RI, Ross TM, Witztum JL, Kolls JK. *J Immunol.* 2009; 183:5301–5310. [PubMed: 19783685]
8. Ye P, Rodriguez FH, Kanaly S, Stocking KL, Schurr J, Schwarzenberger P, Oliver P, Huang W, Zhang P, Zhang J, Shellito JE, Bagby GJ, Nelson S, Charrier K, Peschon JJ, Kolls JK. *J Exp Med.* 2001; 194:519–527. [PubMed: 11514607]
9. Manni ML, Robinson KR, Alcorn JF. *Expert Rev Respir Med.* 2014; 8:25–42. [PubMed: 24325586]
10. Chen K, Pociask DA, McAleer JP, Chan YR, Alcorn JF, Kreindler JL, Keyser MR, Shapiro SD, Houghton AM, Kolls JK, Zheng M. *PLoS One.* 2011; 6:e20333. [PubMed: 21647421]
11. Sonnenberg GF, Nair MG, Kirn TJ, Zaph C, Fouser LA, Artis D. *J Exp Med.* 2010; 207:1293–1305. [PubMed: 20498020]
12. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, Reinhart TA, McAllister F, Edeal J, Gaus K, Husain S, Kreindler JL, Dubin PJ, Pilewski JM, Myerburg MM, Mason CA, Iwakura Y, Kolls JK. *Nat Med.* 2008; 14:275–281. [PubMed: 18264110]
13. Besnard AG, Sabat R, Dumoutier L, Renaud JC, Willart M, Lambrecht B, Teixeira MM, Charron S, Fick L, Erard F, Warszawska K, Wolk K, Quesniaux V, Ryffel B, Togbe D. *Am J Respir Crit Care Med.* 2011; 183:1153–1163. [PubMed: 21297073]
14. Decraene A, Willems-Widyastuti A, Kasran A, De Boeck K, Bullens DM, Dupont LJ. *Respir Res.* 2010; 11:177. [PubMed: 21143945]
15. McAllister F, Henry A, Kreindler JL, Dubin PJ, Ulrich L, Steele C, Finder JD, Pilewski JM, Carreno BM, Goldman SJ, Pirhonen J, Kolls JK. *J Immunol.* 2005; 175:404–412. [PubMed: 15972674]
16. Chan YR, Chen K, Duncan SR, Lathrop KL, Latoche JD, Logar AJ, Pociask DA, Wahlberg BJ, Ray P, Ray A, Pilewski JM, Kolls JK. *J Allergy Clin Immunol.* 2013; 131:1117–1129. 1129 e1111–1115. [PubMed: 22795370]
17. Pezzulo AA, Tang XX, Hoegger MJ, Alaiwa MH, Ramachandran S, Moninger TO, Karp PH, Wohlford-Lenane CL, Haagsman HP, van Eijk M, Banfi B, Horswill AR, Stoltz DA, McCray PB Jr, Welsh MJ, Zabner J. *Nature.* 2012; 487:109–113. [PubMed: 22763554]
18. Way EE, Chen K, Kolls JK. *Eur J Immunol.* 2013; 43:3116–3124. [PubMed: 24130019]
19. Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X, Birdwell D, Alejos E, Silva M, Galanos C, Freudenberg M, Ricciardi-Castagnoli P, Layton B, Beutler B. *Science.* 1998; 282:2085–2088. [PubMed: 9851930]
20. Kumar H, Kawai T, Akira S. *Int Rev Immunol.* 2011; 30:16–34. [PubMed: 21235323]

21. Kawai T, Adachi O, Ogawa T, Takeda K, Akira S. *Immunity*. 1999; 11:115–122. [PubMed: 10435584]
22. Hoebe K, Du X, Georgel P, Janssen E, Tabeta K, Kim SO, Goode J, Lin P, Mann N, Mudd S, Crozat K, Sovath S, Han J, Beutler B. *Nature*. 2003; 424:743–748. [PubMed: 12872135]
23. Kawai T, Akira S. *Nat Immunol*. 2010; 11:373–384. [PubMed: 20404851]
24. Ito T, Wang YH, Liu YJ. *Springer Semin Immunopathol*. 2005; 26:221–229. [PubMed: 15592841]
25. Kondo T, Kawai T, Akira S. *Trends Immunol*. 2012; 33:449–458. [PubMed: 22721918]
26. Bozza S, Zelante T, Moretti S, Bonifazi P, DeLuca A, D'Angelo C, Giovannini G, Garlanda C, Boon L, Bistoni F, Puccetti P, Mantovani A, Romani L. *J Immunol*. 2008; 180:4022–4031. [PubMed: 18322211]
27. Hajjar AM, Harowicz H, Liggitt HD, Fink PJ, Wilson CB, Skerrett SJ. *Am J Respir Cell Mol Biol*. 2005; 33:470–475. [PubMed: 16100080]
28. Abel B, Thieblemont N, Quesniaux VJ, Brown N, Mpagi J, Miyake K, Bihl F, Ryffel B. *J Immunol*. 2002; 169:3155–3162. [PubMed: 12218133]
29. Branger J, Knapp S, Weijer S, Leemans JC, Pater JM, Speelman P, Florquin S, van der Poll T. *Infect Immun*. 2004; 72:788–794. [PubMed: 14742522]
