Th17 cells at the crossroads of innate and adaptive immunity against infectious diseases at the mucosa

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T helper type 17 (Th17) cells are a distinct lineage of T cells that produce the effector molecules IL-17, IL-17F, IL-21, and IL-22. Although the role of Th17 cells in autoimmunity is well documented, there is growing evidence that the Th17 lineage and other interleukin (IL)-17-producing cells are critical for host defense against bacterial, fungal, and viral infections at mucosal surfaces. Here we summarize recent progress in our understanding of the function of IL-17-producing cells as a bridge between innate and adaptive immunity against infectious diseases at the mucosa.

INTRODUCTION

CD4⁺ T helper cells (Th cells) are important mediators of adaptive immune responses. After interaction with antigen-presenting cells, T cells receive signals by engagement of the T-cell receptor (signal 1), co-stimulatory molecules (signal 2), and a complex network of cytokine signals (signal 3) and undergo activation and differentiation into effector CD4⁺ T cells. Their critical role in host defense against infections is clearly manifested in humans with either congenital deficiencies or acquired deficiency (most commonly through human immunodeficiency virus (HIV) infection) of the T-cell lineage. It was recognized shortly after the initial description of AIDS that the primary immunodeficiency was the loss of circulating CD4⁺ T cells and that the risk of opportunistic infection with many pathogens was directly related to the severity of the CD4⁺ T-cell deficiency. Four years after the initial clinical description of AIDS, Mosmann *et al.*¹ described the first two CD4⁺ T-cell subsets based on discrete cytokine profiles. Th1 effectors produce interferon- γ (IFN- γ) and regulate cellular immunity against intracellular infections, whereas Th2 cells produce interleukin (IL)-4, IL-5, and IL-13 and mediate humoral immunity against parasite infections (**Figure 1**). However, this dichotomy of T-cell subsets could not fully explain the infections seen in congenital or acquired absence of CD4⁺ T cells, such as mucosal candidiasis, *Pneumocystis carinii* pneumonia, or some bacterial pneumonias. For example, mice deficient in Th1 or Th2 responses (or both) are not permissive for *P. carinii* pneumonia,² a hallmark infection in AIDS patients with low CD4⁺ T-cell counts. These

data suggested that other CD4⁺ T-cell lineages are critical for host defenses against opportunistic infections. Recent compelling evidence has clearly changed this traditional paradigm of the Th1/Th2 cell dichotomy to include a third subset of T cells referred to as Th17 cells.^{3–6} Th17 cells produce the cytokines IL-17A (IL-17)^{4,5} and IL-17F,³ as well as the cytokines IL-21^{7,8} and IL-22^{9,10} (**Figure 1**). This new Th17 cell lineage fills in some of the missing gaps in host immunity, which is not fully explained by the Th1/Th2 paradigm.

IL-17 is the prototype of Th17 cytokines and is the best studied of the Th17 cytokines. The receptor for IL-17 (IL-17RA) is a type I transmembrane protein and is ubiquitously expressed on various organs, including the lung, kidney, and spleen.¹¹ Cells that express the receptor for IL-17 are leukocytes, epithelial cells, mesothelial cells, vascular endothelial cells, keratinocytes, and fibroblasts and respond to IL-17R-mediated signaling by the production of granulocyte colony-stimulating factor (G-CSF), IL-6, and IL-8 and mediate granulopoiesis, neutrophil recruitment, and inflammatory responses (reviewed in ref. 12). IL-17 was initially identified as a key factor in the induction of inflammation and tissue destruction associated with animal models of autoimmune disease such as multiple sclerosis, collagen-induced arthritis, and experimental colitis (reviewed in refs. 13,14). On the basis of the efficacy of targeting IL-17 in pre-clinical models of these chronic inflammatory conditions, IL-17 is currently a promising therapeutic target.¹⁵ Initial studies^{16–18} implicating IL-17 to be protective against extracellular bacterial infections at the lung mucosal surface was through the effective recruitment of neutrophils

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Received 14 May 2009; accepted 9 June 2009; published online 8 July 2009. doi:10.1038/mi.2009.100

