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Th17 cytokines in mucosal immunity and inflammation

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Abstract

Purpose of the review—Compelling evidence suggests that the Th17 lineage and other IL-17 producing cells play critical roles in host defense against pathogens at mucosal sites. However, IL-17 can also contribute to inflammatory responses at mucosal sites. In this review, we will discuss the recent progress in our understanding of the role of Th17 and other IL-17-producing cells in defining the fine balance between immunity and inflammation at different mucosal sites.

Recent Findings—Recent findings have highlighted that Th17 cytokines are important for the induction of innate and adaptive host responses and contribute to host defense against pathogens at mucosal sites. More recent developments have probed how the Th17 responses are generated in vivo in response to infections and their requirement in maintaining barrier function at mucosal sites. Most importantly, it is becoming apparent that there is a fine balance between protective and pathological manifestation of Th17 responses at mucosal sites that defines immunity or inflammation.

Summary—In this review we have summarized the recent advances in our understanding of Th17 cytokines and how they contribute to immunity versus inflammation at mucosal sites.

Keywords

Th17; Infection; mucosal; inflammation

Introduction

Mucosal surfaces are constantly exposed to foreign material and the ability to protect the host from potentially harmful organisms arises from 'immune surveillance' carried out by several mechanisms at the host-environment interface. When pathogens come in contact with the mucosal surface, the mucosal epithelium functions both as a physical barrier as well as a first line of defense. Interaction of the microbe with epithelial cells at the mucosa as well as resident macrophages takes place by recognition of conserved pathogen associated molecular patterns [PAMPs] on pathogens, and Toll-Like Receptors [TLRs] on host cells. The plethora of cytokines induced in response to this interaction results in a cascade of inflammatory events that mediate either protection or pathology. Beside the epithelial barrier, the induction of anti-microbial peptides at the mucosal surfaces and secreted immunoglobulins [especially Immunoglobulin A] also provide important mechanisms for host defense. Subsequent to these innate mechanisms of protection, $CD4^+$ helper cells belonging to the adaptive immune responses are recruited to mucosal surfaces and provide host resistance. The recent characterization of the T helper 17 [Th17] cells as a distinct lineage of $CD4^+$ cells (1–2) has greatly expanded our knowledge and filled in some of the missing gaps in host immunity not

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fully explained by the T helper cell 1 [Th1]/T helper cell 2 [Th2] dichotomy. Th17 cells were initially identified as a key factor in the induction of inflammation and tissue destruction associated with animal models of autoimmune disease like Multiple Sclerosis, Collagen Induced Arthritis and experimental colitis [reviewed in (3–4)]. However, recent evidence supports a role for Th17 cytokines as a bridge between innate and adaptive immune responses in host defense against a variety of pathogens at the mucosal surfaces. This review will focus on recent advances in our understanding of Interleukin-23 [IL-23] and Th17 cytokines and how they fill in some of the missing gaps in mucosal immunity and inflammation.

Th17 cytokines and cellular sources

Th17 cells produce the cytokines IL-17A [IL-17] (1–2) and IL-17F (5), as well as the cytokines IL-21 (6–7) and IL-22 (8–9). IL-17A and IL-17F act through IL-17 Receptor [IL-17R - comprised of IL-17RA and IL-17RC subunits] via Act1 and TRAF6 to induce the expression of pro-inflammatory cytokines and chemokines [reviewed in (10)]. The IL-17R is a Type I transmembrane protein that is expressed on various cell types including leucocytes, epithelial cells, mesothelial cells, vascular endothelial cells, keratinocytes and fibroblasts and respond to IL-17R-mediated signaling by production of granulocyte colony-stimulating factor [G-CSF], IL-6, IL-8 and mediate granulopoiesis and neutrophil recruitment [reviewed in (11)]. More recently, it is becoming clear that IL-17 can also act on antigen-presenting cells [APCs] such as macrophages and dendritic cells and induce cytokine and chemokine production (12–13).