30. Schurr JR, Young E, Byrne P, Steele C, Shellito JE, Kolls JK. *Infect Immun*. 2005; 73:532–545. [PubMed: 15618193]
31. Cai S, Batra S, Shen L, Wakamatsu N, Jeyaseelan S. *J Immunol*. 2009; 183:6629–6638. [PubMed: 19846873]
32. Lorenz E, Mira JP, Frees KL, Schwartz DA. *Arch Intern Med*. 2002; 162:1028–1032. [PubMed: 11996613]
33. Figueroa L, Xiong Y, Song C, Piao W, Vogel SN, Medvedev AE. *J Immunol*. 2012; 188:4506–4515. [PubMed: 22474023]
34. Schwartz DA. *J Endotoxin Res*. 2001; 7:389–393. [PubMed: 11753209]
35. Najmi N, Kaur G, Sharma SK, Mehra NK. *Tissue Antigens*. 2010; 76:102–109. [PubMed: 20403143]
36. Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, Ermolaeva M, Veldhuizen R, Leung YH, Wang H, Liu H, Sun Y, Pasparakis M, Kopf M, Mech C, Bavari S, Peiris JS, Slutsky AS, Akira S, Hultqvist M, Holmdahl R, Nicholls J, Jiang C, Binder CJ, Penninger JM. *Cell*. 2008; 133:235–249. [PubMed: 18423196]
37. Chaput C, Sander LE, Suttorp N, Opitz B. *Front Immunol*. 2013; 4:393. [PubMed: 24312100]
38. Gasse P, Riteau N, Vacher R, Michel ML, Fautrel A, di Padova F, Fick L, Charron S, Lagente V, Eberl G, Le Bert M, Quesniaux VF, Huaux F, Leite-de-Moraes M, Ryffel B, Couillin I. *PLoS One*. 2011; 6:e23185. [PubMed: 21858022]
39. Ather JL, Ckless K, Martin R, Foley KL, Suratt BT, Boyson JE, Fitzgerald KA, Flavell RA, Eisenbarth SC, Poynter ME. *J Immunol*. 2011; 187:64–73. [PubMed: 21622869]
40. Mills KH, Dungan LS, Jones SA, Harris J. *J Leukoc Biol*. 2013; 93:489–497. [PubMed: 23271701]
41. Yoo JK, Kim TS, Hufford MM, Braciale TJ. *J Allergy Clin Immunol*. 2013; 132:1263–1276. quiz 1277. [PubMed: 23915713]
42. Kudva A, Scheller EV, Robinson KM, Crowe CR, Choi SM, Slight SR, Khader SA, Dubin PJ, Enelow RI, Kolls JK, Alcorn JF. *J Immunol*. 2011; 186:1666–1674. [PubMed: 21178015]
43. Negishi H, Yanai H, Nakajima A, Koshiba R, Atarashi K, Matsuda A, Matsuki K, Miki S, Doi T, Aderem A, Nishio J, Smale ST, Honda K, Taniguchi T. *Nat Immunol*. 2012; 13:659–666. [PubMed: 22610141]
44. Shahangian A, Chow EK, Tian X, Kang JR, Ghaffari A, Liu SY, Belperio JA, Cheng G, Deng JC. *J Clin Invest*. 2009; 119:1910–1920. [PubMed: 19487810]
45. Sun K, Metzger DW. *Nat Med*. 2008; 14:558–564. [PubMed: 18438414]
46. Hamada H, de Garcia-Hernandez ML, Reome JB, Misra SK, Strutt TM, McKinsty KK, Cooper AM, Swain SL, Dutton RW. *J Immunol*. 2009; 182:3469–3481. [PubMed: 19265125]
47. Corbi AL, Lopez-Rodriguez C. *Leuk Lymphoma*. 1997; 25:415–425. [PubMed: 9250811]

48. Guillemins M, Lambrecht BN, Hammad H. *Mucosal Immunol.* 2013; 6:464–473. [PubMed: 23549447]
49. GeurtsvanKessel CH, Willart MA, van Rijt LS, Muskens F, Kool M, Baas C, Thielemans K, Bennett C, Clausen BE, Hoogsteden HC, Osterhaus AD, Rimmelzwaan GF, Lambrecht BN. *J Exp Med.* 2008; 205:1621–1634. [PubMed: 18591406]
50. Schlitzer A, McGovern N, Teo P, Zelante T, Atarashi K, Low D, Ho AW, See P, Shin A, Wasan PS, Hoeffel G, Malleret B, Heiseke A, Chew S, Jardine L, Purvis HA, Hilken CM, Tam J, Poidinger M, Stanley ER, Krug AB, Renia L, Sivasankar B, Ng LG, Collin M, Ricciardi-Castagnoli P, Honda K, Haniffa M, Ginhoux F. *Immunity.* 2013; 38:970–983. [PubMed: 23706669]
51. Rouvier E, Luciani MF, Mattei MG, Denizot F, Golstein P. *J Immunol.* 1993; 150:5445–5456. [PubMed: 8390535]
52. Yao Z, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, Comeau MR, Cohen JJ, Spriggs MK. *Immunity.* 1995; 3:811–821. [PubMed: 8777726]