Figure 1 Current understanding of T-helper cell differentiation. Naive CD4⁺ T cells, after activation by signaling through the T-cell receptor and co-stimulatory molecules such as CD28 and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), can differentiate into three lineages of effector T helper(Th) cells, namely Th1, Th2, or Th17 cells. Th cell subsets produce different cytokines and have distinct immunoregulatory functions. Th2 cells produce interleukin (IL)-4, IL-5, and IL-10 and promote immunity against parasites such as helminths. Th1 cells produce interferon- γ (IFN- γ) and tumor necrosis factor- α (TNF- α) and provide immunity against intracellular pathogens. Th17 cells produce the cytokines IL-17/IL-17F, IL-22, IL-21, and TNF- α and primarily promote immunity against extracellular pathogens.

mediated by chemokine induction. More recent advances in our understanding of the complexity of the Th17 cytokines suggests broader effects for these cytokines in protecting against various pathogenic bacteria, fungi, and viruses at different mucosal surfaces. In this review, we have summarized recent progress in our understanding of the role of Th17 cells and effector cytokines and their function as a bridge between innate and adaptive immunity against infectious diseases at the mucosa.

INNATE RECEPTORS AND SIGNALING PATHWAYS INVOLVED IN THE INDUCTION OF TH17 CELLS DURING INFECTIONS

The differentiation of Th17 cells is determined by the exposure to transforming growth factor- β , IL-6, IL-21, whereas IL-23 further stabilizes the commitment of Th17 cells to this lineage (reviewed in ref. 19). These polarizing cytokines act on newly primed cells to induce the expression of the transcription factors, ROR γ t and ROR α , which induces Th17 differentiation.^{20,21} ROR γ t also controls the expression of IL-23-inducible receptors on newly primed T cells, further expanding their responsiveness to IL-23 to sustain the T-lineage-specific responses. The gp 130–Stat3 pathway is essential for the expression of ROR γ t and Th17 development.^{22–24} Recently, it has been shown that IL-21 acts downstream of these events to further amplify the generation of Th17 cells in an autocrine manner.⁷ Additional cofactors for the differentiation of Th17 are IL-1 β and tumor necrosis factor- α (TNF)- α .^{25,26} Although *in vitro* studies have shown that IL-23 is redundant in the generation of Th17 responses,²⁷ *in vivo* studies in the mouse model^{18,28,29} and in humans³⁰ have shown that IL-23 is critical for the maintenance of Th17 responses *in vivo*. As over-induction of Th17 cells can effect tissue damage due to the induction of inflammatory

pathways, the generation of Th17 cells is strictly regulated. For example, cytokines such as IL-27,^{31,32} those belonging to Th1 (IFN- γ) and Th2 (IL-4^{4,5} and IL-2³³), tightly regulate the induction of Th17 cells. Endogenous lipid mediators such as prostaglandin E2 released under inflammatory conditions promote Th17 cells differentiation,^{34–39} suggesting that external infection-induced mediators can also influence the decision between a Th1/Th2/Th17 and regulatory T-cell responses.

Several of these Th17-polarizing cytokines such as IL-23, transforming growth factor- β , IL-6, and IL-1 β are induced in dendritic cells (DCs) activated by the components of microbes. Several bacteria and its products, such as *Klebsiella pneumoniae*,^{18,40} *Mycobacterium tuberculosis*,^{26,41} *Helicobacter pylori*,⁴² *Francisella tularensis*,⁴³ *Salmonella enterica*,⁴⁴ and *Bordetella pertussis*,⁴⁵ induce these cytokines through Toll-like receptor (TLR) signaling. Further bacterial peptidoglycans can induce the generation of Th17 cells through nucleotide oligomerization domain 2 (NOD2) receptor signaling in DCs.²⁵ Viruses such as herpes simplex virus (HSV)⁴⁶ and fungus and fungal components, such as β -glucans,^{26,47} *Cryptococcus*,⁴⁸ *Candida albicans*,⁴⁷ and *Aspergillus fumigatus*,⁴⁹ can all induce some or all of these polarizing cytokines from DCs and have a role in differentiation of Th17 cells. These studies suggest that relative amounts of the polarizing cytokines induced by the pathogen may define the final outcome of the differentiation of naive T cells into Th1, Th2, Th17, or regulatory T cells during infection.

