

Precarious Balance: Th17 Cells in Host Defense[∇]

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Lineage-specific responses from the effector T-cell repertoire form a critical component of adaptive immunity. The recent identification of Th17 cells—a third, distinct lineage of helper T cells—collapses the long-accepted paradigm in which Th1 and Th2 cells distinctly mediate cellular and humoral immunity, respectively. In this minireview, we discuss the involvement of the Th17 lineage during infection by extracellular bacteria, intracellular bacteria, and fungi. Emerging trends suggest that the Th17 population bridges innate and adaptive immunity to produce a robust antimicrobial inflammatory response. However, because Th17 cells mediate both host defense and pathological inflammation, elucidation of mechanisms that attenuate but do not completely abolish the Th17 response may have powerful implications for therapy.

Different classes of microbes elicit lineage-specific responses from the effector T-cell repertoire. Whereas helper T1 (Th1) cells are involved in cellular immunity against intracellular bacteria and viruses, Th2 cells mediate the humoral response to parasitic infection. Regulating the activation and expansion of these lineages are regulatory T cells (Tregs), a third subset of CD4⁺ T cells that holds the inflammatory response in check. Recently, the identification of a novel lineage of helper T cells, Th17, has collapsed the long-held paradigm that three lineages (Th1, Th2, and Treg) derive from naïve CD4⁺ T cells (Thp). Distinguished by the production of interleukin-17 (IL-17), these Th17 cells develop from Thp progenitors along a fourth distinct pathway under the influence of a network of inflammatory cytokines, including IL-1, IL-6, and transforming growth factor beta (TGF- β), which support commitment to this lineage, and IL-23, which stabilizes the phenotype of differentiated Th17 cells (27, 46, 70, 94). Studies of infectious disease highlight the critical role of the Th17 response in host defense against extracellular pathogens, particularly Gram-negative bacteria that colonize mucosal surfaces. More recent observations implicate Th17 cells in the immune response to facultative and obligate intracellular pathogens, including intracellular bacteria and fungi. However, whether Th17 cells mediate essential antimicrobial mechanisms or drive tissue destruction in these contexts remains unclear. This minireview will focus first on the general mechanistic paradigm associated with IL-17-mediated host defense and then discuss findings on the involvement of the Th17 response during infection by extracellular and intracellular bacteria and fungi. Emerging trends highlight the capacity of Th17 cells to bridge innate and adaptive immunity, while balancing the host on the precarious precipice between protective immunity and pathological inflammation.

PROTECTIVE MECHANISMS OF THE IL-17 AXIS

Seminal studies linked increased morbidity during mucosal infection to dysfunctional IL-17 signaling (22, 61, 99). Consequently, interest grew in the protective mechanisms that characterize the Th17 response (Fig. 1). Production of IL-17 by CD4⁺ T cells has been demonstrated during the first 24 h of infection with extracellular bacteria (12, 26). Such activity is consistent with peripheral populations of constitutively activated IL-17-producing T cells observed in uninfected mice and implicates Th17 cells in immune surveillance and the first line of host defense (74). Additionally, IL-17 production has been observed from CD4⁺ T cells during a later time frame that coincides with the elaboration of adaptive immunity (89, 105). Evidence suggests that efficient Th17 differentiation requires high-dose antigen (Ag) stimulation through the T-cell receptor and additional stimulation through the costimulatory surface receptor CD40. (36, 73) Stimuli associated with severe infection—like coincidental activation of complement and Toll-like receptors (TLRs) or significant apoptosis in the intestinal epithelium—favor Th17 differentiation at the expense of the Th1 lineage (21, 89). Such stimuli promote proinflammatory cytokine release from antigen-presenting cells: of these, dendritic cell (DC)-derived IL-6 is critical for Th17 differentiation in murine models (21, 73, 90). In addition to traditional Th17 cells, CD8⁺ T cells (26), activated memory $\gamma\delta$ T cells (66, 81, 85), and invariant natural killer T cells (19, 56) have been identified as IL-17 producers during the early response to extracellular infection. However, the extent to which IL-17 production from these alternative sources is crucial, compensatory, or redundant likely varies with each infection (26, 81).