The differentiation of Th17 cells takes place following exposure of naive $CD4^+$ T cells to APC-derived polarizing cytokines such as TGF-β, IL-6, IL-21, while IL-23 acts to stabilize the commitment of Th17 cells to this lineage [reviewed in (14)]. The master regulator of Th17 differentiation is transcription factor RORγt and RORα (15–16). Several of these Th17 polarizing cytokines, such as IL-23, TGF-β, IL-6 and IL-1β are induced in APCs following activation with pathogens. For example, *Klebsiella pneumoniae* (17–18), *Mycobacterium tuberculosis* (19–20), *Helicobacter pylori* (21), *Francisella tularensis* (13,22), *Salmonella enteritidis* (23), *Bordetella pertussis* (24), *Cryptococcus* (25), *Candida albicans* (26) and *Aspergillus fumigatus* (27) all induce some or all of the Th17 polarizing cytokines and can drive Th17 cell differentiation. Although these responses are primarily mediated through TLR signaling (19,28), other TLR-independent pathways such as Syk-Card-9 pathway (26) also mediate the induction of Th17 polarizing cytokines in APCs. Furthermore, endogenous lipid mediators such as prostaglandin E2 [PGE_2] (29) and apoptotic signals (30–31) that are released under inflammatory conditions can also drive Th17 cell differentiation. Much of the recent focus has been on IL-17 produced by $CD4^+$ αβ T cells. However, innate cells such as γδ T cells (32–34), NK cells expressing RORγτ+NKp46+ (35–36) and Lymphoid-tissue inducer like cells [Lti] (37) can produce IL-17 and IL-22 and impact the innate response via induction of chemokines and antimicrobial proteins(38–39), as well as cellular recruitment to mucosal infections. These studies therefore suggest that innate IL-17 and IL-22-producing cells as well as adaptive Th17cells function as a bridge between innate and adaptive immune responses at mucosal sites in the host.

Immunity and inflammation at the respiratory mucosa

The respiratory mucosa is constantly challenged with inhaled particulates and infectious agents and is thus a major port of entry for infectious diseases. Although induction of Th17 cytokines may play a protective role against pulmonary pathogens, it is also becoming apparent that these cytokines may be responsible for the pathology associated with inflammatory conditions. One of the best characterized roles for IL-17 in protection against pathogens at the respiratory mucosa is using the gram negative extracellular bacteria *Klebsiella pneumoniae*. Early studies

by Kolls and colleagues showed that IL-17 is important for recruitment of neutrophils in response to pulmonary challenge with *K. pneumoniae* (40). IL-17-dependent induction of key neutrophil chemo-attractants such as macrophage inflammatory protein-2 [MIP-2] and G-CSF was required for effective recruitment of neutrophils and pathogen clearance (41) (Figure 1). Accordingly, absence of IL-17 Receptor signaling showed greater dissemination of the bacteria due to the delay in neutrophil recruitment. The recognition of IL-17-dependent induction of G-CSF for the differentiation of $CD34^+$ progenitors into neutrophil progenitors (42) projected a compelling role for IL-17 in the accumulation of neutrophils during infections. Confirmation that IL-17 was the key mediator of the protective responses in *Klebsiella* infections was shown when over-expression of IL-17 led to reversal of the disease phenotype (40). Subsequently, Kolls and colleagues also identified the cellular source of IL-17 as $CD4^+$ and $CD8^+$ T cells, and that the induction of IL-17 was mediated by TLR4-dependent IL-23 production (18). More recent studies have also shown that IL-22 can synergize with IL-17 and induce anti-microbial peptides like defensins, S-100 Proteins, Lipocalin and chemokines such as CCL3 and CCL20 (39,43). Other studies have suggested a role for IL-17 in recruitment of monocytes, neutrophils and clearance and colonization of another extracellular respiratory pathogen, *Streptococcus pneumoniae* (44). These studies suggest that the Th17 cell lineage and the effector molecules produced by these cells have evolved to contribute to host defense against extracellular pathogens at the respiratory mucosa.