IL-17 AS AN EFFECTOR MOLECULE DURING THE INNATE IMMUNE RESPONSE AFTER INFECTION AT MUCOSAL SITES

Although most of the recent focus has been on IL-17 produced by CD4 α β T cells, $\gamma\delta$ T cells in some cases are more potent

Figure 2 Role of T helper-17 (Th17) cytokines in protective immunity at the mucosa. Infection-induced interleukin (IL)-17 and IL-22 can be produced by several immune cells found in mucosal sites. A critical likely target of IL-17 and IL-22 is the mucosal epithelium, in which IL-17 augments granulocyte colony-stimulating factor (G-CSF) and CXC chemokine production, resulting in the recruitment of neutrophils that contribute to bacterial and fungal clearance at mucosal sites. IL-22 along with IL-17 also augments antimicrobial peptides and epithelial repair function important for control of extracellular fungal pathogens. In the setting of vaccine-induced immunity, Th17 cells can induce the production of ligands for CXCR3 and augment the recruitment of interferon- γ (IFN- γ)-producing Th1 cells to control intracellular pathogen growth.

producers of IL-17 during the early immune response at mucosal sites after infections. In a pulmonary murine model of *M. tuberculosis*⁵⁰ and *M. bovis BCG*,⁵¹ the major producers of IL-17 in T cells isolated from the lungs of infected mice were $\gamma\delta$ T cells. This finding was also highlighted in a recent study, where $\gamma\delta$ T cells were the major source of IL-17 in human tuberculosis patients.⁵² In addition to $\gamma\delta$ T cells, subsets of natural killer T cells (NKT) cells⁵³ and NK cells expressing ROR γ t and Nkp46 +^{54,55} can produce IL-17 and may affect the innate response to infections. Furthermore, the detection of IL-17 mRNA in neutrophils⁵⁶ as well as production of IL-17 and IL-22 by lymphoid tissue inducer-like cells (Lti cells)^{54,55,57–60} suggests that the role of IL-17 during the innate immune response is largely underexplored. It is likely that the production of IL-17 by innate cells at mucosal sites can serve as a mechanism to provide defense mechanism until the adaptive immune cells are recruited to control the infection.

TH17 CYTOKINES AS EFFECTOR MOLECULES DURING THE IMMUNE RESPONSE TO BACTERIAL INFECTIONS AT THE MUCOSA

Early study in establishing a critical role for IL-17 in protective immunity against extracellular bacterial infections was using *K. pneumoniae* in a respiratory infection model.¹⁷ IL-17RA knockout (KO) mice showed significant delays in neutrophil recruitment and had greater dissemination of *K. pneumoniae*. These studies provided early evidence that

IL-17R signaling was important for neutrophil-mediated control of pulmonary *K. pneumoniae* infection by optimal induction of chemokines such as macrophage inflammatory protein-2 and G-CSF (**Figure 2**). IL-17 induces granulopoietic factors (G-CSF and stem cell factor) and CXC chemokines (such as CXCL1, CXCL2, and CXCL5) in fibroblasts and epithelial cells.^{61–63} Furthermore, the IL-17-mediated induction of G-CSF also results in the differentiation of CD34+ progenitors into neutrophil progenitors.⁶¹ Therefore, overexpression of a recombinant adenovirus encoding IL-17 (AdIL-17) reversed the disease phenotype in mice challenged with *K. pneumoniae* by the induction of chemokines, augmented polymorphonuclear leukocyte recruitment, and enhanced bacterial clearance and survival.¹⁶ Further the fact that IL-17 can induce the expression of human β -defensin-2,^{64,65} S100 proteins, and the chemokines (CXCL5, CXCL9, CCL3,⁶⁵ and CCL-20⁶⁶) in lung epithelial cells suggests that IL-17 can also enhance host defense against pathogens by the induction of antimicrobials and chemokines for the recruitment of immune cells. The cellular source of IL-17 was soon identified to be CD4 and CD8 T cells,⁴⁰ was dependent on IL-23, and mediated by TLR4 signaling.¹⁸ More recently, IL-22, another effector cytokine produced by Th17 cells, has been implicated in the induction of host cell antimicrobials and defensins in the respiratory epithelium and is required for early control of *K. pneumoniae*, in part, by regulating the expression of the antimicrobial protein lipocalin-2.⁶⁵ Further the fact that IL-17 and IL-22 function synergistically