The near-ubiquitous expression of the IL-17 receptor facilitates the pleiotropic effector mechanisms of IL-17. Alone or in synergy, the Th17 effector cytokines IL-17 and IL-22 induce an array of antimicrobial peptides, including β -defensin-2, lipocalin 2, and members of the S100 family from colonic, skin, and airway epithelia (4, 11, 41, 50, 105, 106). Cytokines involved in the Th17 response, IL-1 and IL-6, are implicated in protecting the integrity of the colonic epithelium during bacterial infection (17, 48). IL-17 also induces chemokine expression in non-immune cells. Upregulation of neutrophil-chemotactic IL-8 (CXCL8), macrophage inflammatory proteins 1 and 2 (MIP-1

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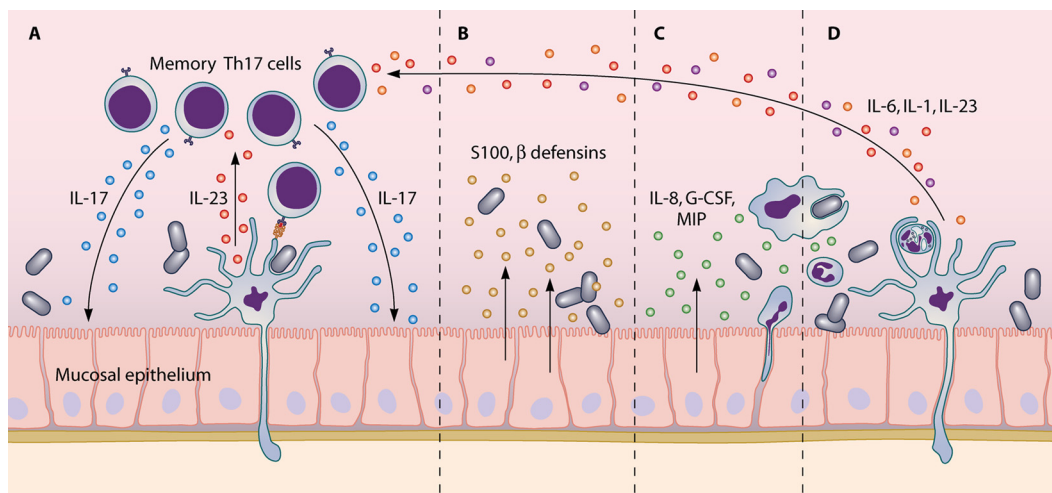


FIG. 1. Mucosal infection engages the Th17 axis of host defense. (A) Peripheral dendritic cells activated by pathogens produce IL-23, which upregulates IL-17 and IL-22 production from resident memory Th17 cells. (B) Synergy between IL-17 and IL-22 induces secretion of antimicrobial peptides from epithelial cells. (C) IL-17 also drives epithelial expression of granulopoietic and chemotactic factors. (D) As innate immune cells accumulate at the mucosal surface, dendritic cells that have phagocytosed infected, apoptotic neutrophils respond by secreting proinflammatory cytokines that support Th17 differentiation from uncommitted infiltrating CD4⁺ T cells.

and -2), and macrophage/monocyte-chemotactic protein 1 (MCP-1) (CCL20) by IL-17 turns infected sites into an innate immune cell sink (45, 61, 99, 105). IL-17 enhances the function and survival of recruited macrophages (80), and its effects on granulocytes appear even more pronounced. In addition to mediating neutrophil recruitment, IL-17 promotes granulopoiesis via the induction of granulocyte colony-stimulating factor (G-CSF) and stem cell factor (SCF) and potentiates neutrophilic cytotoxicity and phagocytosis (32, 53, 99). It is tempting to speculate that this neutrophil influx reinforces the involvement of the IL-17 axis by providing stimuli involved in Th17 differentiation. As recruited neutrophils apoptose and are phagocytosed by resident activated antigen-presenting cells, naïve-T-cell fate may be further biased toward the Th17 lineage (89), thus giving rise to Th17-associated adaptive immunity. Although IL-17 primarily galvanizes the innate branch of host defense, recent evidence suggests a role for this cytokine in initiating the B-cell response, an aspect of immunity typically associated with Th2-related follicular T cells and Th2 cytokines (75, 101). In an ovalbumin-induced murine model of airway inflammation, adoptive transfer of Th17 clones leads to the induction of IgA and IgM and the recruitment of B cells (38), a function that may be supported by the preferential expression of B-cell chemoattractant CXCL13 on Th17 cells (88, 101).