In contrast to a well described role for IL-17 in protection against respiratory extracellular pathogens, IL-17 appears to be dispensable for protection against pulmonary intracellular pathogens such as Mycobacteria. For example, IL-17R, IL-23 or IL-17 is not required for protective immunity to pulmonary challenge with *M.tuberculosis* (20) or *M.bovis* BCG (32, 45). However, the absence of IL-23/Th17 cytokines impacts the generation of granuloma and inflammation mediated as a result of the infection (20,32). Both innate cells such as γδ T cells (32) and $CD4^+$ T cells can produce IL-17 in response to *M.tuberculosis* infection (20). In contrast to Mycobacterial models, pulmonary infection with another intracellular pathogen *Francisella tularensis* LVS also generates a Th17 response (46) and is required for host defense (13). The protective role for IL-17 against pulmonary tularemia is mediated through IL-17-dependent induction of IL-12 and IFNγ production in macrophages and dendritic cells. IL-17 −/− infected mice have lower expression of IFNγ in the lungs and exogenous delivery of IL-17 into IL-17−/− infected mice can rescue the IFNγ responses (13). A similar decrease in Th1 responses was also observed in IL-17−/− mice infected with *M.bovis* BCG (32), suggesting that some intracellular infections can effectively induce IFNγ responses in the host for direct pathogen control, while other pathogens require the IL-17 pathway for indirect induction of host IFNγ responses for pathogen control. It is also becoming clear that intracellular pathogens that require both T cell immunity as well as neutrophil killing for pathogen control may be dependent on IL-17 for protection. For example, the control of intracellular pathogens such as *Mycoplasma pneumoniae* (47) and *Chlamydia muridarum* (48) at the respiratory mucosa is mediated via IL-23-dependent IL-17 recruitment of neutrophils and inflammatory cells. These studies suggest that IL-17 can function directly or indirectly in protection against intracellular bacterial pathogens at the respiratory mucosa.

In models of fungal pulmonary infections such as with *Aspergillus fumigatus* (49) and *Pneumocystis carinii* (50), IL-23 and IL-17 are induced in the lungs following infection and are required for protection primarily for recruitment of neutrophils to the lung mucosa (49–50). Infection with the fungal pathogen *Histoplasma capsulatum* also requires the IL-17/IL-23 pathway, since absence of this pathway coincides with reduced inflammatory cell recruitment and blunted fungal clearance (51). These studies suggest that fungal pathogens at the respiratory mucosa are dependent on IL-17-mediated recruitment of inflammatory cells for fungal control.

Recent studies have addressed whether there is a protective or pathological role for IL-17 in response to viral infections such as influenza. Although some studies have suggested a protective function for IL-17 in host immunity to influenza, other studies have suggested a pathological role. For example, it has been documented that IL-17 depletion resulted in increased weight loss as well as reduced survival in mouse model of influenza (52). Furthermore, that adoptive transfer of Th17 polarized antigen-specific effectors has been shown to protect mice against a lethal influenza challenge suggesting a protective role for IL-17 that is independent on IFNγ (53). On the contrary, the IL-17R−/− mice are not more susceptible than wild type mice to influenza infection, but have reduced neutrophil influx and decreased inflammation, suggesting a pathological role for IL-17 in influenza challenge (54). These data suggest that IL-17 may be contributing to the inflammatory injury in response to infection, but that the recruitment of inflammatory cells may be required for protection.