Table 1 Function of Th17 cells in infectious disease models at the mucosa

Organism	Mucosal surface	Role of Th17 cells	Functional relevance
<i>Klebsiella pneumoniae</i>	Respiratory	Protective	Induction of chemokines, antimicrobials, and neutrophil recruitment ^{16–18,65}
<i>Citrobacter rodentium</i>	Gut	Protective	Induction of chemokines and antimicrobials ^{29,67,68}
<i>Porphyromonas gingivalis</i>	Oral cavity	Protective	Neutrophil recruitment ^{69,70}
<i>Bordetella pertussis</i>	Respiratory	Exacerbation	Inflammation and pathology ^{35,45}
<i>Helicobacter pylori</i>	Gut	Exacerbation	Inflammatory infiltration of neutrophils ^{72,73}
<i>Mycobacterium tuberculosis</i> <i>Mycobacterium bovis BCG</i>	Respiratory	No effect on protection	Impacts granuloma formation ^{41,51,65}
<i>Mycoplasma pneumonia</i>	Respiratory	Protective	Recruitment of neutrophils ⁷⁴
<i>Salmonella typhimurium</i>	Gut	No effect on bacterial burden at the site of primary infection	Impacts epithelial barrier function, recruitment of neutrophils, and increased bacterial translocation to lymph nodes ⁷⁵
<i>Candida albicans</i>	Oral cavity	Protective	Induction of chemokines and antimicrobials and neutrophil recruitment ^{78,79}
<i>Candida albicans</i>	Gut	Exacerbation	Increased neutrophilic recruitment ⁴⁹
<i>Pneumocystis carinii</i>	Respiratory	Protective	Reduced chemokine induction and recruitment of effector CD4 T cells ⁸³
<i>Aspergillus fumigatus</i>	Respiratory	Protective/ exacerbation	Reduced chemokine induction and neutrophil recruitment ⁸⁴ IL-17 exacerbates disease in NADPH oxidase-deficient mice ⁸⁵
Herpes virus	Respiratory	Exacerbation	Recruitment of neutrophils and pathology^{46,88}
Human rhinovirus	Respiratory	Exacerbation	Recruitment of neutrophils and effector T cells and pathology⁸⁹

IL, interleukin; Th cell, T helper cell.

in the induction of antimicrobials such as human β -defensin-2 and S100 proteins⁶⁶ suggests that the Th17 cytokines may have evolved to generate effective host defense mechanisms against extracellular pathogens at mucosal sites. Further studies also show that Th17 cells have protective roles against extracellular bacterial infections in the gut mucosa. *Citrobacter rodentium*, a naturally occurring mouse pathogen, requires the generation of IL-23-dependent protective Th17 cells in the lamina propria for protection.^{67,68} In addition, IL-22 contributes to the early host defense against *C. rodentium* through the direct induction of the Reg family of antimicrobial proteins in colonic epithelial cells.²⁹ IL-17 signaling also appears to be host-protective in the oral mucosa, as IL-17RA-deficient mice are highly susceptible to infection by the Gram-negative anaerobic periodontal pathogen, *Porphyromonas gingivalis*, because of reduced neutrophil mobilization and recruitment.^{69,70}