The mechanisms by which the Th17 response is attenuated postinfection remain ill defined. Binding of IL-17 to its receptor has been proposed to play a role in clearance of this cytokine (85), and the induction of Th17 cells that coexpress the anti-inflammatory cytokine IL-10 may lead to a subsequent stage of dampened inflammation (89). As bacterial burden decreases, phagocytosis of apoptotic but increasingly uninfected neutrophils by DCs may downregulate the Th17-stabilizing cytokine IL-23 (86). Notably, the vaccine-induced kinetics of Th1 and Th17 populations suggest that activation of the IL-17 axis may partially induce a subsequent Th1 response that

then attenuates IL-17 production through inhibitory effects of the Th1-produced cytokine gamma interferon (IFN- γ) (43, 65, 74). On the other hand, abundance of the antiapoptotic protein c-FLIP in Th17 cells decreases their susceptibility to activation-induced cell death, a known mechanism of clearance of Th1 cells (100). The Th17 subset also appears to subvert Treg-driven immunosuppression; unlike IFN- γ , Th17-associated IL-6 inhibits rather than enhances tryptophan catabolism, which is a process associated with Treg induction (18). In the absence of attenuation, Th17-associated effector mechanisms can mediate tissue injury through protracted local inflammation, a feature of certain chronic biofilm infections (20, 29, 78, 84).

EXTRACELLULAR BACTERIAL PATHOGENS

According to the Th1/Th2 paradigm, different subsets of helper T cells protect against distinct types of infections; while Th1 cells primarily respond to intracellular pathogens, Th2 cells are principally associated with humoral immunity. Similarly, Th17 cells are thought to mediate immunity against another class of pathogen: extracellular bacteria, particularly those that colonize exposed surfaces like the airways, skin, and intestinal lumen. Mice infected by *Klebsiella pneumoniae* (25, 99), *Bordetella pertussis* (30), or *Streptococcus pneumoniae* (53, 105), for example, mount a Th17 response, and disruption of IL-17 signaling increases susceptibility in these models. Intact signaling appears particularly critical for the induction of a chemokine gradient that facilitates the recruitment of innate immune cells to the site of infection; however, the extent to which monocytes/macrophages or neutrophils account for the bulk of the IL-17-mediated cellular infiltrate varies with the infection (81, 98, 99, 105). Deficiency in IL-23, a cytokine that induces IL-17 production from memory cells and stabilizes the Th17 phenotype in effector cells (2, 87), also exacerbates pathology, but at least in the case of *K. pneumoniae* infection,

exogenous IL-17 can compensate for the absence of IL-23 (25, 81). A critical role for the IL-23–IL-17 axis in these infectious models is supported by vaccination studies; activation of the Th17 lineage by pertussis toxin and pneumococcal antigen is required to confer full protection against subsequent infection (30, 53, 55).

Although host defense against extracellular bacteria is widely considered the Th17 domain, some evidence indicates that efficient protection requires synergy between the Th1 and Th17 lineages. For example, challenge by *Bordetella pertussis* induces both transient IFN- γ production that coincides with the peak phase of infection and extended IL-17 production that precedes the Th1 response and persists until clearance. Continuous neutralization of IL-17 modestly increases early bacterial load, but neither delays nor impedes ultimate resolution (3). This finding supports other work that suggests a role for the Th1 response in clearance (3, 57). Similarly, IL-12- and IL-23-deficient mice have targeted defects in the Th1 and Th17 networks, respectively, but both experience increased though comparable susceptibility to *Klebsiella pneumoniae*. Administration of IL-17 more effectively attenuates pathology in IL-23-deficient than in IL-23-/IL-12-deficient mice, suggesting a unique protective role for the Th1 axis (25). Thus, whether it would be more accurate to classify extracellular bacterial pathogens under a shared Th1/Th17 domain of host defense remains to be elucidated. Further contributing to this uncertainty are indications of the potentially detrimental nature of the Th17 response elicited by certain extracellular pathogens. Th17 cell infiltrates contribute to pathological abscess formation in response to *Bacteroides fragilis* (12), and modulation of macrophage function toward a Th17-conducive phenotype may facilitate persistent colonization by *Bordetella bronchiseptica* (82).

Chronic microbial infections in the setting of human disease underscore the precarious balance between inadequate host defense and unregulated inflammation. Immunocompromised hosts with defects in Th17 expansion, including HIV/AIDS patients and individuals with hyperimmunoglobulin E syndrome (HIES, or Job's syndrome), are susceptible to opportunistic infections by *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, among others (15, 31, 59, 72). In HIV infection, Th17 cells are preferentially depleted from the gastrointestinal lymphocyte compartment, despite the unresponsiveness of this subset to viral antigens (9). Because the Th17 lineage is critical for mucosal homeostasis, their selective depletion compromises intestinal integrity and facilitates the translocation of microbial products across the epithelial barrier during progressive disease (10). However, there is some indication that infection does not similarly deplete the bronchoalveolar Th17 population (9), so the precise link between defects in the IL-17 axis and the high incidence of pneumonia remains unclear. In the case of HIES, mutations in the signal transducer and activator of transcription-3 (STAT3) gene preclude the generation observed in healthy patients of Th17 memory cells against common microbes, such as *Staphylococcus aureus* and *Candida albicans* (54, 58). Although HIES is characterized by a systemic deficiency in IL-17 production, recurrent staphylococcal infections are typically confined to the skin and lung. However, the bronchial and dermal epithelium appears particularly sensitive to synergy between

IL-17 and classical proinflammatory cytokines, and such dependence may account for this apparent contradiction (59).