Data from several other respiratory tract disease models suggest that the induction of IL-17 during infection is a double edged sword resulting in inflammation and damage to the respiratory tract. For example, *Bacillus pertussis* is a gram negative extracellular pathogen that causes whooping cough and results in pathological consequences reflected in the form of persistent cough and bronchiectasis. Infection with *B.pertussis* results in production of IL-23, IL-1β and IL-6 from DCs and generation of Th17 differentiation which correlates with severe respiratory pathology (24). This suggests that infection induced IL-17 responses may contribute to excessive inflammation in the lungs and destructive changes in the airways leading to infection-induced bronchiectasis. Furthermore, the persistent lung inflammation that occurs in cystic fibrosis patients due to chronic colonization and biofilm formation by *Pseudomonas aeruginosa* correlates with higher levels of IL-17 and IL-23 in the sputum (55–56). Human rhinoviral infections are often associated with exacerbations of asthma and chronic obstructive pulmonary disease. IL-17 has been shown to work synergistically with human respiratory rhinovirus to induce IL-8 from epithelial cells that results in induction of inflammatory cells resulting in airway disease (57). These studies clearly suggest there is a fine balance that defines a protective versus pathological role for IL-17 in respiratory tract mucosal infections (Table 1).

Immunity and inflammation at the Oral mucosa

Commensal organisms that are present in the oral mucosal surfaces can become pathogenic due to breakdown of mucosal barrier or due to loss of host defense mechanisms. Oro-pharyngeal candidiasis [OPC] is a common infection in HIV infected individuals and immunity was thought to be mediated by Th1 responses and neutrophils (58–59). However, recent mechanistic studies using gene deficient mice has shown that the IL-17 pathway is critical for induction of CXC-chemokines and neutrophil activating factors required for recruitment of neutrophils to the oral mucosa (60–61). Also key antimicrobials such as B-defensins were suppressed in IL-17R−/− mice following OPC infection, suggesting that immunity to OPC is regulated by the Th17 pathway (60). Further, that Th17 cytokines may be good correlates of protection comes from studies showing that patients with Chronic mucocutaneous candidiasis [CMC] produce significantly lower levels of IL-17 and IL-22 mRNA and protein in vitro following antigen stimulation when compared to healthy individuals (62). Importantly, patients with autosomal dominant hyper-IgE syndrome [HIES, 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 (63–65). In support of a role for STAT-3 in driving Th17 cellular responses, these patients do not generate *C.albicans*- and *S.aureus*- specific Th17 cellular responses (63). Therefore, the inability to generate Th17 responses is believed to be the mechanism underlying the susceptibility to recurrent fungal infections commonly seen in these patients (63–65). In contrast to these studies, a gastric model of *C. albicans* infection stimulates severe gut pathology that is

exacerbated by IL-23 and IL-17 (27). Zymosan, a β-glucan- containing preparation of yeast cell walls, is a potent producer of IL-23 and can generate Th17 responses (19) via Dectin 1-Syk CARD9 signaling pathway (26). Also, *Candida* mannan can interact with the macrophage mannose receptor and mediate adaptive immune activation and the induction of Th17 cell differentiation (66). Therefore it is likely that *Candida* can induce the induction of both IL-23 and IL-17 for recruitment of neutrophils and pathogen clearance, but that in the absence of regulation may result in inflammatory responses. Peridontitis is a chronic infectious inflammatory disease characterized by cellular infiltrates resulting in alveolar bone loss and has been associated with infiltration of Th1 cells at the mucosal surface (67). However, recent evidence supports a protective role for IL-17 in chronic periodontitis induced by *Porphyromonas gingivalis* infection (68) and in periapical lesions induced by bacterial infections of the dental pulp (69). These studies suggest that IL-17 plays a protective role in infectious diseases at the oral mucosa, likely through their role in recruitment of neutrophils and pathogen clearance, but can also cause pathology if the Th17 responses are not regulated.