53. Aggarwal S, Ghilardi N, Xie MH, de Sauvage FJ, Gurney AL. *J Biol Chem.* 2003; 278:1910–1914. [PubMed: 12417590]
54. Smith-Garvin JE, Koretzky GA, Jordan MS. *Annu Rev Immunol.* 2009; 27:591–619. [PubMed: 19132916]
55. Korn T, Bettelli E, Oukka M, Kuchroo VK. *Annu Rev Immunol.* 2009; 27:485–517. [PubMed: 19132915]
56. Melton AC, Bailey-Bucktrout SL, Travis MA, Fife BT, Bluestone JA, Sheppard D. *J Clin Invest.* 2010; 120:4436–4444. [PubMed: 21099117]
57. Kudo M, Melton AC, Chen C, Engler MB, Huang KE, Ren X, Wang Y, Bernstein X, Li JT, Atabai K, Huang X, Sheppard D. *Nat Med.* 2012; 18:547–554. [PubMed: 22388091]
58. McGeachy MJ, Chen Y, Tato CM, Laurence A, Joyce-Shaikh B, Blumenschein WM, McClanahan TK, O'Shea JJ, Cua DJ. *Nat Immunol.* 2009; 10:314–324. [PubMed: 19182808]
59. Basu R, O'Quinn DB, Silberberger DJ, Schoeb TR, Fouser L, Ouyang W, Hatton RD, Weaver CT. *Immunity.* 2012; 37:1061–1075. [PubMed: 23200827]
60. Kim JS, Smith-Garvin JE, Koretzky GA, Jordan MS. *J Exp Med.* 2011; 208:2201–2207. [PubMed: 21948082]
61. Marks BR, Nowyhed HN, Choi JY, Poholek AC, Odegard JM, Flavell RA, Craft J. *Nat Immunol.* 2009; 10:1125–1132. [PubMed: 19734905]
62. Rivera A, Hohl TM, Collins N, Leiner I, Gallegos A, Saijo S, Coward JW, Iwakura Y, Pamer EG. *J Exp Med.* 2011; 208:369–381. [PubMed: 21242294]
63. Shan M, Cheng HF, Song LZ, Roberts L, Green L, Hacken-Bitar J, Huh J, Bakaeen F, Coxson HO, Storness-Bliss C, Ramchandani M, Lee SH, Corry DB, Kheradmand F. *Sci Transl Med.* 2009; 1:4ra10.
64. Furuhashi K, Suda T, Hasegawa H, Suzuki Y, Hashimoto D, Enomoto N, Fujisawa T, Nakamura Y, Inui N, Shibata K, Nakamura H, Chida K. *Am J Respir Cell Mol Biol.* 2012; 46:165–172. [PubMed: 21908266]
65. Shafiani S, Tucker-Heard G, Kariyone A, Takatsu K, Urdahl KB. *J Exp Med.* 2010; 207:1409–1420. [PubMed: 20547826]
66. O'Sullivan B, Thomas R. *Crit Rev Immunol.* 2003; 23:83–107. [PubMed: 12906261]
67. Lin Y, Ritchie S, Logar A, Slight S, Messmer M, Rangel-Moreno J, Gugliani L, Alcorn JF, Strawbridge H, Park SM, Onishi R, Nyugen N, Walter MJ, Pociask D, Randall TD, Gaffen SL, Iwakura Y, Kolls JK, Khader SA. *Immunity.* 2009; 31:799–810. [PubMed: 19853481]
68. Khader SA, Bell GK, Pearl JE, Fountain JJ, Rangel-Moreno J, Cilley GE, Shen F, Eaton SM, Gaffen SL, Swain SL, Locksley RM, Haynes L, Randall TD, Cooper AM. *Nat Immunol.* 2007; 8:369–377. [PubMed: 17351619]
69. Murdock BJ, Huffnagle GB, Olszewski MA, Osterholzer JJ. *Infect Immun.* 2013
70. Do JS, Fink PJ, Li L, Spolski R, Robinson J, Leonard WJ, Letterio JJ, Min B. *J Immunol.* 2010; 184:1675–1679. [PubMed: 20061408]

71. Jensen KD, Su X, Shin S, Li L, Youssef S, Yamasaki S, Steinman L, Saito T, Locksley RM, Davis MM, Baumgarth N, Chien YH. *Immunity*. 2008; 29:90–100. [PubMed: 18585064]
72. Shibata K, Yamada H, Sato T, Dejima T, Nakamura M, Ikawa T, Hara H, Yamasaki S, Kageyama R, Iwakura Y, Kawamoto H, Toh H, Yoshikai Y. *Blood*. 2011; 118:586–593. [PubMed: 21606479]
73. Ribot JC, deBarros A, Pang DJ, Neves JF, Peperzak V, Roberts SJ, Girardi M, Borst J, Hayday AC, Pennington DJ, Silva-Santos B. *Nat Immunol*. 2009; 10:427–436. [PubMed: 19270712]
74. Turchinovich G, Hayday AC. *Immunity*. 2011; 35:59–68. [PubMed: 21737317]
75. Sutton CE, Mielke LA, Mills KH. *Eur J Immunol*. 2012; 42:2221–2231. [PubMed: 22949320]
76. Spits H, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, McKenzie AN, Mebius RE, Powrie F, Vivier E. *Nat Rev Immunol*. 2013; 13:145–149. [PubMed: 23348417]