Excessive activation of the Th17 lineage may help precipitate and sustain inflammatory diseases in which microbial antigens contribute to disease etiology and/or pathogenesis. For example, deficiency in IL-17 inhibits the development of a canonical form of hypersensitivity pneumonitis (40, 84), a set of pulmonary disorders that results from chronic exposure to inhaled antigen, including *Saccharopolyspora rectivirgula* and other pathogenic bacteria (5). Likewise, animal models of allergen-induced airway and contact hypersensitivity suggest that the hyperreactivity of the Th17 lineage toward microbial antigens and homologous endogenous ligands contributes to pathology (64, 71, 92, 96). This has potential implications for our understanding of their human counterparts—severe asthma and allergen contact dermatitis, in which elevated levels of IL-17 have been observed (39, 47, 52, 62). Thus, establishing the mechanisms that regulate the Th17 response without entirely abolishing it will have important implications for therapy development.

FUNGAL PATHOGENS

Studies examining T-cell polarization in response to pathogen-associated molecular patterns (PAMPs) have identified an array of fungal components that preferentially induce the Th17 lineage (1, 9), suggesting a role for Th17 cells in fungus-induced host defense. Interestingly, recognition of these fungal PAMPs can occur independently of signaling by Toll-like receptors (TLRs), the primary but not exclusive receptors for PAMPs (93). For example, deficiency in the adaptor TRIF (TIR domain-containing adapter-inducing IFN- β), a downstream mediator of TLR signaling, does not preclude Th17 development in response to infection by *Candida albicans* (18). Indeed, under certain conditions, TRIF deficiency even enhances IL-17 production by dampening signals from the Th1 and Treg lineages that inhibit Th17 development (6, 18). Accordingly, alternative pathogen recognition receptors have been identified that bypass TLR signaling to activate the Th17 lineage. One such cascade engages dectin-1, a β -glucan receptor on antigen-presenting cells that can signal in concert with or independently of TLR2. In response to certain fungal glucans, dectin-1 sidesteps synergy with TLR2 and activates DCs by engaging the kinase Syk and adaptor CARD9, ultimately resulting in the induction of Th17 cells (49). In another example, monocytes activated through the mannose receptor by *C. albicans* mannan drive IL-17 production during coculture with human memory T cells (93). Such findings may have important implications not only for understanding the host response to fungal pathogens, but also in the context of autoimmunity. Further studies of these alternative PAMP receptors may suggest new targets for adjuvants that preferentially skew the T-cell repertoire toward certain lineages and may also reveal homologous endogenous ligands that drive autoimmune pathology (7).

Consistent with the ability of fungal components to drive IL-17 production, some animal models of opportunistic fungal infections suggest a positive, and in some cases essential, role for Th17 cells. Neutralization of or deficiency in IL-23 or IL-17 during disseminated and oral candidiasis and pulmonary as-

pergillus, among others, exacerbates pathology characterized by inadequate neutrophil recruitment, increased fungal burden, and reduced chemokine and antimicrobial expression (13, 35, 77, 95). In support of these findings, reexposure to antigen drives IL-17 production by human memory T cells specific for *C. albicans* antigen (1, 93, 95). However, vaccination models of Ag-induced protection and infection by *C. albicans* in TRIF^{-/-} mice have linked the Th17 lineage to deleterious inflammation rather than protective immunity and buttress the prior emphasis on the Th1 lineage for host defense (7, 18, 68). Several of the fungal antigens identified as nonprotective in vaccine drive DCs toward an alternative activation state characterized by IL-23 rather than IL-12 production, thus supporting the expansion of the Th17 (sometimes concomitantly with the Th2) lineage at the expense of the Th1 and Treg lineages (18). Such bias results in tissue injury and reduced fungal clearance, in part by impairing the killing activity while extending the viability of recruited neutrophils (8, 102). Furthermore, expansion of the Th17 subset establishes a positive feedback loop that favors the Th17 response (18, 102) and inhibits the induction of Tregs required for homeostatic tolerance to commensal but opportunistic fungal pathogens (6, 63).

