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T Cell–Mediated Host Immune Defenses in the Lung

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Abstract

Evidence has increasingly shown that the lungs are a major site of immune regulation. A robust and highly regulated immune response in the lung protects the host from pathogen infection, whereas an inefficient or deleterious response can lead to various pulmonary diseases. Many cell types, such as epithelial cells, dendritic cells, macrophages, neutrophils, eosinophils, and B and T lymphocytes, contribute to lung immunity. This review focuses on the recent advances in understanding how T lymphocytes mediate pulmonary host defenses against bacterial, viral, and fungal pathogens.

Keywords

pneumonia; inflammation; coinfection

INTRODUCTION

Many pulmonary diseases are associated with or directly result from aberrant immunological responses. Most, if not all, of these immunological disorders are directly or indirectly involved with host defense pathways. The common causes of major pulmonary diseases listed by the American Lung Association and their relation to host defenses are summarized in Table 1.

T cells play critical roles in the immune system: $CD4^+$ (helper) T cells help B cells to mount antibody responses, provide feedback to dendritic cells (DCs) via costimulatory molecules and the elaboration of cytokines, and enhance and maintain responses of $CD8^+$ (cytotoxic) T cells. Moreover, $CD4^+$ T cells have direct effector activity, including performing cytotoxic functions (1), mediating macrophage activation, and inducing genes in mucosal tissues that contribute to host defense. $CD8^+$ T cells contribute to cytokine production and more importantly kill viral-infected cells directly. γδ T cells and invariant natural killer T (iNKT) cells as well as the newly discovered innate lymphoid-like cells (ILCs) play critical roles in early responses to many pulmonary infections as well. Both $CD4^+$ and $CD8^+$ T cells can form immunological memory and benefit the host when the host encounters secondary challenge from the same or related pathogens.

The massive surface area of the lung epithelium and the intimate association of an extensive capillary network to facilitate gas exchange also places the lung in a potentially vulnerable

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position in relation to the external environment. As a consequence, the respiratory tract is constantly exposed to the external environment and can serve as a major portal of entry for many pathogens. The immune system of the respiratory tract consists of a specialized network of cells including secretory Clara cells, ciliated cells, and mucus-producing goblet cells as well as submucosal glands. The major resident myeloid-derived cell on the luminal side of the lung is the highly phagocytic alveolar macrophage. This system effectively controls many pulmonary pathogens and protects the host. However, many pathogens that escape these innate defenses require the T cell subsets mentioned above for ultimate control of the infection.

T cells play critical roles in pulmonary host defense against bacterial, viral, and fungal pathogens, as discussed in this review. In general, an insufficient T cell response in the course of an ongoing infection renders the host susceptible to infection and delayed clearance of the pathogen. Moreover, insufficient T cell immunity may also increase the likelihood of pathogen dissemination from the lung. In contrast, dysregulation of T cell responses during an immune response could also damage host tissues and have detrimental effects for the host itself. T cell responses in the lung can be dynamically regulated through many mechanisms such as the local environmental cytokine milieu, expression of costimulatory/coinhibitory molecules, and epigenetic regulation of genomic loci encoding cytokines and transcription factors. Dysregulated T cell responses have been associated with many chronic lung diseases, and thus T cell subsets are attractive targets for pharmaceutical intervention. In contrast, the generation of mucosal pathogen-specific T cell responses may be desired for advances in vaccine development.

T CELLS IN PULMONARY HOST DEFENSE

$CD4^+$ T Cells

$CD4^+$ T cells are a major T cell subset that plays a central role in immune system function when naive $CD4^+$ T cells differentiate into effector and/or memory cells after encountering their cognate antigen via antigen-presenting cells (APCs). The phenotypes of effector $CD4^+$ T cells differ depending on the stimulating conditions and can be categorized into various lineages. In the lungs, DCs bridge innate and adaptive immunity, and depending on context, they also induce various $CD4^+$ T cell responses to infectious agents. During steady state, the lung contains two major subsets of $CD11c^{hi}$ conventional (c)DCs ($CD103^-$ $CD11b^+$ cells in the lamina propria and $CD103^+CD11b^-$ cells in the epithelial layer). A population of $CD11c^{dim}$ plasmacytoid (p)DCs can also be found in the conducting airways (reviewed in Reference 2). When inflammation occurs, additional $CD11b^+$ monocyte-derived DCs, expressing Ly6C and FcεRI, are recruited to the lungs (reviewed in Reference 3). In response to pathogen inhalation or in the case of concomitant exposure to harmless antigen with inhaled environmental adjuvants such as cigarette smoke, fine particulate matter, or bacterial contaminants, lung DCs produce IL-12p70, leukotriene C4, IL-6, IL-23p19, TGF-β, or IL-1β. MHC class II–restricted presentation of cognate antigen to $CD4^+$ T cells in these different cytokine milieus can initiate different T cell responses. T cell activation is thought to be initiated in the lung-draining lymph nodes after lung DCs endocytose antigen and travel to that location. However, lymphotoxin-$\alpha^{-/-}$ mice, which lack peripheral lymph nodes (4), are able to generate antigen-specific $CD8^+$ T cell responses as well as to produce high titers of influenza-specific IgM, IgG, and IgA antibodies (5). Moreover, these mice clear low-dose influenza infection (5), which supports the argument that the initiation of T cell activation in the lung can occur outside of lymph nodes. Further support comes from the infection of $CCR7^{-/-}$ mice with *Mycobacterium tuberculosis*. These mice have defective DC trafficking from the lung to the lung-draining lymph nodes, yet they exhibit ectopic proliferation of *M. tuberculosis*–specific $CD4^+$ T cells in the lungs (6).

$CD4^+$ T cells represent an important component in pulmonary host defense against various pathogens, and perhaps the best example for this is demonstrated in HIV. HIV targets $CD4^+$ T cells, causing the patient to progress to AIDS, which is defined either by $CD4^+$ T cell numbers below 200 cells per μL or by the occurrence of specific diseases in association with an HIV infection. Many of these AIDS-defining illnesses are pulmonary infections, including *Pneumocystis jiroveci* pneumonia, tuberculosis (TB), candidiasis of the lung, histoplasmosis, or recurrent bacterial pneumonia (7). More recently, investigators have shown an increased susceptibility of AIDS patients to influenza viruses, *Streptococcus pneumoniae*, *Haemophilus influenzae* (reviewed in Reference 8), and *Aspergillus fumigatus* (reviewed in Reference 9).

Evidence of distinctive lineages of effector $CD4^+$ T cells first came from the analysis of mouse $CD4^+$ T cell clones by Mosmann & Coffman (10). Two distinct populations of $CD4^+$ T cells were then designated as T helper (Th)1 and Th2 cells, distinguished mainly by the effector cytokines they produce but also by their expression of different patterns of cell surface molecules and transcription factors. The signature cytokine of Th1 cells is interferon (IFN)-γ, but they are also potent IL-2 producers (11). Moreover, these cells can also coexpress TNF-α (11). In contrast, Th2 cells fail to produce IFN-γ and produce the signature cytokines IL-4, IL-5, and IL-13. The Th1/Th2 paradigm dominated the field of T cell immunology for about 15 years, until 2003–2005, when a third distinctive effector lineage of $CD4^+$ T cells, termed Th17 cells, was first demonstrated in mouse models of autoimmune encephalitis (12–17), although an IL-17-producing $CD4^+$ T cell population, distinct from Th1 and Th2, was first demonstrated in 2000 (18).

In addition to their ability to differentiate into effector T cells, $CD4^+$ T cells can also become cells with a regulatory function to suppress ongoing effector T cell responses (often referred to as inducible Treg cells or iTregs, discussed further below) (20–23). More recently, the $CD4^+$ T cell subset found in the germinal center, T follicular helper (Tfh) cells, which help in antigen-specific antibody production, have emerged as a possible fifth lineage of $CD4^+$ T cells (23).

All the above-mentioned T helper lineages are important in pulmonary host defenses. Figure 1 summarizes the cytokines required for differentiation, lineage-specific transcription factors, and the functions in pulmonary host defense for each T helper lineage.

Th1 Cells

Th1 cells are characterized by the production of their signature cytokine, IFN-γ. The differentiation of Th1 cells requires the cytokine IL-12, the master transcription factor TBX21, and the signaling transducer and activator of transcription STAT4 (see Figure 1). Humans carrying mutations in the IFNGR1 subunit of the IFN-γ receptor are susceptible to mycobacterial disease (24). Humans with a deleterious mutation in IL-12B (encoding IL-12p40) (7, 25) and *IL12RB1* (encoding IL-12Rβ1) (26, 27) can suffer from infections with *Mycobacterium bovis* and *M. avium*. These bacteria are usually nonpathogenic in healthy individuals, but patients with these mutations suffer a defect in IFN-γ response that leads to infection. Thus, genetic evidence from both mouse and human demonstrates that many defects in the IFN-γ and IL-12 pathways can lead to profound mycobacterial susceptibility (reviewed in Reference 28). The WHO estimates the risk of developing TB to be between 20 and 37 times greater in people living with HIV than among those without HIV infection due to the loss of $CD4^+$ T cells and consequent lack of IFN-γ response. HIV infection is one of the most powerful risk factors for progressing from TB infection to disease (29), which underscores the importance of $CD4^+$ T cells in developing TB. IFN-γ secretion was significantly decreased in a study of HIV and TB dually infected patients when compared to healthy subjects and HIV^- TB^+ patients (30). Taken together, these data

illustrate the critical role of Th1 cells and IFN-γ in *M. tuberculosis* resistance. Th1 cells are considered to be indispensable and play an essential role in combating TB.