77. Kleinjan A, Klein Wolterink RG, Levani Y, de Bruijn MJ, Hoogsteden HC, van Nimwegen M, Hendriks RW. *J Immunol*. 2014; 192:1385–1394. [PubMed: 24415780]
78. Li BW, Hendriks RW. *Immunology*. 2013; 140:281–287. [PubMed: 23866009]
79. Kim HY, Lee HJ, Chang YJ, Pichavant M, Shore SA, Fitzgerald KA, Iwakura Y, Israel E, Bolger K, Faul J, Dekruff RH, Umetsu DT. *Nat Med*. 2014; 20:54–61. [PubMed: 24336249]
80. Ness-Schwickerath KJ, Jin C, Morita CT. *J Immunol*. 2010; 184:7268–7280. [PubMed: 20483730]
81. Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. *Immunity*. 2009; 31:321–330. [PubMed: 19682928]
82. Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, Zecchi R, D'Angelo C, Massi-Benedetti C, Fallarino F, Carvalho A, Puccetti P, Romani L. *Immunity*. 2013; 39:372–385. [PubMed: 23973224]
83. Gaffen SL. *Nat Rev Immunol*. 2009; 9:556–567. [PubMed: 19575028]
84. Hartupée J, Liu C, Novotny M, Li X, Hamilton T. *J Immunol*. 2007; 179:4135–4141. [PubMed: 17785852]
85. Hamilton T, Li X, Novotny M, Pavicic PG Jr, Datta S, Zhao C, Hartupée J, Sun D. *J Leukoc Biol*. 2012; 91:377–383. [PubMed: 22167720]
86. Kreindler JL, Bertrand CA, Lee RJ, Karasic T, Aujla S, Pilewski JM, Frizzell RA, Kolls JK. *Am J Physiol Lung Cell Mol Physiol*. 2009; 296:L257–266. [PubMed: 19074559]
87. Newcomb DC, Boswell MG, Sherrill TP, Polosukhin VV, Boyd KL, Goleniewska K, Brody SL, Kolls JK, Adler KB, Peebles RS Jr. *Am J Respir Cell Mol Biol*. 2013; 48:711–716. [PubMed: 23392574]
88. Sabat R, Ouyang W, Wolk K. *Nat Rev Drug Discov*. 2013; 13:21–38. [PubMed: 24378801]
89. Pociask DA, Scheller EV, Mandalapu S, McHugh KJ, Enelow RI, Fattman CL, Kolls JK, Alcorn JF. *Am J Pathol*. 2013; 182:1286–1296. [PubMed: 23490254]
90. Martin JC, Beriou G, Heslan M, Chauvin C, Utriainen L, Aumeunier A, Scott CL, Mowat A, Cerovic V, Houston SA, Leboeuf M, Hubert FX, Hemont C, Merad M, Milling S, Josien R. *Mucosal Immunol*. 2014; 7:101–113. [PubMed: 23653115]
91. Podschun R, Ullmann U. *Clin Microbiol Rev*. 1998; 11:589–603. [PubMed: 9767057]
92. Happel KI, Zheng M, Young E, Quinton LJ, Lockhart E, Ramsay AJ, Shellito JE, Schurr JR, Bagby GJ, Nelson S, Kolls JK. *J Immunol*. 2003; 170:4432–4436. [PubMed: 12707317]
93. Happel KI, Dubin PJ, Zheng M, Ghilardi N, Lockhart C, Quinton LJ, Odden AR, Shellito JE, Bagby GJ, Nelson S, Kolls JK. *J Exp Med*. 2005; 202:761–769. [PubMed: 16157683]
94. Bhan U, Ballinger MN, Zeng X, Newstead MJ, Cornicelli MD, Standiford TJ. *PLoS One*. 2010; 5:e9896. [PubMed: 20360853]
95. Happel KI, Odden AR, Zhang P, Shellito JE, Bagby GJ, Nelson S. *Alcohol Clin Exp Res*. 2006; 30:1200–1207. [PubMed: 16792568]
96. Shellito JE, quan Zheng M, Ye P, Ruan S, Shean MK, Kolls J. *Alcohol Clin Exp Res*. 2001; 25:872–881. [PubMed: 11410724]
97. Khader SA, Pearl JE, Sakamoto K, Gilmartin L, Bell GK, Jelley-Gibbs DM, Ghilardi N, deSavauge F, Cooper AM. *J Immunol*. 2005; 175:788–795. [PubMed: 16002675]

98. Freches D, Korf H, Denis O, Havaux X, Huygen K, Romano M. *Immunology*. 2013; 140:220–231. [PubMed: 23721367]
99. Peng MY, Wang ZH, Yao CY, Jiang LN, Jin QL, Wang J, Li BQ. *Cell Mol Immunol*. 2008; 5:203–208. [PubMed: 18582402]
100. Lockhart E, Green AM, Flynn JL. *J Immunol*. 2006; 177:4662–4669. [PubMed: 16982905]
101. van de Veerdonk FL, Teirlinck AC, Kleinnijenhuis J, Kullberg BJ, van Crevel R, van der Meer JW, Joosten LA, Netea MG. *J Leukoc Biol*. 2010; 88:227–232. [PubMed: 20299682]