These studies provide clear evidence that Th17 cytokines are critical for protection against various extracellular bacteria and are perfectly poised to control infection either by the recruitment of protective cells or by the induction of antimicrobials during the early immune responses at mucosal sites (Table 1). However, the Th17 response in some cases can also be a double-edged sword, and the balance between protection and pathology may define the outcome of the infection. For example, whooping cough caused by *B. pertussis*, a Gram-negative extracellular bacterial infection in the respiratory tract, results in persistent cough as one of the hallmarks of the clinical disease. Accumulating evidence suggests that the *B. pertussis* infection may bias the host response toward the produc-

tion of Th17 cytokines^{35,45} by preferentially inhibiting IL-12 and inducing IL-23.⁴⁵ *B. pertussis* causes severe respiratory pathology including bronchiectasis, whereas *B. parapertussis* causes less-severe disease pathology.⁷¹ Interestingly, *B. pertussis* lipooligosaccharide induces potent production of IL-23, IL-1 β , and IL-6 from DCs and drives a more robust differentiation of naive CD4 T cells into Th17 cells compared with DCs activated with Lipopolysaccharides from *B. parapertussis*.⁴⁵ The current emerging hypothesis is that the host bias toward Th17 results after *B. pertussis* infection in inflammation and destruction of the airways, leading to bronchiectasis and causes persistent cough. This hypothesis is further supported by another cause of bronchiectasis, cystic fibrosis (CF), which is highly associated with bronchiectasis because of chronic biofilm infection with *Pseudomonas aeruginosa* and elevated IL-17 and IL-22 responses in draining lung lymph node cells.⁶⁵ These disease models may serve as an example for the role of IL-17 in mediating pathology while conferring protection against extracellular bacterial infections in the respiratory mucosa. Another fine example of how a protective Th17 response may culminate in a pathogenic inflammatory response is evident in *H. pylori* infections in the gut mucosa. *H. pylori* is a Gram-negative bacteria that colonizes the gastric mucosa and induces an inflammatory infiltration of neutrophils associated with robust IL-17 production by CD4 and CD8 T cells.^{72,73} These data suggest that the IL-23/IL-17 pathway has a crucial role in defining the ongoing gastric inflammation in *H. pylori*-infected patients.

Although a clear protective role for Th17 cytokines in extracellular bacterial infections is emerging, Th17 effector

cytokines appear to be dispensable for protection against most studied intracellular bacterial infections at the mucosal sites. The absence of the IL-23/IL-17 axis impacts the formation of granulomas⁵¹ and inflammation after mycobacterial pulmonary infection.⁴¹ However, IL-23 KO mice and IL-17RA KO mice are not more susceptible than wild-type control mice to *M. tuberculosis*^{41,65} and *M. bovis* BCG pulmonary infections.⁵¹ Interestingly, pulmonary, but not intradermal, route of infection with an intracellular bacteria *F. tularensis* LVS induces Th17 cells and inhibits Th1 cell generation.³⁶ However, whether IL-17 is required for protection against *F. tularensis* respiratory infection is not known. These studies implicate that the host Th17 effector cytokines have evolved as protective immune mechanisms against extracellular bacteria and are dispensable for primary protection against most intracellular pathogens that require a Th1 pathway for protection.

In contrast, intracellular pathogens that may require both CD4 Th1 cells and neutrophils for protection at mucosal sites may be dependent on the IL-23/IL-17 axis for pathogen control (**Figure 1**). For example, the induction of IL-17 and IL-17F production after acute *Mycoplasma pneumonia* pulmonary infection is IL-23-dependent and contributes to neutrophil recruitment and mediates protection against the infection.⁷⁴ In addition, infection with *Salmonella typhimurium*, which can exist as an intracellular pathogen, results in the induction of IL-17 and IL-22 in the ileal mucosa, and the absence of IL-17R signaling results in increased translocation of the bacteria to the mesenteric lymph nodes, reduced induction of chemokines and antimicrobials, and reduced neutrophilic recruitment to the ileal mucosa.⁷⁵ These studies show that IL-17 may be critical for the complete induction of immune responses that lead to neutrophil influx and contribute to bacterial control in some intracellular infections.