INTRACELLULAR BACTERIAL PATHOGENS

Infection by intracellular bacteria is classically considered the Th1 domain of host defense. However, current knowledge of the immune response during listeriosis illustrates the degree of uncertainty that remains about the role of IL-17 in host defense against this class of pathogen. A facultative intracellular bacterium, *Listeria monocytogenes*, tends to colonize phagocytes and induces a robust response associated with the prototypical Th1 cytokine IFN- γ (23, 33, 34). However, the essential role of IFN- γ has been called into question by studies demonstrating that IFN- γ deficiency does not preclude the generation of Ag-specific CD4⁺ T cells (28). Indeed, additional factors unassociated with the Th1 lineage, including IL-1 and IL-6, have been increasingly recognized for their protective role (37, 51, 67, 76). Additionally, production of IL-6 is linked to early neutrophilia, a phenomenon required for resolution of *L. monocytogenes* infection (16).

At the time of these studies, Th17 cells had not yet been distinguished as a distinct subset of helper T cells. Given that IL-6 and IL-1 are cytokines intimately associated with the Th17 lineage, which is known to mediate granulopoiesis and neutrophil chemotaxis, the possibility emerges that the Th17 lineage may be critical for the early host response to *L. monocytogenes*. Recent studies verify this link, with some evidence arguing for an essential role for IL-17. IL-17 production is localized to a third of hepatic $\gamma\delta$ T cells and increases during the first 5 days of *L. monocytogenes* infection (24). IL-17A^{-/-} mice experience higher morbidity than their wild-type counterparts, and infection in knockouts is characterized by increased bacterial burden, decreased neutrophilic induction, and malformed granulomatous lesions (24, 60). However, other evidence suggests that the contribution of IL-17 may serve a more compensatory function under unfavorable conditions. The absence of type I and II interferon signaling abrogates the Th1 response; in this situation, a low-magnitude Th17 response to *Listeria* is observed. This shift in CD4⁺ T-cell lineage commitment does not

preclude resolution of infection (69). Cross-protection may be another method by which the Th17 lineage is recruited for anti-*L. monocytogenes* responses. Mice infected with *Mycoplasma pulmonis* exhibit enhanced protection against secondary infection with *L. monocytogenes* resulting from IL-17-induced neutrophil mobilization (83).

The lingering doubt about the role of IL-17 during *L. monocytogenes* infection reflects our generally incomplete picture of the Th17 lineage during host defense against intracellular bacteria. Studies of other intracellular infections, such as *Salmonella enterica* serovar Enteritidis (79), *Toxoplasma gondii* (42), and *Chlamydia trachomatis* (103), indicate a nonredundant role for IL-17 in complete bacterial clearance. Synergy between the Th1 and Th17 lineages has also been observed in response to postvaccination *Mycobacterium tuberculosis* challenge and *Chlamydia muridarum*, with some suggestion that deficiency in IL-17 impairs the expansion of antigen-specific Th1 cells (43, 91). Additionally, studies of primary infection by *Mycobacterium tuberculosis* indicate that the IL-23/IL-17 axis accounts for the modest protective response observed in the absence of Th1-associated IL-12 (14, 44). However, others suggest that the induction of a robust Th17 response is a detrimental supplement or even a malignant subversion of the protective Th1 response (97, 107). Another important consideration in evaluating the protection afforded by the Th17 lineage is the stage of infection. Some reports identify IL-17 function as part of the innate $\gamma\delta$ T-cell response and neutrophil induction during the early response to intracellular bacteria (24, 79). However, findings diverge on the involvement of classical CD4⁺ Th17 cells and the Th17 adaptive immune response to these infections (79, 104). Some evidence indicates that IL-17 may bridge the innate and adaptive immune responses by supporting the generation of Th1 adaptive immunity; indeed, a murine model of vaccination against *Mycobacterium tuberculosis* suggests that IL-17 may play a crucial albeit indirect role in the recruitment of the Th1 cells required for efficient recall responses (43). It will be interesting to see whether underlying these diverging observations there are as yet undiscovered mechanisms that dictate the role of the IL-17 axis during infection by intracellular pathogens.

SUMMARY

A population that bridges innate and adaptive immunity, Th17 cells are uniquely primed to mediate surveillance and early defense during mucosal infections by extracellular bacteria. However, the intensity of IL-17-driven inflammation may undermine the Th1 lineage and subvert more sustainable antimicrobial responses during intracellular infection by certain bacterial and fungal pathogens. Thus, elucidation of mechanisms that govern the amplification and attenuation of the Th17 lineage will have important implications for therapy. Particularly in the context of chronic infectious diseases that afflict both immune-compromised and immunocompetent hosts, strategies that restrain but do not entirely abolish the Th17 response will likely be critical to avoid magnifying susceptibility or pathological inflammation.

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