102. Teixeira-Coelho M, Cruz A, Carmona J, Sousa C, Ramos-Pereira D, Saraiva AL, Veldhoen M, Pedrosa J, Castro AG, Saraiva M. *Int Immunol*. 2011; 23:89–96. [PubMed: 21156751]
103. Umemura M, Yahagi A, Hamada S, Begum MD, Watanabe H, Kawakami K, Suda T, Sudo K, Nakae S, Iwakura Y, Matsuzaki G. *J Immunol*. 2007; 178:3786–3796. [PubMed: 17339477]
104. Cowan J, Pandey S, Fillion LG, Angel JB, Kumar A, Cameron DW. *Clin Exp Immunol*. 2012; 167:317–329. [PubMed: 22236009]
105. Jurado JO, Pasquinelli V, Alvarez IB, Pena D, Rovetta AI, Tateosian NL, Romeo HE, Musella RM, Palmero D, Chuluyan HE, Garcia VE. *J Leukoc Biol*. 2012; 91:991–1002. [PubMed: 22416258]
106. Woodland DL, Hogan RJ, Zhong W. *Immunol Res*. 2001; 24:53–67. [PubMed: 11485209]
107. Li C, Yang P, Sun Y, Li T, Wang C, Wang Z, Zou Z, Yan Y, Wang W, Chen Z, Xing L, Tang C, Ju X, Guo F, Deng J, Zhao Y, Tang J, Wang H, Zhao Z, Yin Z, Cao B, Wang X, Jiang C. *Cell Res*. 2012; 22:528–538. [PubMed: 22025253]
108. Li W, Moltedo B, Moran TM. *J Virol*. 2012; 86:12304–12312. [PubMed: 22951826]
109. Didierlaurent A, Goulding J, Patel S, Snelgrove R, Low L, Bebie M, Lawrence T, van Rijt LS, Lambrecht BN, Sirard JC, Hussell T. *J Exp Med*. 2008; 205:323–329. [PubMed: 18227219]
110. Robinson KM, Choi SM, McHugh KJ, Mandalapu S, Enelow RI, Kolls JK, Alcorn JF. *J Immunol*. 2013; 191:5153–5159. [PubMed: 24089191]
111. Latge JP. *Clin Microbiol Rev*. 1999; 12:310–350. [PubMed: 10194462]
112. Cenci E, Mencacci A, Bacci A, Bistoni F, Kurup VP, Romani L. *J Immunol*. 2000; 165:381–388. [PubMed: 10861075]
113. Zelante T, De Luca A, Bonifazi P, Montagnoli C, Bozza S, Moretti S, Belladonna ML, Vacca C, Conte C, Mosci P, Bistoni F, Puccetti P, Kastelein RA, Kopf M, Romani L. *Eur J Immunol*. 2007; 37:2695–2706. [PubMed: 17899546]
114. Romani L, Fallarino F, De Luca A, Montagnoli C, D'Angelo C, Zelante T, Vacca C, Bistoni F, Fioretti MC, Grohmann U, Segal BH, Puccetti P. *Nature*. 2008; 451:211–215. [PubMed: 18185592]
115. Werner JL, Metz AE, Horn D, Schoeb TR, Hewitt MM, Schwiebert LM, Faro-Trindade I, Brown GD, Steele C. *J Immunol*. 2009; 182:4938–4946. [PubMed: 19342673]
116. Saijo S, Ikeda S, Yamabe K, Kakuta S, Ishigame H, Akitsu A, Fujikado N, Kusaka T, Kubo S, Chung SH, Komatsu R, Miura N, Adachi Y, Ohno N, Shibuya K, Yamamoto N, Kawakami K, Yamasaki S, Saito T, Akira S, Iwakura Y. *Immunity*. 2010; 32:681–691. [PubMed: 20493731]
117. Robinson MJ, Osorio F, Rosas M, Freitas RP, Schweighoffer E, Gross O, Verbeek JS, Ruland J, Tybulewicz V, Brown GD, Moita LF, Taylor PR, Reis e Sousa C. *J Exp Med*. 2009; 206:2037–2051. [PubMed: 19703985]
118. Vautier S, MacCallum DM, Brown GD. *Cytokine*. 2012; 58:89–99. [PubMed: 21924922]
119. Xu X, Weiss IDHHZ, Singh SP, Wynn TA, Wilson MS, Farber JM. *J Immunol*. 2014
120. Gessner MA, Werner JL, Lilly LM, Nelson MP, Metz AE, Dunaway CW, Chan YR, Ouyang W, Brown GD, Weaver CT, Steele C. *Infect Immun*. 2012; 80:410–417. [PubMed: 22038916]
121. Gresnigt MS, Becker KL, Smeekens SP, Jacobs CW, Joosten LA, van der Meer JW, Netea MG, van de Veerdonk FL. *J Immunol*. 2013; 190:5629–5639. [PubMed: 23645883]
122. Mear JB, Gosset P, Kipnis E, Faure E, Dessein R, Jawhara S, Fradin C, Faure K, Poulain D, Sendid B, Guery B. *Infect Immun*. 2014; 82:306–315. [PubMed: 24166952]
123. Kumar P, Thakar MS, Ouyang W, Malarkannan S. *Mucosal Immunol*. 2013; 6:69–82. [PubMed: 22739232]