M. tuberculosis, an intracellular bacterium, is transmitted via aerosol droplets and primarily targets the respiratory system. Once the host inhales the bacterium, *M. tuberculosis* is phagocytosed by alveolar macrophages and myeloid DCs (mDCs), which actively circulate around the mucosal environment (31). Upon infection, mDCs migrate to the draining lymph nodes and initiate the *M. tuberculosis*–specific adaptive immune responses (31, 32). A delay in the priming phase of the adaptive immune response can lead to the establishment of bacterial persistence (32, 33). A successful priming of the adaptive immune response by DCs triggers the expansion and phenotypic and functional maturation of *M. tuberculosis*–specific T cells, which enter the circulation and home to the site of infection. Matured *M. tuberculosis*–specific T cells activate infected macrophages through the secretion of the Th1 signature cytokines IFN-γ and TNF-α (34, 35). Studies in *Ifng*-disrupted mice show defects in the induction of nitric oxide synthase, reactive nitrogen intermediates (26), and reactive oxygen species (25) (see Figure 2). These cytokines are important mediators for sequestering intraendosomal *M. tuberculosis* growth, achieving microbial killing, and perhaps more importantly, aiding the formation and maturation of the granuloma, a cellular aggregate found in *M. tuberculosis*–infected patients that has long been considered necessary for containment of infection (36, 37). The structure of a granuloma and the function of Th1 cells are summarized in Figure 2.

IFN-γ can also inhibit IL-17 production by $CD4^+$ T cells and may reduce pathogenic neutrophil recruitment in *M. tuberculosis* infection (38). Although many other cell types, such as macrophages, $CD8^+$ T cells, NKT cells, and γδ T cells, can also produce IFN-γ, the IFN-γ production, especially from $CD8^+$ T cells, is $CD4^+$ dependent, underscoring the importance of Th1 cells in *M. tuberculosis* infection (39). Recent studies have suggested that rapid *M. tuberculosis*–specific Th1 cell depletion may contribute to the early onset of TB in individuals with latent *M. tuberculosis* reactivation (40). Th1 cells, mainly through the production of their signature cytokine, IFN-γ, and in certain cases TNF-α as well, are also involved in controlling pulmonary infection from intracellular bacteria such as *Francisella tularensis* (41) and *Chlamydia pneumoniae* (42) and from extracellular bacteria such as *Klebsiella pneumoniae* (43, 44). Several small clinical trials with inhaled recombinant IFN-γ have shown that the cytokine is well tolerated and associated with reduced organism burden in sputum (19, 45). A randomized placebo-controlled trial has also been conducted of parenteral IFN-γ treatment (1×10^6 IU of recombinant human IFN-γ given intramuscularly, daily for one month and then three times per week up to six months as adjuvant to daily oral azithromycin, ciprofloxacin, ethambutol, and rifampin) in pulmonary atypical mycobacterial infection. This trial showed faster resolution of symptom scores and a trend toward faster microbiological and radiological improvement (46). IFN-γ is also critical for the restriction of *Legionella pneumophila* infection in vivo; however, the important cellular sources appear to be natural killer (NK) cells (27). In mice, exogenous administration or transient transgenic expression of IFN-γ resulted in improvement in bacterial clearance (47), and in humans, peripheral blood mononuclear cells (PBMCs) from patients who had recovered from Legionnaire's disease released reduced amounts of IFN-γ after lipopolysaccharide stimulation (48), suggesting that impaired IFN-γ production may contribute to susceptibility to *L. pneumophila* infection.

Th1 cells are also essential for host defense against many viruses. Influenza viruses are an important cause of respiratory tract infections and are responsible for 3–5 million clinical infections and 250,000–500,000 fatal cases annually (49). Infections with influenza virus trigger robust host immune responses that result ultimately in controlling and eradicating virus replication. Although it is commonly thought that viral-specific memory $CD8^+$ T cells

are critical for heterosubtypic immunity in immune-competent healthy individuals, the importance of $CD4^+$ T cells in vaccine-induced heterosubtypic protection has been proven in murine models (50, 51), likely through IFN-γ- and IL-2-dependent mechanisms.

Respiratory syncytial virus (RSV) is another clinically significant virus and is an important cause of acute respiratory tract infections in infants and the elderly, causing significant morbidity and mortality. The WHO estimates the global burden of RSV disease at 64 million cases and 160,000 deaths annually. In the United States, RSV is responsible for 85,000–144,000 infant hospitalizations annually (52). Infection by RSV can cause extensive inflammation, mucus hypersecretion, airway obstruction, and lung damage in susceptible hosts (such as preterm infants or infants exposed to secondhand tobacco smoke) because of a Th2-biased immune response that can lead to persistent airway hyperresponsiveness in the host (6). An effective induction of Th1 immunity against RSV during childhood is thought to counteract this Th2-like immune response triggered by the natural RSV infection. Indeed, in mouse models, prevention of the immunopathology caused by RSV can be achieved through the generation of RSV-specific Th1 cells by a recombinant vaccine (53) or through the enhancement of Th1 responses by downregulation of IL-4Rα, a receptor expressed on Th2 cells (54). Data from these models support the hypothesis that Th1 cells play a protective role in host defense against RSV. Intranasal treatment with recombinant mouse IFN-γ in experimental RSV could also enhance classic activation of neonatal alveolar macrophages, reduce lung viral titers, and improve weight gain with no detectable increase in $CD4^+$ or $CD8^+$ T cell infiltration (55). This finding suggests that intranasal IFN-γ is a viable treatment option and should be considered for further studies in neonatal RSV disease.

Protective immunity to fungi also requires a robust Th1 response. Experimental data have shown the deleterious effects of the ablation of IL-12 (a crucial mediator for Th1 induction) or of IFN-γ during fungal infections (reviewed in Reference 56). For example, functional IFN-γ signaling is required for mice to confine the cryptococcal infection, given that IFN-$\gamma R^{-/-}$ mice do not have the ability to resolve the cryptococcal infection (57); neutralization of IL-12 also prevented lung leukocyte production of IFN-γ in response to the infection (58). By producing IFN-γ and providing help for the generation of opsonizing antibodies, the activation of Th1 cells is also instrumental in the optimal activation of phagocytes at sites of infection. The roles of IFN-γ and TNF-α in fungal infections in macrophage activation do not differ from the roles already described in other infectious diseases. Th1 cytokines promote the release of nitric oxide and reactive oxygen species, both crucial cellular effectors against fungi. Not surprisingly, Th1 cells are beneficial, if not indispensable, in many fungal infections in the lungs, such as *Aspergillus*. In patients with clinical evidence of invasive aspergillosis, a favorable response to antifungal therapy correlates with higher IFN-γ production from *Aspergillus* extract–stimulated PBMCs (59). Although aerosol administration of recombinant murine IFN-γ reduced the intensity of *Pneumocystis* infection in CD4-depleted mice (60), IFN-γ-deficient mice can clear *Pneumocystis*, suggesting that the role of Th1 cells in *Pneumocystis* infection is dispensable (61). In a murine model of *Coccidioides immitis* infection, treatment of the susceptible BALB/c mice with recombinant IFN-γ significantly protected mice against systemic challenge, and neutralization of IFN-γ significantly decreased the capacity to control disease by the resistant DBA/2 mice (62). Administration of recombinant IL-12 to the susceptible mouse strain also resulted in a reduction in the fungal load in the lungs (63), suggesting a crucial role of Th1 cells in host defense against *Coccidioides*.

In individuals with immune deficiency, histoplasmosis is a severe and potentially fatal disease. IFN-γ is the critical cytokine in activating macrophages to kill the organism (64). Mice that had an IFN-γ deficiency or that had been treated with an IFN-γ-neutralizing

antibody were susceptible to *Histoplasma capsulatum* infection (65), indicating an indispensable role for IFN-γ in host defense against *H. capsulatum*.