Using a macaque model of Simian immunodeficiency virus (SIV) to study HIV human disease and related complications arising due to bacterial co-infections such as *S. typhimurium*, it was found that SIV co-infection selectively inhibits Th17 responses elicited by *S. typhimurium*, probably due to the depletion of CD4⁺ T cells in the ileal mucosa.⁷⁵ This results in an inability of SIV-infected macaques to mount normal mucosal inflammatory response to *S. typhimurium* infection and allows dissemination of bacteria to the mesenteric lymph node. These data may provide a basis for the observation that individuals with HIV are at an increased risk of developing bacteremia due to the dissemination of bacteria resulting from reduced CD4 Th17 responses.

TH17 CYTOKINES AS EFFECTOR MOLECULES DURING THE IMMUNE RESPONSE TO FUNGAL INFECTIONS AT THE MUCOSA

Inflammation is a critical component of the protective host response to fungal infections. However, resolution of inflammation is essential for reducing the immunopathology resulting from the infection. *C. albicans* infection models appear to reflect this dichotomy. *C. albicans* is a commensal organism of the oral cavity and gastrointestinal tract, but can become

pathogenic in settings of immunodeficiency. The most commonly used experimental model of *Candida* infection represents the disseminated form of disease, which in humans occurs as a nosocomial infection with a 40% mortality rate. In mice, IL-17R signaling is highly protective in this setting, acting through the recruitment and expansion of neutrophils.⁷⁶ In the oral cavity, *Candida* causes thrush (oropharyngeal candidiasis), which occurs in >90% of HIV⁺ individuals.⁷⁷ In a mouse model of oropharyngeal candidiasis, Th17 cells and IL-17RA signaling, but not Th1 cells and IFN- γ , are necessary for host protection.^{78,79} New data show that Th17-based immunity appears to be mediated primarily through the macrophage mannose receptor.⁸⁰ Patients with chronic mucocutaneous candidiasis (CMC) produced significantly lower amounts of IL-17 and IL-22 mRNA and protein levels *in vitro* after antigen stimulation compared with healthy individuals, suggesting that Th17 cytokine production correlates with protection.⁸¹ Even more compelling, patients with autosomal-dominant hyper-IgE syndrome (Job's syndrome) resulting from a mutation in the *STAT-3* gene are extremely susceptible to bacterial infections such as *S. aureus* and mucocutaneous fungal infections caused by *Candida* species. In line with a critical role for *STAT-3* in driving Th17 cellular responses, these patients do not generate *C. albicans*- and *S. aureus*-specific Th17 cellular responses.²⁴ Therefore, the mechanism underlying the susceptibility to recurrent fungal infections commonly seen in these patients is likely an inability to mount Th17 responses.^{23,24,82} In contrast, a gastric model of *C. albicans* infection stimulates severe gut pathology, which is exacerbated by IL-23 and IL-17.⁴⁹ Finally, *C. albicans* also causes vaginal yeast infections. Interestingly, female HIV⁺ patients do not experience a high incidence of vaginal *Candida* infections, despite their high incidence of thrush.⁷⁷ It is believed that the vaginal epithelial cells have a far more critical role in this setting, but the role of IL-17 is not well defined. Therefore, the route of entry and the site of infection dictate the consequence of Th17-mediated immunity in fungal infections.

In respiratory tract models of fungal infections using *P. carinii*⁸³ and *A. fumigatus*,⁸⁴ induction of IL-23 and IL-17 after pathogen challenge is protective, as IL-23 KO mice or neutralization of the IL-23/IL-17 axis resulted in impaired clearance of the pathogen. Although these studies suggest that the production of IL-23 and IL-17 is protective during fungal infections, it has been suggested that heightened IL-23-dependent Th17 responses against two major fungal pathogens, *C. albicans* and *A. fumigatus*, mediates neutrophilic inflammation and severe tissue pathology.⁴⁹ Furthermore, phagocytes from patients with chronic granulomatous disease (CGD) lack NADPH oxidase activity and, hence, the ability to generate reactive oxygen species, resulting in recurrent bacterial and fungal infections. In a mouse model of CGD, pulmonary aspergillosis infection is lethal due to heightened Th17 response and inflammatory lung pathology.⁸⁵ Although IL-17 neutralization was moderately beneficial, complete cure and reversal of the phenotype was only achieved with replacement therapy with a natural kynurenine.⁸⁵ In the context of CGD, the inflammatory pathology mediated by IL-17 is suggested to be pathogenic rather than protective. Therefore,

it appears that the early induction of IL-23 and IL-17 during fungal infections is protective. However, heightened Th17 responses that follow may result in the generation of pathological rather than protective outcomes during fungal infections.