124. Paget C, Ivanov S, Fontaine J, Renneson J, Blanc F, Pichavant M, Dumoutier L, Ryffel B, Renauld JC, Gosset P, Si-Tahar M, Faveeuw C, Trottein F. *J Biol Chem*. 2012; 287:8816–8829. [PubMed: 22294696]
125. Guo H, Topham DJ. *J Virol*. 2010; 84:7750–7759. [PubMed: 20504940]
126. Ivanov S, Renneson J, Fontaine J, Barthelemy A, Paget C, Fernandez EM, Blanc F, De Trez C, Van Maele L, Dumoutier L, Huerre MR, Eberl G, Si-Tahar M, Gosset P, Renauld JC, Sirard JC, Faveeuw C, Trottein F. *J Virol*. 2013; 87:6911–6924. [PubMed: 23596287]
127. Al-Ramli W, Prefontaine D, Chouiali F, Martin JG, Olivenstein R, Lemiere C, Hamid Q. *J Allergy Clin Immunol*. 2009; 123:1185–1187. [PubMed: 19361847]
128. McKinley L, Alcorn JF, Peterson A, Dupont RB, Kapadia S, Logar A, Henry A, Irvin CG, Piganelli JD, Ray A, Kolls JK. *J Immunol*. 2008; 181:4089–4097. [PubMed: 18768865]
129. Nanzer AM, Chambers ES, Ryanna K, Richards DF, Black C, Timms PM, Martineau AR, Griffiths CJ, Corrigan CJ, Hawrylowicz CM. *J Allergy Clin Immunol*. 2013; 132:297–304. e293. [PubMed: 23683514]
130. Kreindler JL, Steele C, Nguyen N, Chan YR, Pilewski JM, Alcorn JF, Vyas YM, Aujla SJ, Finelli P, Blanchard M, Zeigler SF, Logar A, Hartigan E, Kurs-Lasky M, Rockette H, Ray A, Kolls JK. *J Clin Invest*. 2010; 120:3242–3254. [PubMed: 20714107]
131. Nguyen NL, Chen K, McAleer J, Kolls JK. *Infect Immun*. 2013; 81:1510–1519. [PubMed: 23439304]
132. Moreira AP, Cavassani KA, Ismailoglu UB, Hullinger R, Dunleavy MP, Knight DA, Kunkel SL, Uematsu S, Akira S, Hogaboam CM. *J Clin Invest*. 2011; 121:4420–4432. [PubMed: 22005301]
133. Lilly LM, Gessner MA, Dunaway CW, Metz AE, Schwiebert L, Weaver CT, Brown GD, Steele C. *J Immunol*. 2012; 189:3653–3660. [PubMed: 22933634]
134. Chang Y, Al-Alwan L, Risse PA, Halayko AJ, Martin JG, Bagloli CJ, Eidelman DH, Hamid Q, Faseb J. 2012; 26:5152–5160. [PubMed: 22898922]
135. Takahashi K, Hirose K, Kawashima S, Niwa Y, Wakashin H, Iwata A, Tokoyoda K, Renauld JC, Iwamoto I, Nakayama T, Nakajima H. *J Allergy Clin Immunol*. 2011; 128:1067–1076. e1061–1066. [PubMed: 21794904]
136. Chen K, Kolls JK. *Annu Rev Immunol*. 2013; 31:605–633. [PubMed: 23516986]
137. Kumar P, Chen K, Kolls JK. *Curr Opin Immunol*. 2013; 25:373–380. [PubMed: 23669353]
138. Ye P, Garvey PB, Zhang P, Nelson S, Bagby G, Summer WR, Schwarzenberger P, Shellito JE, Kolls JK. *Am J Respir Cell Mol Biol*. 2001; 25:335–340. [PubMed: 11588011]
139. Chen K, McAleer JP, Lin Y, Paterson DL, Zheng M, Alcorn JF, Weaver CT, Kolls JK. *Immunity*. 2011; 35:997–1009. [PubMed: 22195749]
140. Priebe GP, Walsh RL, Cederroth TA, Kamei A, Coutinho-Sledge YS, Goldberg JB, Pier GB. *J Immunol*. 2008; 181:4965–4975. [PubMed: 18802100]
141. Higgins SC, Jarnicki AG, Lavelle EC, Mills KH. *J Immunol*. 2006; 177:7980–7989. [PubMed: 17114471]
142. Lu YJ, Gross J, Bogaert D, Finn A, Bagrade L, Zhang Q, Kolls JK, Srivastava A, Lundgren A, Forte S, Thompson CM, Harney KF, Anderson PW, Lipsitch M, Malley R. *PLoS Pathog*. 2008; 4:e1000159. [PubMed: 18802458]
143. Malley R, Srivastava A, Lipsitch M, Thompson CM, Watkins C, Tzianabos A, Anderson PW. *Infect Immun*. 2006; 74:2187–2195. [PubMed: 16552049]
144. Malley R, Trzcinski K, Srivastava A, Thompson CM, Anderson PW, Lipsitch M. *Proc Natl Acad Sci U S A*. 2005; 102:4848–4853. [PubMed: 15781870]
145. Gopal R, Lin Y, Obermajer N, Slight S, Nuthalapati N, Ahmed M, Kalinski P, Khader SA. *Eur J Immunol*. 2012; 42:364–373. [PubMed: 22101830]