Th2 Cells

In vitro, Th2 cell differentiation requires the cytokine IL-4 and is controlled by master transcription factors GATA3 and STAT6. Th2 immune responses are characterized by the production of IL-4, which can serve as an autocrine factor for Th2 differentiation and can stimulate activated B cells and promote differentiation of B cells into plasma cells. Th2 cells also produce IL-5, a key mediator of eosinophilopoiesis and eosinophil activation. IL-13, a product of Th2 cells, has some overlapping functions with IL-4 but in the lung is a critical inducer of airway hyperresponsiveness, goblet cell metaplasia, and mucus hypersecretion. IL-4 and IL-13 are also produced in abundance by mast cells, eosinophils, basophils, and alternatively activated macrophages (reviewed in Reference 66). Recently, cytokines regulating IL-4 and IL-13, such as epithelial-derived thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, have received attention for their role in allergic inflammation. TSLP is induced during influenza A infection and augments viral-specific $CD8^+$ T cell responses by affecting DC function (67). IL-33 is also induced by influenza virus in murine lungs (4); however, it acts on type 2 ILCs to promote IL-13 production and induce airway hyperreactivity (68). Airway epithelial cell–derived IL-25 augments Th2 responses in NK cell–deficient mice during RSV infection (69).

Th2 cell cytokines can mediate host protective responses against helminth parasites. Parasitic pneumonia is a rare cause of pneumonia, occurring almost exclusively in immunocompromised persons, but HIV infection and use of immunosuppressive drugs have resulted in a resurgence of parasitic lung infections (70). *Schistosome cercariae* and hookworms typically migrate into the lungs transiently and cause lung inflammation before ultimately reaching other tissue sites for adult development (71). A recent study has suggested that the helminth-induced Th2-type response—which results when parasitic nematode larvae transiently migrate through the lung—mediates acute wound healing and control of inflammation that is initiated by IL-17 through IL-4 receptor signaling (72). This finding indicates a beneficial role for pulmonary Th2 responses in host defense against parasites, albeit in an indirect manner. Th2 cytokines, specifically IL-4, regulate the induction of cross-reactive IgE antibodies to aeroallergens by parasitic infection, suggesting that the immune responses to parasites can induce allergic disease (73). Pulmonary bacterial infections generally do not evoke strong Th2 responses. However, preexisting helminth infection inhibits anti-TB defense through the IL-4 receptor pathway (74).

Viral clearance and long-term humoral immunity to viral reinfections are largely dependent on the generation of neutralizing antibodies. Thus, investigators originally thought that IL-4-producing Th2 cells were required for optimal B cell and antibody responses against viral infection. However, the fact that Th2 cells were dominated by Th1 cells during viral infection was somewhat surprising (75). Nevertheless, the significance of Th2 immune responses in influenza infection is likely critical. On the one hand, Th2 cells drive the expansion, differentiation, and isotype switching of B cells and ultimately lead to the production of neutralizing antibodies (76, 77). These antibodies, at least in murine models of disease, are essential in viral clearance and protection from reinfection (78, 79). On the other hand, influenza virus–induced Th2 immune responses can also contribute to immunopathology in primary infection similar to RSV infection (80). In fact, a Th2-biased response to certain vaccine candidates, such as the formalin-inactivated RSV vaccine tested in the 1960s, leads to exacerbated pulmonary disease upon wild-type viral challenge (81).

The Th2 lineage effector cells in fungal infections are considered to be deleterious in part because they dampen the protective Th1 cell responses (82). The detrimental Th2 responses

in pulmonary fungal infections cause significant clinical problems because Th2 responses are closely related to allergic inflammation and asthma. One example of fungal Th2 responses in the lung is allergic bronchopulmonary aspergillosis (ABPA), which can result from exposure to inhaled fungal spores and a skewed Th2 immune response to *Aspergillus* spp. ABPA causes airway inflammation, which can ultimately be complicated by bronchiectasis. Several genes have been implicated in the development of ABPA, including surfactant protein A2, HLA-DR, and mutations in the cystic fibrosis (CF) transmembrane regulator. In fact, ABPA can occur in 4–15% of patients with CF. This may be due to prolonged retention of *Aspergillus* spp. in the lung as well as to diminished Treg cell response to fungal antigens. Vitamin D deficiency has also been noted as an independent risk factor for ABPA (83). The dampening of Th2 responses can be achieved by the addition of vitamin D in vitro, which alters the Treg/Th2 balance in the T cells isolated from ABPA patients by reducing DC expression of a costimulatory molecule, OX40L, and increasing DC expression of TGF-β (83). Furthermore, IL-4-deficient mice are resistant to invasive pulmonary aspergillosis owing to enhanced IL-12 and IFN-γ production; however, IFN-γ-deficient mice are highly susceptible to experimental invasive pulmonary aspergillosis (84), underscoring the potential deleterious effects of Th2 responses and protective effects of the Th1 response.

However, Th2 cell–dependent humoral immune responses could confer some protection in immunocompromised hosts against opportunistic fungal pathogens such as *Pneumocystis* (85). Indeed, animals with defective secretory IgM production have compromised fungal recognition and showed delayed *Pneumocystis* clearance, which is associated with suboptimal Th2 as well as Th17 responses (86). However, more data support the notion that a predominant Th2 response during fungal infection is generally associated with detrimental effects to the host.

Th17 Cells

Although Th17 cells, as the third T helper lineage, were discovered in a mouse model of autoimmune disease, the pivotal roles of IL-17 and IL-17 receptor signaling in pulmonary host defense were well recognized and appreciated even before the discovery of the Th17 lineage (87). Mice deficient in either IL-17 or IL-17RA have increased susceptibility to gram-negative bacteria, such as *Klebsiella pneumoniae* (87) and *Mycoplasma pneumoniae* (88). In the *K. pneumoniae* model, IL-17RA knockout mice showed decreases in pulmonary G-CSF production, granulopoiesis, and neutrophil recruitment, resulting in higher bacterial burdens in the lung as well as in increased systemic dissemination to the spleen (87). Early IL-17 production in response to *K. pneumoniae* requires signaling via TLR4 and IL-23 production (66). Mice that do not express IL-23p19 have decreased levels of IL-17 and exhibit a similar phenotype to IL-17RA knockout mice, with diminished production of G-CSF and CXCL1, 2, and 5 (89). In IL-23p19 knockout mice, treatment with recombinant IL-17 restores chemokine production and neutrophil recruitment and results in reduced bacterial burden both locally and systemically (89). Similar results have also been observed in *M. pneumoniae* infection (88).

In contrast, data suggest that IL-23 and IL-17 are dispensable for protection against primary infection by the intracellular pathogen *Mycobacterium tuberculosis*. Genetic deletion of neither IL-17RA nor IL-23p19 in mice perturbs clearance of *M. tuberculosis* (90, 91). However, IL-23p19 expression is induced by *M. tuberculosis*, and use of IL-23 as a vaccine adjuvant in *M. tuberculosis* vaccination results in a more robust antigen-specific Th1 response (92–94). Repeated exposure of *M. tuberculosis*–infected animals to mycobacterial antigens can initiate immune-mediated pathology. Specifically, the exposure of *M. tuberculosis*–infected guinea pigs to either live mycobacteria or mycobacterial antigens

results in necrotic inflammation at the site of challenge, a response that has been termed the Koch phenomenon (95). In a mouse model of the Koch phenomenon, *M. tuberculosis*–infected mice were repeatedly vaccinated subcutaneously with BCG (bacillus Calmette-Guérin) and developed an IL-23p19- and IL-17-dependent immunopathologic response, indicating a possible pathological consequence of vaccine-induced Th17 responses (96).

Interestingly, IL-17 is required for host defense against primary infection with a different intracellular pathogen, *Francisella tularensis*. This organism is a weak inducer of IL-12p70 in lung macrophages and DCs, and IL-17 expression is required for IL-12p70 production in DCs and macrophages. This IL-17-mediated induction of IL-12p70 is critical for the generation of Th1 responses that ultimately bring the infection under control (97). The IL-23/IL-17 axis is also critical in regulating lung neutrophil recruitment in response to mucoid *Pseudomonas aeruginosa*, but IL-23 was dispensable for bacterial clearance in the lung (98). IL-23 and IL-17 are also important in controlling methicillin-sensitive *Staphylococcus aureus* infection in the lung (99). *S. aureus* is also a known complication of pulmonary influenza infection, and one potential mechanism is the suppression of IL-23 and IL-17 by type I IFNs. Indeed, susceptibility to *S. aureus* infection can be restored by genetic deletion of the type I IFNAR in mice or by exogenous IL-23 to restore lung IL-17 responses. Figure 3 shows a schematic representation of the suppression of antibacterial Th17 responses by preexisting antiviral responses.