TH17 CYTOKINES AS EFFECTOR MOLECULES DURING THE IMMUNE RESPONSE TO VIRAL INFECTIONS AT THE MUCOSA

CD4 T cells can regulate the adaptive immune responses to viruses by providing help to CD8 and B cells and also by direct antiviral activity. Documentation of the presence of viral-specific CD4 Th17 cells in HIV infection,⁸⁶ cytomegalovirus-specific IL-17-producing cells in humans,⁸⁶ and in mice⁸⁷ suggests that Th17 cells may have a role to function in viral infections. HSV-1 infection of the cornea results in early induction of IL-23⁴⁶ and IL-17,⁸⁸ and mice that lack IL-17RA showed reduced early infiltration of neutrophils and corneal opacity after HSV infection.⁸⁸ On the contrary, IL-23 KO mice showed a more severe disease phenotype to HSV infection, probably as a consequence of increased IL-12 responses and higher numbers of IFN- γ -producing cells.⁴⁶ Human rhinovirus infections are associated with exacerbations of asthma and chronic obstructive pulmonary infiltration, and IL-17 was shown to function synergistically with human rhinovirus to induce IL-8 from epithelial cells and may contribute to the recruitment of neutrophils, immature DCs, and memory T cells to the lung, thus contributing to severe inflammatory profiles seen during viral exacerbations of airway disease.⁸⁹ More recently, neutralization of IL-17 responses during a influenza challenge in mice resulted in increased weight loss and reduced survival of mice.⁹⁰ These studies suggest that the fine balance between protection and pathological manifestations of Th17 responses will define the outcome of viral infections at the mucosa and further research is required to clarify the Th17 cellular balance at the mucosa.

ROLE OF IL-17 IN VACCINE-INDUCED IMMUNITY AND IMMUNOTHERAPY

Convincing data show a protective role for IL-17 in immunity to primary infections against extracellular pathogens and fungal infections. However, the role of IL-17 in memory immune responses to infections is less well studied and understood. IL-23 was initially reported to act on memory or activated T cells that express the IL-23 receptor and produce IL-17,⁹¹ and therefore it is likely that these cells may have a role to function in vaccine-induced immunity. Although IL-17 responses are induced during primary *M. tuberculosis* pulmonary infection, it is dispensable for protection against primary challenge with *M. tuberculosis*.⁴¹ However, induction of IL-17 during a memory response to *M. tuberculosis* challenge correlates with protection. After challenge with *M. tuberculosis*, protection is associated with the recruitment of protective Th1 cells and production of IFN γ , which results in macrophage activation and mycobacterial killing. In this vaccine-induced protection model, Th17 cells upregulate CXCR3-ligating chemokines and accelerate the recruitment of Th1 cells that express the receptor CXCR3²⁸ (Figure 2). Furthermore, the peripheral blood of mycobacteria-