146. Gopal R, Rangel-Moreno J, Slight S, Lin Y, Nawar HF, Fallert Junecko BA, Reinhart TA, Kolls J, Randall TD, Connell TD, Khader SA. *Mucosal Immunol*. 2013; 6:972–984. [PubMed: 23299616]
147. Dhiman R, Periasamy S, Barnes PF, Jaiswal AG, Paidipally P, Barnes AB, Tvinnereim A, Vankayalapati R. *J Immunol*. 2012; 189:897–905. [PubMed: 22711885]

148. Cruz A, Fraga AG, Fountain JJ, Rangel-Moreno J, Torrado E, Saraiva M, Pereira DR, Randall TD, Pedrosa J, Cooper AM, Castro AG. *J Exp Med*. 2010; 207:1609–1616. [PubMed: 20624887]
149. Wuthrich M, Gern B, Hung CY, Ersland K, Rocco N, Pick-Jacobs J, Galles K, Filutowicz H, Warner T, Evans M, Cole G, Klein B. *J Clin Invest*. 2011; 121:554–568. [PubMed: 21206087]
150. Nanjappa SG, Heninger E, Wuthrich M, Gasper DJ, Klein BS. *PLoS Pathog*. 2012; 8:e1002771. [PubMed: 22829762]
151. Hung CY, Gonzalez A, Wuthrich M, Klein BS, Cole GT. *Infect Immun*. 2011; 79:4511–4522. [PubMed: 21859851]
152. Gopal R, Rangel-Moreno J, Fallert Junecko BA, Mallon DJ, Chen K, Pociask DA, Connell TD, Reinhart TA, Alcorn JF, Ross TM, Kolls JK, Khader SA. *Am J Pathol*. 2014; 184:55–63. [PubMed: 24183780]
153. Jarchum I, Pamer EG. *Curr Opin Immunol*. 2011; 23:353–360. [PubMed: 21466955]
154. Huang YJ, Charlson ES, Collman RG, Colombini-Hatch S, Martinez FD, Senior RM. *Am J Respir Crit Care Med*. 2013; 187:1382–1387. [PubMed: 23614695]
155. Lynch SV, Bruce KD. *Cold Spring Harb Perspect Med*. 2013; 3:a009738. [PubMed: 23457293]
156. Lemon KP, Klepac-Ceraj V, Schiffer HK, Brodie EL, Lynch SV, Kolter R. *MBio*. 2010; 1.
157. Charlson ES, Bittinger K, Haas AR, Fitzgerald AS, Frank I, Yadav A, Bushman FD, Collman RG. *Am J Respir Crit Care Med*. 2011; 184:957–963. [PubMed: 21680950]
158. Morris A, Beck JM, Schloss PD, Campbell TB, Crothers K, Curtis JL, Flores SC, Fontenot AP, Ghedin E, Huang L, Jablonski K, Kleerup E, Lynch SV, Sodergren E, Twigg H, Young VB, Bassis CM, Venkataraman A, Schmidt TM, Weinstock GM. *Am J Respir Crit Care Med*. 2013; 187:1067–1075. [PubMed: 23491408]
159. Ghannoum MA, Jurevic RJ, Mukherjee PK, Cui F, Sikaroodi M, Naqvi A, Gillevet PM. *PLoS Pathog*. 2010; 6:e1000713. [PubMed: 20072605]
160. Handley SA, Thackray LB, Zhao G, Presti R, Miller AD, Droit L, Abbink P, Maxfield LF, Kambal A, Duan E, Stanley K, Kramer J, Macri SC, Permar SR, Schmitz JE, Mansfield K, Brenchley JM, Veazey RS, Stappenbeck TS, Wang D, Barouch DH, Virgin HW. *Cell*. 2012; 151:253–266. [PubMed: 23063120]
161. Cox MJ, Allgaier M, Taylor B, Baek MS, Huang YJ, Daly RA, Karaoz U, Andersen GL, Brown R, Fujimura KE, Wu B, Tran D, Koff J, Kleinhenz ME, Nielson D, Brodie EL, Lynch SV. *PLoS One*. 2010; 5:e11044. [PubMed: 20585638]
162. Rogers GB, van der Gast CJ, Cuthbertson L, Thomson SK, Bruce KD, Martin ML, Serisier DJ. *Thorax*. 2013; 68:731–737. [PubMed: 23564400]
163. Rogers GB, Hart CA, Mason JR, Hughes M, Walshaw MJ, Bruce KD. *J Clin Microbiol*. 2003; 41:3548–3558. [PubMed: 12904354]
164. Carmody LA, Zhao J, Schloss PD, Petrosino JF, Murray S, Young VB, Li JZ, Lipuma JJ. *Ann Am Thorac Soc*. 2013; 10:179–187. [PubMed: 23802813]
165. Zemanick ET, Harris JK, Wagner BD, Robertson CE, Sagel SD, Stevens MJ, Accurso FJ, Laguna TA. *PLoS One*. 2013; 8:e62917. [PubMed: 23646159]
166. Molyneaux PL, Mallia P, Cox MJ, Footitt J, Willis-Owen SA, Homola D, Trujillo-Torralbo MB, Elkin S, Kon OM, Cookson WO, Moffatt MF, Johnston SL. *Am J Respir Crit Care Med*. 2013; 188:1224–1231. [PubMed: 23992479]
167. Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, Davies J, Ervine A, Poulter L, Pachter L, Moffatt MF, Cookson WO. *PLoS One*. 2010; 5:e8578. [PubMed: 20052417]
168. Beck JM, Young VB, Huffnagle GB. *Transl Res*. 2012; 160:258–266. [PubMed: 22683412]
169. Ichinohe T, Pang IK, Kumamoto Y, Peaper DR, Ho JH, Murray TS, Iwasaki A. *Proc Natl Acad Sci U S A*. 2011; 108:5354–5359. [PubMed: 21402903]
170. Abt MC, Osborne LC, Monticelli LA, Doering TA, Alenghat T, Sonnenberg GF, Paley MA, Antenus M, Williams KL, Erikson J, Wherry EJ, Artis D. *Immunity*. 2012; 37:158–170. [PubMed: 22705104]
171. Herbst T, Sichelstiel A, Schar C, Yadava K, Burki K, Cahenzli J, McCoy K, Marsland BJ, Harris NL. *Am J Respir Crit Care Med*. 2011; 184:198–205. [PubMed: 21471101]

172. Russell SL, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M, Gill N, Blanchet MR, Mohn WW, McNagny KM, Finlay BB. EMBO Rep. 2012; 13:440–447. [PubMed: 22422004]
173. Palucka K, Banchereau J. Immunity. 2013; 39:38–48. [PubMed: 23890062]
174. Ganal SC, Sanos SL, Kallfass C, Oberle K, Johnner C, Kirschning C, Lienenklaus S, Weiss S, Staeheli P, Aichele P, Diefenbach A. Immunity. 2012; 37:171–186. [PubMed: 22749822]

Fig. 1. Regulation of IL-17 and IL-22 production by dendritic cell subsets

Dendritic cells (DCs) and alveolar macrophages identify pathogens through PRRs. Bacterial cell walls, viral nucleic acids, and fungal cell walls are detected by cell surface TLRs, intracellular TLRs, and Dectin-1, respectively. Alveolar macrophages produce IL-1β in response to bacteria, stimulating IL-17 secretion from innate lymphocytes. Other stimuli that activate NLRP3 also contribute to IL-1β production. DCs influence effector CD4⁺ T-cell polarization by providing antigens, costimulatory molecules, and cytokines. IL-1β and IL-23 produced by CD11b⁺ DCs in response to bacteria or fungi induces Th17 differentiation. The activation of NF-κB and STAT3 transcription factors in lymphocytes favors RORγt expression and IL-17/IL-22 production. Viruses stimulate plasmacytoid DCs to secrete type I IFNs, inhibiting the expression of Th17 polarizing cytokines. In this way, viruses suppress anti-bacterial Th17 immunity. Other cytokines that activate STAT1 and suppress IL-17/IL-22 production include IFN-γ and IL-27.

Fig. 2. Roles of IL-17 and IL-22 in host defense

Infections and inflammatory diseases increase the accumulation of IL-17 producing cells in lung tissue. Airway epithelium responds to IL-17 by producing antimicrobial proteins and neutrophil chemoattractants, helping to eradicate bacteria and fungi. In response to viruses, IL-17RA signaling contributes to acute lung injury through neutrophil recruitment, increasing levels of oxidized phospholipids. IL-22 is important for epithelial repair following injury. The major sources of IL-17 and IL-22 include innate lymphocytes during primary responses and antigen-specific CD4⁺ T cells during secondary responses. Vaccines that prime Th17 immunity have demonstrated protection against bacteria and fungi. Interleukin-17 stimulates DCs to produce IL-12 while inhibiting IL-10, augmenting Th1 differentiation. Further, lung-resident Th17 cells induce the secretion of CXCR3 ligands, recruiting Th1 cells during infections. Direct stimulation of macrophages with IL-17 also increases their bactericidal activity. The pleiotropic functions of IL-17 and IL-22 are protective against infections but contribute to chronic inflammation in the presence of allergens.