In primary infection, cellular sources of IL-17 have been carefully examined in various models, and Th17 cells are only one source of IL-17. γδ T cells and newly discovered ILCs are also major sources of IL-17 and IL-22, another Th17 signature cytokine. In contrast, in the vaccinated host, Th17 cells can be the dominant source of IL-17 (92, 100). In *M. tuberculosis*, vaccination induces Th17 cells that populate the lung earlier than Th1 cells and, after challenge, trigger the production of the chemokines CXCL9 and CXCL10 (ligands for CXCR3) that recruit Th1 cells, which ultimately restrict bacterial growth. However, in *K. pneumoniae*, Th17 cells proliferate and contract in response to conserved outer membrane proteins to a much greater extent than do Th1 cells. Vaccine-induced Th17 cells are $CD44^{hi}CD62L^{-}$ and are capable of conferring serotype-independent protection against bacteria with differing polysaccharide capsules. Th17-mediated serotype-independent protection has also been observed in mouse models of *Streptococcus pneumoniae* (101) and *Pseudomonas aeruginosa* (102). Taken together, these data support the hypothesis that antigen-specific memory Th17 cells confer a host advantage by providing heterologous mucosal immunity independent of serotype-specific antibodies.

Th17 and IL-17 responses in the lung are not always protective. In the setting of experimental primary influenza infection with PR8, IL-17 responses are detrimental to the host. In experiment models, elevated expression of IL-17 has been observed in IFN-γ knockout mice after influenza challenge and is associated with more weight loss and a longer time to recovery (103). IL-17RA knockout mice also showed significant reduction in weight loss, in neutrophil migration, in oxidized phospholipid generation, and in tissue myeloperoxidase upon lethal challenge of influenza (104), indicating a pathological role of IL-17RA ligands in host defense against influenza. Time-dependent increases in pulmonary IL-6, IL-23, and IL-17 expression were observed in a mouse model of RSV infection (105). Blockade of the IL-17 pathway by neutralizing antibody or gene knockout resulted in significant inhibition of mucus production, reduced inflammation, and decreased viral load, which is associated with significantly increased RSV-specific $CD8^{+}$ T cells (105), supporting a pathogenic role of IL-17 during RSV infections.

The critical role of IL-17RA in antifungal host defense was first demonstrated in a murine model of systemic candidiasis (106). IL-17RA knockout mice had increased mortality,

impaired peripheral neutrophil responses, and impaired neutrophil migration to the site of infected organs. Although there is a significant amount of evidence demonstrating a beneficial role for IL-17 in host defense against systemic and oral candidiasis (107), a similar phenomenon has not been seen in pulmonary fungal infections. A study using a mouse model of pulmonary *Cryptococcus* infection suggested that IL-17A may play a role in the early immune response to *Cryptococcus neoformans* but is dispensable for classical macrophage activation and control of fungal burden (108). However, the development of Th1 cells is crucial for long-term immunity following pulmonary *C. neoformans* infection, as demonstrated in *Ifng*$^{-/-}$ mice that had increased pulmonary fungal burden compared with wild-type mice (109). In humans, *Aspergillus fumigatus* induced a very limited Th17 response in PBMCs, and very low IL-17 levels were observed in bronchoalveolar lavage fluid and serum of patients with invasive aspergillosis (110). However, robust antigen-specific Th17 responses have been seen in the lungs of CF patients when stimulated with antigens from *Pseudomonas aeruginosa* and *Aspergillus* spp., although understanding the exact function of these cells requires further characterization (111). Furthermore, intranasal infection of mice with *A. fumigatus* induced detrimental Th17 responses because of the negative regulation of protective Th1 responses. Neutralization of IL-23 or IL-17 greatly increased resistance to *Aspergillus* infections (112). In a mouse model of chronic granulomatous disease (CGD), IL-17 produced by γδ T cells contributed to pathogenic inflammation (96). The IL-17 pathway may play a protective role in *Pneumocystis murina* infection (113). An IL-23 message was induced in alveolar macrophages with stimulation of *P. murina* organisms, and neutralization of IL-23 or IL-17 increased fungal burden in the lung during *Pneumocystis* infection in wild-type mice.

Overall, these data indicate that Th17 responses induced by fungal pathogens can be both protective and deleterious to the host depending on the context of infection, particularly the integrity of the downstream effector responses. For example, in the CGD model, neutrophils lack fungicidal activity and therefore fail to clear antigen. This failure may be important in driving the IL-17 pathology in this model (96). Recently, IL-23-dependent pathogenic Th17 cells have been discovered to emerge in the absence of TGF-β (114). Careful phenotyping of pathogenic and nonpathogenic Th17 cells in above-mentioned models may reconcile the discrepancies. However, another important issue that may regulate protective versus pathogenic Th17 responses is host factors, including the integrity of downstream effectors of IL-17R signaling in the epithelium or the integrity of neutrophil function. Thus, the structural integrity of the mucosa may be important in the outcome of fungal-induced Th17 responses.

Although data conflict regarding whether Th17 cells are protective or detrimental in primary fungal infection, vaccine-induced Th17 responses were necessary and sufficient to protect against the three major systemic mycoses (*Coccidioides posadasii*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*) in North America (115). Antifungal Th17 memory responses were further examined using a TCR transgenic mouse (116) that was generated with CD4^{+} T cells that specifically recognize an antigen from *B. dermatitidis*. These TCR transgenic CD4^{+} T cells recognize and proliferate in response to evolutionarily related systemic dimorphic fungi based on rRNA homology. When polarized to Th17 cells, these transgenic T cells can provide protection not only against *B. dermatitidis* but also against related fungi such as *H. capsulatum*. These fungi presumably express conserved antigens.

In the context of pulmonary host defense, the advantage of T cell–encoded effector cytokines could be threefold, as illustrated in Figure 4:

- T cells can rapidly divide and undergo apoptosis, providing a mechanism for rapid amplification and termination of Th1, Th2, and Th17 responses. This fulfills the

requirements of massive cytokine production upon pathogen invasion and prevents collateral damage once pathogens are cleared from the respiratory tract (Figure 4*a*).

- T cells can traffic to and from mucosal sites to provide immune reconnaissance. This can be achieved by chemotaxis between the interactions of chemokine receptors on T cells and the chemogradient induced by infection. This ability to traffic between mucosal sites is particularly important in pulmonary infection because one critical effector cell population, the neutrophil, matures and resides in the bone marrow. T cells serve as excellent candidate cells to emigrate outside the lung to control systemic responses to infection (Figure 4*b*). Supporting evidence comes from a mouse model of *Klebsiella pneumoniae*, in which migration of IL-17-producing cells to the bone marrow via the CXCL12/CXCR4 axis was partially responsible for controlling bacterial-induced G-CSF expression (M. Zheng & J.K. Kolls, unpublished observations).
- The generation of memory T helper cells might also confer an advantage to the host above and beyond what a pathogen-specific antibody can provide. We provide evidence (100) that outer membrane proteins conserved across several serotypes of *K. pneumoniae* are responsible for antigen-specific Th17 cell priming in mediastinal lymph nodes during vaccination, resulting in long-term protection against strains that are not effectively neutralized by antibodies, suggesting a possible evolutionary advantage for the acquisition of IL-17 expression by $CD4^+$ T cell subsets. Immunization with pneumococcal cell wall antigen also confers cross-serotype protection in mice infected with *Streptococcus pneumoniae* (117), and the protection is Th17 (101) and neutrophil (118) dependent, suggesting a potential novel antibody-independent immunization strategy against *S. pneumoniae* (Figure 4*c*).

IL-22, another major effector cytokine produced by Th17 cells, plays a critical role in pulmonary host defense, although the cellular sources can be more than just Th17 cells. In response to *K. pneumoniae* infection, IL-22 from $CD90^+$ T cells increased lung epithelial cell proliferation and increased transepithelial resistance to injury (119). IL-22 expression was also found in the lung of *M. tuberculosis*–infected patients as well as in *M. tuberculosis*–infected rhesus macaques. However, mice lacking IL-22 are unaffected in their ability to control *M. tuberculosis* (11). Thus, the exact role of IL-22 in *M. tuberculosis* remains to be explored. IL-22 is also essential in tissue repair after influenza infection, and both conventional NK cells (120, 121) and iNKT cells (122) are IL-22 producers, based on reports that used different strains and dosages of viruses as well as various time points after infection. IL-22 appeared to be critical for host defense against *A. fumigatus*, given that mice deficient in IL-22 or receiving neutralization antibody against IL-22 demonstrated a higher lung fungal burden after *A. fumigatus* challenge (123).

T Regulatory Cells

Two main types of regulatory T (Treg) cells have been identified: Extrathymically derived adaptive (or induced) $CD4^+Foxp3^+$ regulatory T (iTreg) cells can be phenotypically and functionally distinguished from thymus-derived natural $Foxp3^+$ regulatory T (nTreg) cells. Both play significant roles in tuning down effector immune responses, however. Mutations of the *FOXP3* gene in humans cause IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), a rare disorder that usually results in death in early infancy or childhood. Lung pathology has been revealed by postmortem examination of IPEX patients (124).