Immunity and inflammation at the gastrointestinal mucosa

The IL-23/IL-17 axis also appears to influence the fine balance between tolerance and immunity in the intestine. Accordingly, Th17 cells have been reported to be enriched in the intestine and the migration of Th17 cells in Peyer's patches and other related tissues in the gut are dependent on expression of the chemokine receptor CCR6 in mice (70) and humans (71) and C-type lectin-like receptor CD161, in humans (72). Intestinal bacterial infections such as those caused by enterohemorrhagic *Escherichia coli* and enteropathogenic *E.coli* are a major cause of mortality worldwide (73). *Citrobacter rodentium* is a naturally occurring pathogen in mice and experimental studies with *C.rodentium* has provided a model for understanding the immunity required for protection against these attaching and effacing bacterial pathogens. Initial work by Weaver and colleagues provided evidence that IL-23 dependent Th17 responses are critical for host defense against *C. rodentium*, since IL-23 gene deficient mice are susceptible to *C.rodentium* infection (74). Furthermore, IL-17A and IL-17F gene deficient mice are also susceptible to *C.rodentium* infection as a result of decreased induction of antimicrobial peptides such as Beta-defensin 1, 3 and 4 (12). More recently, studies have also shown that the induction of Th17 cells during *C.rodentium* infection is dependent on infection-induced apoptosis, since blocking apoptosis during infection reduced the accumulation of Th17 cells in the gut (31). In addition to IL-17, IL-22 is also required for protection against *C.rodentium*, primarily by mediating the induction of innate antimicrobial peptides such as Reg family proteins in colonic epithelial cells (38). Accordingly, exogenous RegIIIγ fusion protein significantly protected IL-22 gene deficient mice from weight loss following *C.rodentium* infection. The IL-22 responses have been shown to be IL-23 dependent, since IL-23 gene deficient mice had reduced expression of IL-22 and increased susceptibility to *C.rodentium* infection (38). One of the major sources of innate IL-22 in the gut has been identified to be Natural killer cells [NK-22], detected in the small intestine lamina propria of mice infected with *C.rodentium* (35–36). That depletion of NK1.1 cells in Rag−/− mice at the early stages of infection resulted in accelerated mortality of infected mice (35–36) suggests a critical role for innate IL-22 in conferring host resistance to *C.rodentium*. Overall, these studies have provided novel and important insights into the role of Th17 cytokines in protective host responses against bacterial attaching and effacing pathogens in the gut.

The intracellular pathogen *Salmonella enterica* serotype *Typhimurium*, elicits an inflammatory pathway in the intestinal mucosa of humans resulting in severe pathology due to neutrophil recruitment (75). Use of streptomycin-pretreated serotype *S. Typhimurium* infected animal models to model this disease, has shown that IL-23 is required for the initiating the T cell-dependent amplification of inflammatory responses in the intestinal mucosa. IL-23 gene deficient infected mice exhibited decreased inflammation, decreased induction of IL-17, IL-22

and neutrophil attracting chemokines as well as reduced recruitment of neutrophils (76). The induction of the inflammatory responses is dependent on $CD3^+$ T cells, since depletion of T cells resulted in reduction of IFNγ, IL-17, IL-22 as well as chemokines and antimicrobial peptides in the inflamed caecum (77). These studies demonstrate that IL-23 and Th17 cytokines are protective against extracellular bacteria, but drive the pathological inflammatory responses associated with intracellular pathogens at the gut mucosa.

Significant $CD4^+$ T cell depletion occurs during acute HIV infection, especially in the Gut Associated Lymphoid Tissue [GALT] (78) and significantly impacts the ability of the intestinal mucosa to respond to other immunological challenges. Interestingly, Th17 cells of the α4 +β7hi $CD4^+$ memory subset are preferentially infected and depleted during acute SIV infection and this alters the balance between Th1 and Th17 responses (79). Highly viremic animals were found to have a predominance of Th1 response, and the frequency of Th17 cells found at mucosal sites was shown to negatively correlate with the plasma virus level (80). Furthermore, depletion of Th17 cells in the ileal mucosa of rhesus macaques impairs mucosal barrier function to *SalmonellaTyphimurium* dissemination (81). This may be the basis behind why *Salmonella Typhimurium*, which normally causes localized enteric infection in normal hosts, can lead to life threatening bacteremia in HIV-infected hosts as a result of loss of mucosal barrier function (81). Accordingly, HIV-infected individuals that receive anti-retroviral therapy undergo effective $CD4^+$ T cell restoration and this is associated with enhanced $CD4^+$ Th17 cell accumulation (82). These studies suggest that IL-23 can trigger a plethora of different pro-inflammatory cytokines in the gut that can impact both acute innate as well as adaptive responses leading to protection or pathological consequences in the gut mucosa (Table 2).