exposed healthy adults express *M. tuberculosis*-specific memory Th17 cells producing IL-17 or the related cytokine IL-22,⁹² suggesting that the IL-23/IL-17 axis contributes to protective immunity during tuberculosis. In support for a protective role for IL-23 and IL-17 in immunotherapy against *M. tuberculosis*, overexpression of an recombinant adenovirus expressing IL-23 when delivered before the *M. tuberculosis* pulmonary infection results in increased IFN- γ and IL-17 responses in the lung and mediates improved protection compared with control adenovirus-treated mice.⁹³ In the absence of effective current vaccines against tuberculosis, the protective role for Th17 cells in the generation of memory immunity will have a critical role in designing new vaccines against tuberculosis. Furthermore, vaccine-induced protection against another pulmonary pathogen *B. pertussis* is mediated by IL-17. Th17 cells are induced by vaccination with whole-cell pertussis vaccines (Pw) and neutralization of IL-17 reduces protection after a pulmonary challenge with *B. pertussis*. In contrast to the *M. tuberculosis* model, in this model IL-17 was suggested to have a protective role through the direct activation of macrophages and *B. pertussis* killing.⁹⁴ In a CD4 T-cell-dependent, antibody-independent model of vaccine-induced protection after *S. pneumoniae* challenge, treatment with antiserum to IL-17 resulted in reduced immunity to pneumococcal colonization compared with the control serum-treated mice.⁹⁵ In viral vaccine-induced responses, mucosal immunization of mice with rotavirus V6 protein reduces rotavirus fecal shedding and was associated with the presence of memory Th1 and Th17 cells in the intestine.^{96,97} Although it is believed that the Th1 response is the major protective mechanism in this model, it is suggested that the Th17 response may have an indirect protective role. These data suggest a protective role for IL-17 in vaccine-induced immune responses against bacterial, fungal, and viral infections. However, further studies are required to dissect the direct and indirect pathways and molecular mechanisms involved in protection.

MUCOSAL IMMUNITY VS. TISSUE PATHOLOGY AND INFLAMMATION

A protective vs. pathogenic role for IL-17 in the settings of chronic infections that occur in diseases such as CF, recurrent fungal infections or CGD is currently an area of extensive research. IL-17 induction associated with these diseases may often be pathologic rather than protective, as a result of severe defects in downstream effector functions of responding cells. For example, bacterial infections such as *Klebsiella* and *Pseudomonas* that are often associated with CF disease, induce IL-17-dependent neutrophil recruitment and induction of antimicrobial proteins,^{65,98} and under normal conditions this IL-17-dependent response is protective. However, in the context of chronic biofilm infection in CF patients, the resulting induction of IL-17 and neutrophil recruitment may not result in bacterial clearance but in inflammation, possibly due to the defective mucociliary clearance mechanisms in CF respiratory epithelial cells.⁹⁸ Similarly, in a mouse model of CGD, *A. fumigatus* induces IL-17 and recruits high numbers of neutrophils.⁸⁵ However, the lack of NADPH oxidase activity and the inability to generate

reactive oxygen species by the neutrophils render this downstream effector IL-17 ineffective, resulting in acute inflammatory responses and inability to clear the pathogen. Similarly in the oral cavity, chronic periodontal infection has been associated with elevated IL-17 levels.⁷⁰ Taken together, these data suggest that Th17 mucosal immunity requires functional downstream effector cells, either epithelial cells or neutrophils for effective clearance of the pathogen.

SUMMARY AND OUTLOOK

Evidence suggests that Th17 cells have evolved to mediate protective immunity against various pathogens at different mucosal sites. Moreover, the lack of Th17 responses appears to explain, in part, some of the immunodeficiency observed in both AIDS and patients with Job's syndrome, particularly in terms of mucosal infection with *C. albicans* and some cases of bacterial pneumonia. These data may lead to new avenues of immunotherapy to treat or prevent these infections in these patient groups. In addition, the emerging evidence that Th17 cells are crucial players in the generation of vaccine-induced protective responses against various pathogens suggests that the incorporation of this knowledge into the design of current and future vaccines against infectious diseases should be an active area of research. It is also becoming apparent that the fine balance between protection and pathological manifestations of Th17 responses will define the outcome of infections and further research is required to define the Th17 cellular balance at mucosal sites.

ACKNOWLEDGMENTS

This study was supported, in part, by the Pennsylvania Department of Health, Tobacco Formula Funding, and R01HL079142 and P50HL084932 from the National Institutes of Health to J.K.K.; Pennsylvania Department of Health, Tobacco Formula Funding, R00AI075106 from the National Institute of Allergy and Infectious Diseases and Children's Hospital of Pittsburgh to S.A.K. S.L.G. was supported by AR054389 and DE018822 from the National Institutes of Health.

DISCLOSURE

The author declared no conflict of interest.

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