Generation of iTreg cells depends on productive antigen presentation by APCs in a microenvironment rich in TGF-β and IL-2 (125). Depending on the type and stage of

infection, suppression of inflammatory responses by iTreg cells can be both beneficial and deleterious in host defense. In the lung, these cells play a critical role in mediating tolerance to inhaled antigen (68).

The immune response must eradicate the invading pathogens with the minimal cost of damage to self-tissues. The average adult takes 15 to 20 breaths a minute—over 20,000 breaths a day. The average adult at rest inhales and exhales 7 or 8 liters of air per minute, or approximately 11,000 liters of air in a day. Air at sea level contains 78% nitrogen and 21% oxygen, but inspired air can also contain large concentrations of antigens, including organic dusts, inorganic particles, and biological agents such as bacteria, viruses, and fungal spores. In most cases, these antigens are cleared by mucociliary clearance and coughing. However, if the antigens manage to persist in the lung long enough, they will be detected by the immune system and trigger immune responses. To maintain a tolerogenic environment that protects the host from inflammatory damage, the immune response in the lungs must be tightly regulated.

Treg cells serve as critical cells in controlling excess inflammation and in maintaining and restoring a homeostatic environment. In *Chlamydia pneumoniae* infection, which is associated with induction and exacerbation of asthma, Treg cells seem to play a protective role because depletion of Treg cells in a mouse model exacerbated allergic airway sensitization and eosinophilic airway inflammation (126). In mice acutely infected with *Pseudomonas aeruginosa*, depletion of Treg cells with anti-CD25 antibody did not affect airway neutrophil infiltration or overall survival, indicating that Treg cells do not contribute significantly to host defense against *Pseudomonas* (127).

In chronic infection, Treg cells can be exploited by the pathogen, such as in *M. tuberculosis* infection, to suppress protective immune responses and benefit its survival in the host. Treg cells are increased in TB patients and may contribute to suppression of Th1-mediated immune responses (128). In a C57BL/6 mouse model, depletion of Treg cells early after infection resulted in a small increase in cytokine production but did not alter the course of either *M. tuberculosis* or BCG infections (129). Moreover, Treg inactivation by CD25 neutralizing antibody during BCG vaccination did not affect protection against virulent challenge (130). However, in BALB/c mice, the attenuation of Treg subsets during BCG vaccination had a positive impact on the protective capacity of this vaccine against *M. tuberculosis* infection (131). A recent study found that Treg cells recognizing *M. tuberculosis* antigens suppressed protective immune response during TB, supporting a pathogenic role for Treg cells in TB (3). The observed discrepancies in the roles of Treg cells in two different mouse strains can likely be explained by different host genetic backgrounds (132).

Influenza A virus infection results in the robust induction of a Treg response in mice (133, 134), and virus-specific Treg cells can be detected long after viral clearance in humans (135), suggesting a potential role for Treg cells in limiting excessive inflammation induced by influenza A virus infection. Furthermore, adoptive transfer of polyclonal Treg cells into influenza-infected, lymphocyte-deficient mice prolongs survival and reduces the innate inflammatory response (136). However, depletion of Treg cells by anti-CD25 antibody did not alter influenza A virus–induced mortality, weight loss, viral clearance, or cellularity within the lung (134). In RSV infection models, Treg cells limit immunopathology by influencing the trafficking and effector function of virus-specific $CD8^+$ T cells in the lungs and draining lymph nodes (137, 138). Similar beneficial roles of Treg cells have been observed in infections with fungal pathogens such as *Paracoccidioides brasiliensis*. In a mouse model of paracoccidioidomycosis, the absence of TLR4 signaling did not increase mortality rates but resulted in less severe inflammatory reactions in the lung, which is

associated with increased numbers of Treg cells (139). Mouse models of *Pneumocystis* clearly demonstrate that adoptive transfer of $CD4^+CD25^+$ Treg cells can inhibit pulmonary inflammation caused by $CD4^+CD25^-$ effector cells and enhance survival of the host (140, 141).

Some HIV patients experience immune reconstitution inflammatory syndrome (IRIS) as a result of pathological responses induced during immune restoration following the initiation of highly active antiretroviral therapy (HAART). The presence of antigenic stimulus, whether infectious or noninfectious, is reportedly a prerequisite to developing IRIS (142). Interestingly, elevation of IL-6, IL-10, and IFN-γ expression in IRIS patients has been observed (143), suggesting a potential link between IRIS and Treg cells.

A comprehensive analysis of Treg cells in peripheral blood has been carried out with a large cohort of HIV-infected patients ($n = 131$) (144). In this study, investigators observed a significantly increased proportion of Treg cells in the remaining $CD4^+$ T cells of HIV-positive patients compared with that of healthy controls, suggesting that Treg cells might be relatively more resistant to HIV depletion. Additionally, the relative frequency of Treg cells directly correlated with HIV viral load and inversely with $CD4^+$ T cell counts, indicating a deleterious role for Treg cells in antiviral responses. However, the absolute Treg cell number was reduced in HIV-infected patients compared with healthy controls, and this reduction could be what leads to the lack of anti-inflammatory responses in IRIS patients.

Thus, although not involved in clearing pulmonary pathogens directly, Treg cells orchestrate their functions by modulating other lineages of $CD4^+$ T cells, $CD8^+$ T cells, and myeloid cells as well.

T Follicular Helper Cells

Tfh cells express the chemokine receptor CXCR5 to home to developing germinal centers, where they instruct B cells to class switch. However, their roles in pulmonary host defense have been underexplored. A recent study has shown that IL-21, a cytokine produced by Tfh, promotes the pathogenic inflammatory effect of pneumovirus in mice (145). The exact role of Tfh in this model has yet to be defined. Tfh cells can be induced in mice infected with influenza A virus (146). The development of B cell responses to influenza A was impaired by high-dose IL-2, and this was associated with impaired Tfh responses (147). However, whether Tfh cells are required for viral clearance has not been examined. A recent study suggests that Tfh and Th1 cells share a transient Tfh-like cell stage, raising the question of whether Tfh cells are a distinct lineage of $CD4^+$ T cells (148).

$CD8^+$ T Cells

$CD8^+$ T cells are cytotoxic T cells and are also major producers of IFN-γ, TNF-α, and IL-2. Generation of strong antigen-specific $CD8^+$ T cell responses to protective dominant epitopes of influenza in the lungs occurs after infection or immunization and is critical for clearance of the virus (149). However, the release of cytotoxic molecules (e.g., granzyme and perforin) and antiviral cytokines (e.g., TNF-α and IFN-γ) can also contribute to lung pathology (150). Transgenic mice with an elevated precursor frequency of anti-influenza $CD8^+$ T cells are protected against low-dose viral challenge but succumb to high viral dose owing to exacerbation in viral pathology. This difference suggests a critical antigen threshold in $CD8^+$ T cell activation that determines protection versus immunopathology during influenza (151). In RSV infection, $CD8^+$ T cells are induced and recruited into the lungs but show significantly impaired expression of effector activity (152). Indeed, priming a RSV-specific $CD8^+$ T cell response using recombinant vaccinia virus encoding the immunodominant RSV $CD8^+$ T cell epitope inhibited formalin-inactivated RSV vaccine–

induced pulmonary eosinophilia and disease exacerbation (153). These data support a requirement for sufficient viral-specific $CD8^+$ T cell priming in RSV vaccine development.

The protective role that $CD8^+$ T cells play in immunity to *M. tuberculosis* has also been well appreciated. Antigen-specific $CD8^+$ T cells recognize and lyse *M. tuberculosis*–infected cells and produce cytokines such as TNF-α and IFN-γ, both of which are critical for macrophage activation (reviewed in Reference 154). In a mouse model of *Streptococcus pneumoniae* infection, $CD8^{-/-}$ mice exhibited significantly increased bacterial dissemination, enhanced lung inflammation, and significantly higher mortality compared with wild-type mice. Perforin$^{-/-}$ and IFN-$\gamma^{-/-}$ mice also exhibited enhanced lethality compared with wild-type mice (155), underscoring the importance of $CD8^+$ T cells and potentially their effector molecules in bacterial pneumonia. In a cohort of HIV-infected women, lower $CD8^+$ T cell counts were associated with increased risk for bacterial pneumonia and all-cause mortality (156), further supporting the protective role of $CD8^+$ T cells in host defense against pulmonary bacterial infections.