Conclusions

Several lines of evidence suggest that Th17 cells mediate innate and adaptive immunity against a variety of pathogens at different mucosal sites. The increased incidence of mucosal infections seen in the absence of Th17 responses, as in patients with immunodeficiency [AIDS and Hyper-IgE syndrome] have opened novel avenues for immunotherapy to treat or prevent these infections. Also, the emerging evidence that Th17 cells are crucial players in generation of vaccine-induced protective responses in the respiratory tract and the gut, suggests that the targeting IL-17 has the potential to substantially impact vaccine strategies against infectious diseases. Most importantly, it is becoming apparent that there is a fine balance between protective and pathological manifestation of Th17 responses at mucosal sites. Further research for a better understanding of this fine balance will be key to defining the outcome of the infection at mucosal sites.

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Abbreviations

IL	Interleukin
IFN-γ	Interferon gamma
MIP-2	macrophage inflammatory protein-2
G-CSF	Granulocyte colony stimulating factor
CXCR-3	chemokine CXC motif receptor 3
Th1	T Helper Cell 1

Th2	T Helper Cell 2
Th17	T Helper Cell 17

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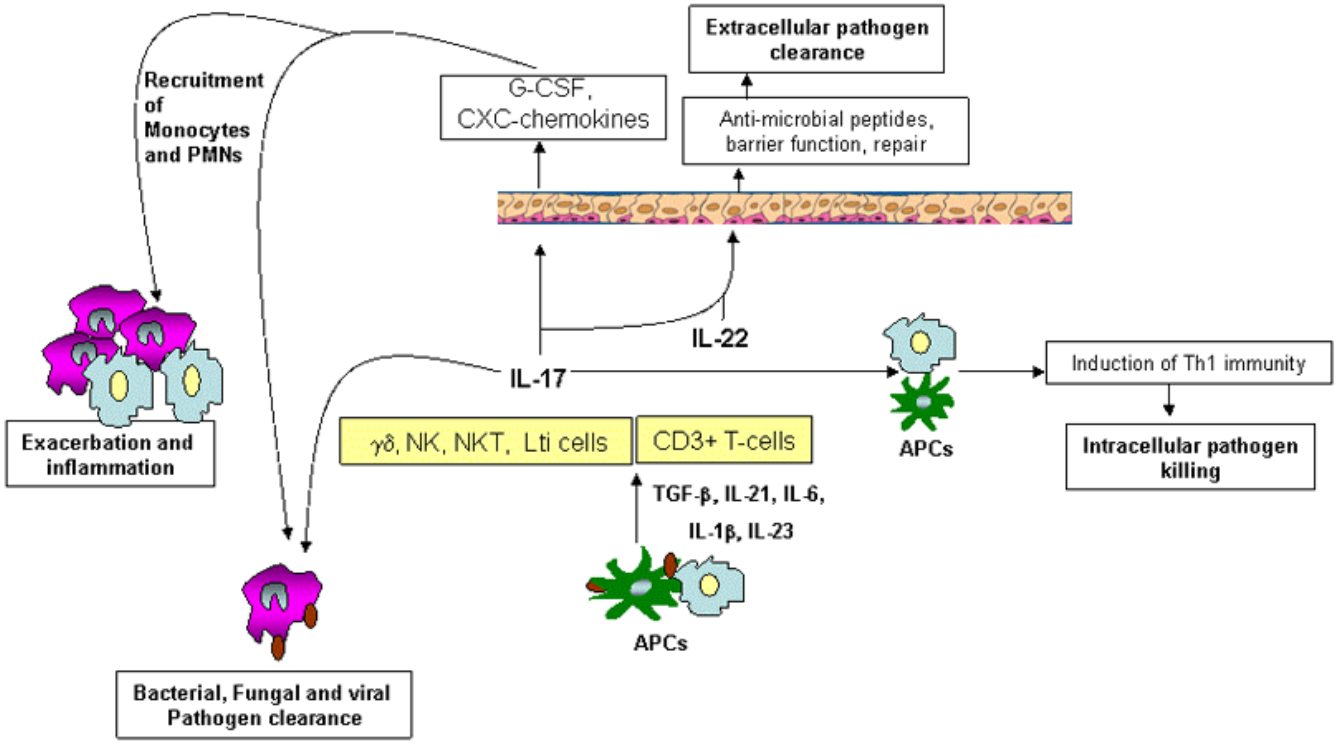