$CD8^+$ T cells in the naturally occurring host response to fungal pathogens in the lung have not been well documented, although *Aspergillus*-specific $CD8^+$ T cells have been shown to be present in mice (157) as well as in healthy humans (158). Lack of activation of the protective memory $CD8^+$ T cell population in $TLR3^{-/-}$ mice is associated with higher susceptibility to pulmonary aspergillosis (159), suggesting a protective role of $CD8^+$ T cells in pulmonary antifungal immunity. $CD8^+$ T cells are also recruited to the lung in large numbers in response to *Pneumocystis* infection, and they are associated with some level of host defense (160) as well as with lung injury (161). This discrepancy can be explained at least partially by the heterogeneity of antigen-specific $CD8^+$ T cells induced by *Pneumocystis* infection because $CD8^+$ T cells with a T-cytotoxic 1 (Tc1) phenotype seem to be protective, whereas non-Tc1 cells seem to contribute to immunopathology. Recently, IL-17-producing $CD8^+$ T cells (Tc17) were shown to provide host protection against both pulmonary viral and fungal pathogens. Tc17 cells can be found in the lung following primary influenza challenge, and in vitro–generated Tc17 cells expand after transfer to naive recipients following viral challenge and confer protection against lethal influenza infection (162). In $CD4^+$ T cell–depleted mice, Tc17 cells are induced upon vaccination and mediate protection against *Blastomyces dermatitidis* and *Histoplasma capsulatum* in a neutrophil-dependent manner (163). IL-17- and IL-22-producing $CD8^+$ T cells are also found in SIV-infected rhesus macaques (K. Chen & J.K. Kolls, unpublished data). Taken together, these data suggest that Tc17 cells can confer protection in HIV patients and can also be exploited as a vaccine target for pulmonary host defense in immunocompromised individuals.

γδ T, Invariant NKT, and Innate Lymphoid Cells

γδ T cells, iNKT cells, and ILCs are all capable of responding immediately to cytokines produced by DCs and macrophages in the course of infection in the lung. These three cell types are critical for producing $CD4^+$ T cell– and $CD8^+$ T cell–derived cytokines before an adaptive immune response fully develops, bridging the innate and adaptive systems and optimizing the adaptive immune response against various pathogens.

γδ T cells represent a small subset of T cells that have a T cell receptor composed of one γ chain and one δ chain, as opposed to conventional T cells that have a T cell receptor made up of α and β chains. γδ T cells are a major source of IFN-γ, TNF-α, and IL-17 in mice infected with *Klebsiella* (100, 164), and mice lacking γδ T cells exhibit higher bacterial dissemination and poor survival (164). γδ T cells are also the dominant source of IL-17 during *Mycobacterium tuberculosis* infection (165) and a critical cellular source of TNF-α in *Streptococcus pneumoniae* infection (166). iNKT cells share properties of both T cells and NK cells and recognize antigens presented by the CD1d molecule. iNKT cells express

limited T cell receptors: Vα14 for mouse and Vα24 for human. iNKT cells can be activated by an innate cytokine-and antigen-driven pathway, produces IFN-γ, and play a role in numerous bacterial infections in the lung including *S. pneumoniae* and *Pseudomonas aeruginosa* (reviewed in Reference 167). In response to viral infection, such as influenza, iNKT cells produce IL-22 and participate in the repair of the lung epithelium (122) and influence $CD8^+$ T cell responses by promoting respiratory DC maturation (168). γδ T cells produce IL-17 in influenza-infected mice and seem to contribute to pathogenic inflammation (104), whereas a subset of human γδ T cells produces IFN-γ after influenza stimulation (169). Unlike iNKT and γδ T cells, ILCs found in the lung in response to influenza only produce type 2 cytokines and participate in tissue repair and allergic inflammation (170).

Little is known about the role of ILCs in antifungal immunity in the lung. The roles of γδ T and iNKT cells in host defense against *Cryptococcus* have been investigated. Activation of iNKT cells by their natural ligand, α-galactosylceramide, results in enhanced IFN-γ production and protective Th1 responses (171), whereas γδ T cells seem to downmodulate this protective Th1 response, given that γδ T cell–deficient mice have increased IFN-γ production and reduced fungal burden (172). γδ T cell–deficient mice also show a more rapid and complete resolution of *Pneumocystis* infection than do C57BL/6 controls. This augmented resolution is associated with elevated IFN-γ levels in bronchoalveolar lavage fluid predominantly produced by $CD8^+$ T cells (173).

T CELL–MEDIATED HOST DEFENSE IN COINFECTIONS, CHRONIC OBSTRUCTIVE PULMONARY DISEASE, AND CYSTIC FIBROSIS

The normal lung microbiome remains to be defined. However, there is significant evidence that some bacterial infections occur in otherwise healthy hosts in the setting of a prior or concomitant viral infection. Recently, several studies have shed light on the immunological mechanisms that underlie these coinfections.

Streptococcus pneumoniae, *Haemophilus influenzae*, and *Staphylococcus aureus* were the most common bacterial coinfection during the 2009 H1N1 influenza pandemic and were associated with a higher risk of morbidity and mortality (174). In a murine coinfection model, severe bronchopneumonia with massive hemorrhage in influenza- and *Streptococcus pneumoniae*–coinfected mice was associated with augmented type 1 proinflammatory responses (175). Pulmonary IFN-γ produced during T cell responses to influenza infection can also suppress innate immunity against *S. pneumoniae* by downregulating the expression of the class A scavenger receptor MARCO on alveolar macrophages (91). Furthermore, antiviral responses to influenza can also sensitize hosts to secondary bacterial pneumonia by inhibiting the production of neutrophil chemoattractants CXCL1 and CXCL2 (176). In another mouse model of coinfection of influenza and *S. aureus*, influenza A was shown to strongly induce type I IFN and subsequently suppress the Th17 response, which was required for *S. aureus* clearance (99). These studies suggest that alteration of the normal T cell response by influenza likely compromises the host defense mechanism and worsens the outcome of subsequent bacterial infection. Coinfection of RSV and bacteria such as *S. pneumoniae*, *H. influenzae*, and *S. aureus* have also been reported (177). However, the immune responses in these patients are currently underexplored, and animal models to study these coinfections are also limited.

Viral and bacterial infections are often observed in chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and CF. In fact, coinfections are associated with most severe COPD exacerbations requiring hospitalization, and the presence of infection is related to exacerbation severity (178). Interestingly, blunted γδ T lymphocyte responses have been observed in COPD patients (179), suggesting that γδ T cells may be critical for

host defense in COPD. Although the Th1 immune response to gram-negative bacterial infections is impaired in COPD [because PBMCs from COPD patients had reduced IFN-γ production upon lipopolysaccharide stimulation (180)], the Th17 response augmented by cigarette smoke seems to involve disease pathogenesis through induction of CCL2 and matrix metalloproteinase (2). Furthermore, the induction of osteopontin expression on lung APCs seemed to be responsible for the cigarette smoke–induced pathological Th17 responses in emphysema (181). Rhinovirus is responsible for the common cold and is currently the most important trigger of COPD exacerbations (182). The mechanisms of virus-induced exacerbations are not well understood. Although currently there is no direct evidence that rhinovirus infection triggers IL-17 production, IL-1β, a Th17-promoting cytokine, is released by human bronchial epithelial cells after infection with rhinovirus (183). IL-17A also synergistically enhances human rhinovirus-16-induced epithelial production of CXCL8, a neutrophil chemoattractant (184), which may contribute to viral-induced exacerbation. COPD exacerbations are often associated with increased levels of mediators including TNF-α, IL-6, and CXCL8 and inflammatory cells such as neutrophils and eosinophils (reviewed in Reference 111). All of these mediators are related to Th1 and Th17 responses, which suggests that T cells may play an important role in viral-induced COPD exacerbation.

In CF, significantly elevated levels of the Th17 cytokines IL-17A and IL-17F were found in the sputum of patients who were colonized with *Pseudomonas aeruginosa* at the time of pulmonary exacerbation, and the levels declined with therapy directed against *P. aeruginosa* (185). Th17 cells are also found in the airway submucosa in CF (186), suggesting a pathogenic role of Th17 cells in that disease. However, the inability of dysfunctional epithelial cells to respond to Th17 cytokines in CF can also contribute to *Pseudomonas* colonization and lead to disease exacerbation. In normal lungs, where infection can be resolved in a timely fashion, the development of a memory response is protective and results in more efficient clearance of the pathogen with subsequent infections. In CF patients, the inability to clear *Pseudomonas aeruginosa* because of abnormalities in the airway surface liquid (ASL) and ciliary functions leads to persistent activation of inflammatory pathways that promote chronic IL-17 production and the development of a Th17 phenotype (Figure 5). Despite persistent neutrophilia in the lung, this response cannot effectively clear the pathogen (187). One hypothesis is that this may be partially due to an intrinsic defect in CF neutrophils (188). Failure of pathogen eradication would lead to further neutrophil recruitment, and thus chronic lung injury would be promoted over time (189). More recently, a defect in airway epithelial HCO_3^- secretion has been observed in a porcine CF model, which leads to a decrease of ASL pH and the inhibition of antimicrobial protein activity (190). Moreover, IL-17A induces bicarbonate secretion in human bronchial epithelial cells in a CFTR-dependent manner (191), suggesting that despite robust Th17 responses in the CF lung, a defect in bicarbonate secretion may render this Th17 response ineffective (Figure 5). T cell responses in asthma have been recently reviewed extensively (192) and are not discussed here.

CONCLUSIONS

Th1 and $CD8^+$ T cells mainly contribute to successful host defense against viral pathogens such as influenza and RSV, whereas Th2 and Th17 responses are often detrimental and exacerbate diseases in RSV and influenza, respectively. Th1 and Th17 cells as well as γδ T cells are essential components of the armamentarium against bacterial and fungal infections. Treg cells benefit the host by repressing excessive inflammation during infection. γδ T cells, iNKT cells, and ILCs are also important mediators in pulmonary host defense that allow immediate responses to pathogens.

Investigators have long appreciated T cell diversity, but there is now increased recognition of T cell plasticity (193). It is challenging but promising to utilize the plastic nature of T cells to manipulate immune responses in the lung and ultimately balance immunological activation and tolerance in host defense and inflammation.

ILCs have emerged as a major immune modulator in the mucosal site, and their role seems to parallel that of the known T helper subsets: Th1, Th2, and Th17. Currently, only type 2 ILCs have been identified in the lung (170). Whether other types of ILCs are present in the lung and whether ILCs show plasticity remain to be addressed. The roles of Th17 cells in diseased lung are still controversial. A clear understanding of the Th17 pathway is critical to determining whether therapy targeting Th17 cells will be helpful in preventing inflammation-mediated damage. The challenges of developing safe and effective immunosuppressive therapy are significant.

Th17-based mucosal vaccines against extracellular bacterial and fungal pathogens seem promising. However, because of the proinflammatory nature of Th17 cells, safety issues have to be carefully addressed. The discovery of Tc17 cells opens up opportunities for development of a $CD8^+$ T cell–based mucosal vaccine against pulmonary pathogens for immunocompromised people, especially HIV-infected patients.

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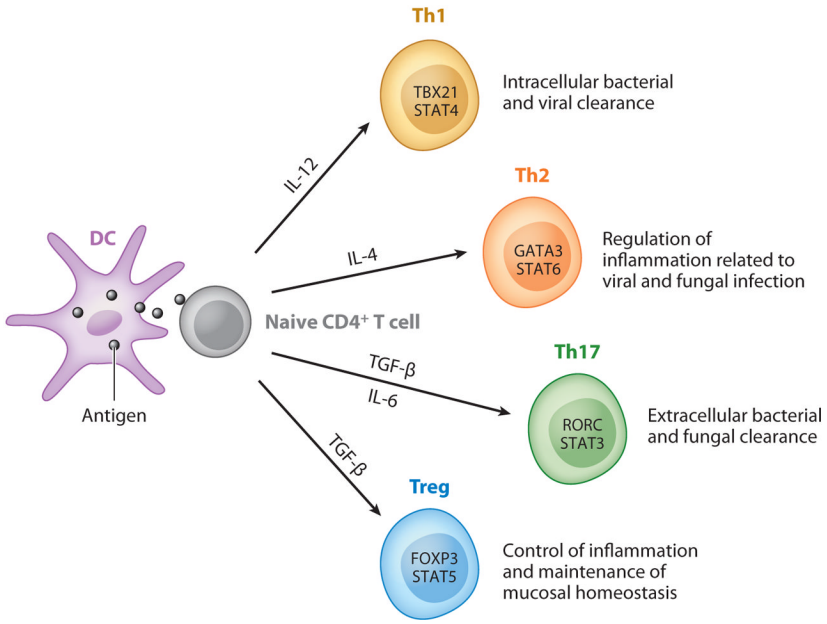

Figure 1.

Major CD4$^+$ T cell subsets in pulmonary host defense. Naive CD4$^+$ T cells differentiate into Th1, Th2, Th17, and Treg cells after antigen encounter presented by DCs followed by lineage specification that is controlled by certain cytokine environments (IL-12, IL-4, TGF-β/IL-6, or TGF-β, respectively) that regulate the expression of lineage-specific transcription factors (depicted within the respective T helper lineage cells). These effector T cells play critical roles in mediating pulmonary host defense, as noted in the figure.

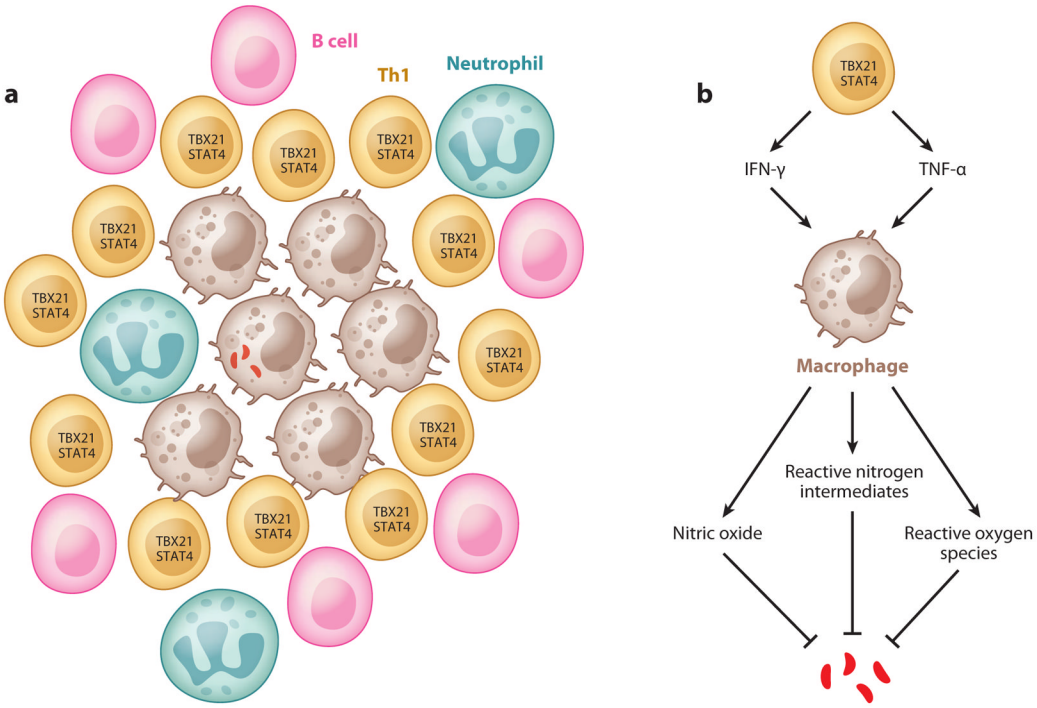

Figure 2.

Th1 cells and granuloma formation. (*a*) Schematic representation of granuloma structure: An infected macrophage is surrounded by many cell types such as uninfected macrophages, Th1 cells, B cells, and neutrophils. (*b*) Functions of Th1 cells in tuberculosis: Th1 cells activate macrophages via cytokines such as TNF-α and IFN-γ. Activated macrophages kill bacteria through nitric oxide, reactive nitrogen intermediates, and reactive oxygen species (see text for details).

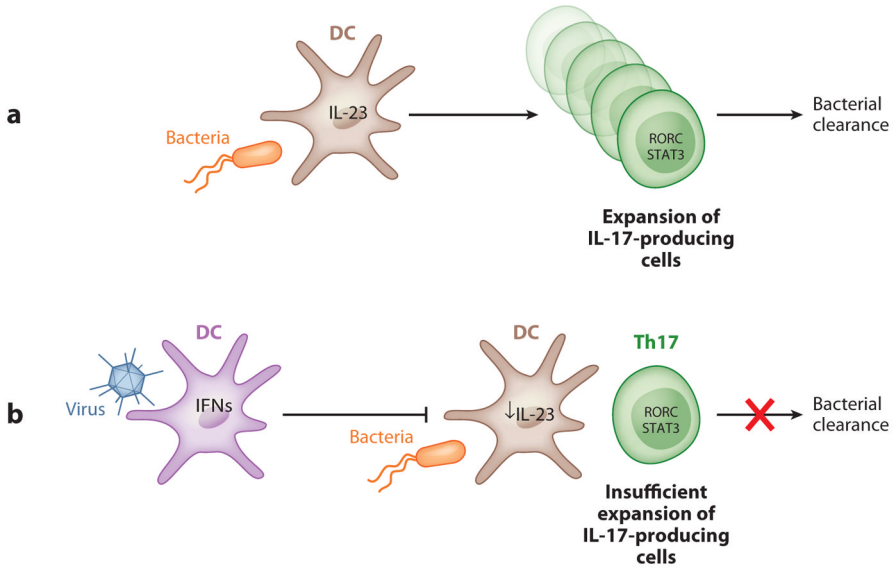

Figure 3.

Suppression of antibacterial Th17 responses by preexisting antiviral responses. (*a*) Under normal conditions, infection by a bacterial pathogen induces IL-23 production by dendritic cells (DCs) and leads to the generation and expansion of Th17 cells, which are essential for bacterial clearance. (*b*) In a coinfection condition, viral infection induces type I interferon (IFN) production by DCs, which can inhibit IL-23 production by these cells. This viral-induced reduction in IL-23 results in compromised IL-17 responses due to insufficient expansion of IL-17-producing cells, leading to reduced host defenses against bacterial infection.