Figure 1. Role of Th17 cytokines in protection versus pathology at the mucosal surfaces

Infection-induced IL-17 and IL-22 can be produced by several immune cells found in mucosal sites. One of the targets of IL-17 and IL-22 are mucosal epithelial cells, where IL-17 augments G-CSF and CXC chemokine production resulting in recruitment of neutrophils, monocytes and other inflammatory cells that contribute to bacterial, fungal and viral clearance at mucosal sites. However, the resulting cellular infiltration can cause resulting inflammation and damage at mucosal surfaces. IL-17 can synergize with IL-22 and induce antimicrobial peptides and epithelial repair function important for control of extracellular pathogens. IL-17 can also act directly on APCs and induce cytokines such as IL-12 and drive Th1 differentiation required for intracellular pathogen clearance.

Table 1

Protective versus pathological roles for Th17 cytokines in generating immunity against respiratory tract pathogens.

Mucosal surfaces and Organisms	Type of Organism	Role of IL-17 and/or Th17 cells	Functional Significance
Klebsiella pneumoniae	Bacteria	Protective	Neutrophil recruitment and induction of key chemokines and anti-microbials (17–18,39–40)
Streptococcus pneumoniae	Bacteria	Protective	Recruitment of monocytes, neutrophils (48)
Mycobacteria *(M. tuberculosis* and *M.bovis* BCG]	Bacteria	No effect on protection	Impacts granuloma formation (20,32)
Francisella tularensis LVS	Bacteria	Protective	IL-23/Th17 pathway dependent initiation of Th1 protective immune response (46)
Mycoplasma pneumoniae	Bacteria	Protective	Recruitment of neutrophils (47)
Chlamydia muridarum	Bacteria	Protective	IL-17 induced production of chemokines by Chlamydia infected cells and neutrophils recruitment (48)
Aspergillus fumigatus	Fungi	Protection vs exacerbation	Reduced chemokine induction and neutrophils recruitment (27,49)
Pneumocystis carinii	Fungi	Protective	Reduced recruitment of effector $CD4^+$ T cells and chemokine induction (50)
Histoplasma capsulatum	Fungi	Protective	Recruitment of neutrophils (51)
Influenza	Virus	Protective and exacerbation	Transfer of Th17 cells is protective (53), but absence of IL-17R results in reduced inflammation due to reduced neutrophil influx (54)
Human *rhinovirus*	Virus	Exacerbation	Recruitment of neutrophils and effector T cells and pathology (57)

Table 2

Protective versus pathological roles for Th17 cytokines in generating immunity against oral and gut pathogens.

Mucosal surfaces and Organisms	Type of Organism	Role of IL-17 and/or Th17 cells	Functional Significance
Citrobacter rodentium	Bacteria	Protective	Induction of innate antimicrobial peptides and IL-23 dependent Th17 cell response (12,38,74)
SalmonellaTyphimurium	Bacteria	Exacerbation	IL-23 dependent initiation of T cell response and Th17 cytokines (76–77)
Candida [gastric]	Fungi	Exacerbation	Increased recruitment of neutrophils (27)
Candida [oral mucosal]	Fungi	Protective	Neutrophil recruitment with induction of CXC chemokines and antimicrobials [beta-defensins] (60)
Porphyromonas gingivalis [oral]	Bacterial	Protective	Neutrophil recruitment and pathogen clearance (68)