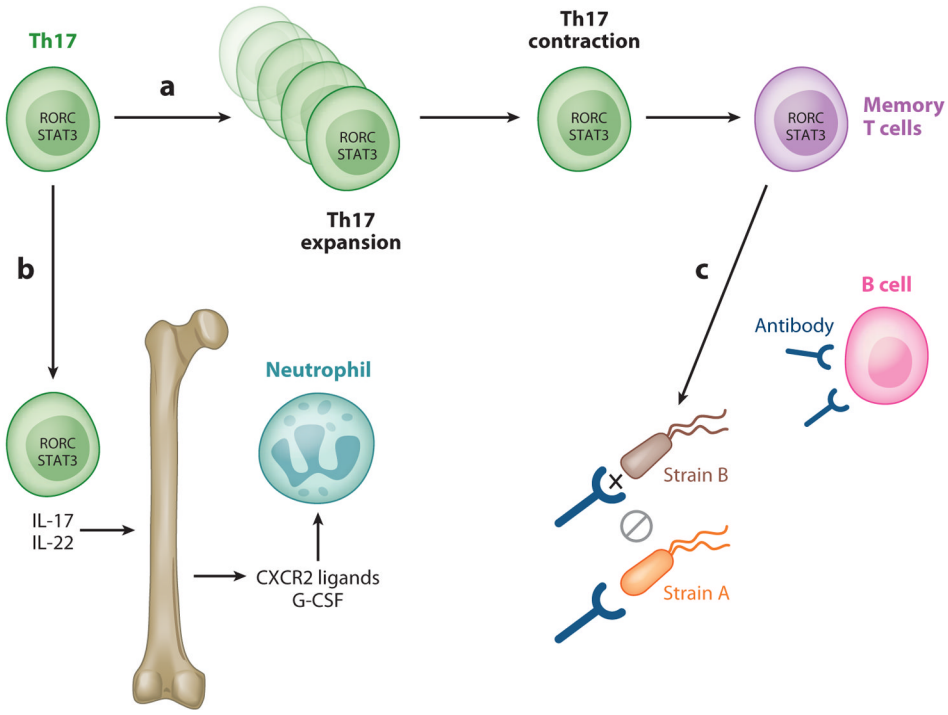

Figure 4.
Current hypotheses of the requirement for T cell immunity in the lung. (*a*) T cell responses can be turned on and off quickly through clonal expansion and apoptosis. (*b*) T cells can migrate to a distal site such as bone marrow to mobilize neutrophils through CXCL1 and G-CSF. (*c*) Memory T cells recognize conserved bacterial antigen and provide serotype-independent protection.

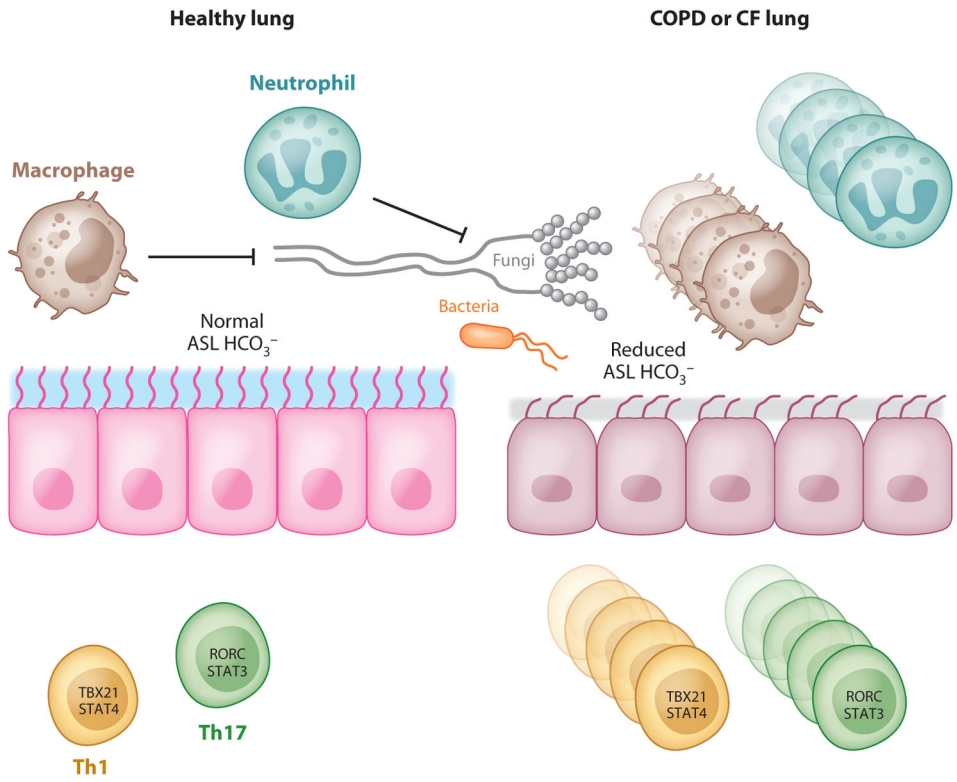

Figure 5.
Proposed model of T cell responses in chronic lung disease. In the context of COPD or CF, lung epithelial cells have reduced anion transport (Cl^- and HCO_3^-), leading to reduced airway surface liquid (ASL) volume and reduced antimicrobial activity. This can result in pathogen persistence and constitutive T cell activation and proliferation, leading to parenchymal lung damage.

Table 1

List of lung diseases from the American Lung Association and their relations to host defense

Name of the lung disease	Definition of disease	Relation to host defense
Acute bronchitis	Inflammation of the bronchial tubes	Usually direct
Asbestosis	Scarring of lung tissue as a result of breathing in asbestos fibers	Pathway involved
Asthma	A lung disease that makes it harder to move air in and out	Pathway involved
Bronchiolitis	An inflammation of the bronchioles	Pathway involved
Bronchopulmonary dysplasia	A lung disease that occurs most often in premature babies	Indirect
Byssinosis	A lung disease caused by exposure to dusts from cotton processing, hemp, and flax	Pathway involved
Chronic bronchitis	Chronic inflammation of the airways or bronchial tubes	Pathway involved
Coccidioidomycosis	An infection of the lungs caused by inhaling spores of the fungus *Coccidioides immitis*	Direct
Chronic obstructive pulmonary disease	Also known as emphysema and chronic bronchitis	Pathway involved
Cryptogenic organizing pneumonia	A disease in which the bronchioles and alveoli become inflamed with connective tissue	Pathway involved
Cystic fibrosis	An inherited disease that causes thick, sticky mucus in the lungs, pancreas, and other organs	Pathway involved
Emphysema	A lung disease that makes it hard to breathe	Pathway involved
Hantavirus pulmonary syndrome	A disease that comes from contact with infected rodents or their urine, droppings, or saliva	Direct
Histoplasmosis	An infection in the lungs caused by inhaling the spores of the fungus *Histoplasma capsulatum*	Direct
Human metapneumovirus	Infections that cause colds, pneumonia or bronchitis	Direct
Hypersensitivity pneumonitis	A disease in which lungs become inflamed when a patient breathes in certain fungal dusts	Pathway involved
Influenza	A serious respiratory illness caused by infection with three influenza virus families: A, B, or C	Direct
Lung cancer	The second most commonly diagnosed cancer and the most common cause of cancer death	Pathway involved
Lymphangiomatosis	A disease of the lymphatic system	Indirect
Mesothelioma	An uncommon form of cancer that involves the mesothelium	None
Nontuberculous mycobacterium	An infection caused by mycobacteria that are found in water and soil and only infect some people	Direct
Pertussis	A respiratory infection caused by the bacteria *Bordetella pertussis*	Direct
Pneumoconiosis	An occupational lung disease caused by inhaling coal dust	Indirect
Pneumonia	A common lung infection caused by bacteria, a virus, or fungi	Direct
Primary ciliary dyskinesia	Blockage and infections caused when mucus accumulates due to cilia dysfunction	Direct
Pulmonary fibrosis	A disease marked by scarring in the lungs	Direct
Pulmonary vascular disease	A disease that affects the blood circulation in the lungs	None
Respiratory syncytial virus	The most common cause of bronchiolitis and pneumonia in children younger than age one in the United States	Direct
Sarcoidosis	A disease caused by small areas of inflammation	Direct
Severe acute respiratory syndrome	A disease caused by a group of viruses called the coronaviruses	Direct

Name of the lung disease	Definition of disease	Relation to host defense
Silicosis	A disease caused by inhaling tiny bits of silica	Direct
Tuberculosis	A common infectious disease caused by various mycobacteria, usually *Mycobacterium tuberculosis*	Direct