Immunology
The Journal of cells, molecules, systems and technologies

British Society for immunology

IMMUNOLOGY REVIEW ARTICLE

Interleukin-17 in host defence against bacterial, mycobacterial and fungal pathogens

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doi:10.1111/j.1365-2567.2008.03017.x
Received 1 November 2008; revised 6 November 2008; accepted 7 November 2008.
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Summary

The mammalian immune system is intricately regulated, allowing for potent pathogen-specific immunity to be rapidly activated in response to infection with a broad and diverse array of potential pathogens. As a result of their ability to differentiate into distinct effector lineages, CD4 T cells significantly contribute to pathogen-specific adaptive immune responses. Through the production of effector cytokines, CD4 T helper (Th) cells orchestrate the precise mobilization of specific immune cells to eradicate infection. The protective effects of the newly identified lineage of Th17 cells against pathogens like *Klebsiella pneumoniae*, *Citrobacter rodentium* and *Candida albicans* indicate the capacity of Th17 cells to confer protection against extracellular bacterial and fungal pathogens, filling a critical void in host immunity not covered by the classically described Th1 lineage that activates immunity to intracellular pathogens or the Th2 lineage that is important in protection against mucosal parasitic pathogens. Host defence by Th17 cells extends beyond protection against extracellular bacterial and fungal pathogens, as demonstrated in infections against intracellular bacteria like *Listeria monocytogenes* and *Salmonella enterica*, as well as *Mycobacterium tuberculosis*. Herein, we summarize both experimental data from mouse infection models and epidemiological studies in humans that demonstrate the protective effects of interleukin-17 and Th17 CD4 T cells in immunity to bacterial, mycobacterial and fungal pathogens.

Keywords: bacterial; CD4 T cell; fungal; interleukin-17; mycobacterial; Th17

Introduction

Responding to environmental factors produced by antigen-presenting cells, naïve CD4 T cells proliferate and differentiate into effector cells in an antigen-specific fashion upon encounter with their cognate antigen.[1] Effector CD4 T cells tailor their functions to the nature of the microbial threat, and to date, three distinct CD4 T-cell effector lineages have been described: T helper type 1 (Th1), Th2 and Th17.[2–6] The Th1 CD4 T cells confer immunity to infection by intracellular pathogens through production of the effector cytokines interferon-γ (IFN-γ) and interleukin-2 (IL-2), while Th2 CD4 T cells promote the clearance of multicellular helminths and ectoparasites by producing IL-4, IL-5 and IL-13.[3] The most recently described lineage, Th17 CD4 T cells, confers protection against extracellular bacteria and fungi, particularly at epithelial surfaces.[4–6] The Th17 cells produce the lineage-defining cytokines IL-17A and IL-17F, as well as IL-21 and IL-22,[7–10] and through the production of these pro-inflammatory cytokines, Th17 cells also trigger the production of other cytokines (IL-6, granulocyte–macrophage colony-stimulating factor, granulocyte colony-stimulating factor), chemokines (CXCL1, CXCL2, CXCL5, CXCL8), and metalloproteinases in a broad range of cell types.[11]

Co-ordinated and precisely controlled T-cell responses act to promote pathogen eradication and minimize pathogen dissemination thereby protecting the host from infection; however, in contrast to their protective functions, effector CD4 T cells when dysregulated also have the potential to cause immunopathology. The Th2 cells orchestrate allergic responses, while Th1 and Th17 cells

have both been implicated in organ-specific and systemic autoimmune diseases.[2,5,12–16] Before the appreciation that Th17 cells were a separate and distinct effector CD4 T-cell lineage, organ-specific and systemic inflammatory autoimmunity was believed to be mediated almost exclusively by self-reactive Th1 cells.[17] Confounding this notion, however, was the observation that mice deficient in the Th1 lineage-defining cytokine IFN-γ have exacerbated disease in two well-characterized murine models of autoimmunity: experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA).[18–20] Experiments performed in mice deficient in the p19 subunit of IL-23 first shed light on the involvement of Th17 cells in autoimmune diseases. The IL-23p19-deficient mice did not develop disease under conditions that readily triggered EAE or CIA in normal mice, and this level of resistance was associated with dramatic reductions in numbers of IL-17-producing CD4 T cells without a concomitant loss of IFN-γ-producing T cells.[21,22] Additional epidemiological and experimental evidence now confirms the pathological role of Th17 cells in various autoimmune diseases. Patients with rheumatoid arthritis, multiple sclerosis and psoriasis display increased expression of IL-17 in target tissue.[23] The IL-23/IL-17 axis contributes to both the onset and destruction phases of autoimmune arthritis with disease significantly reduced in both IL-23p19-deficient and IL-17-deficient animals, as compared to wild-type animals.[24] Th17 cells induce EAE, and in their absence, disease is greatly delayed with reduced severity and early recovery.[25] Because of the continuing evidence that Th17 cells play a role in autoimmunity, targeted therapies that specifically antagonize IL-17 are being developed and early studies have shown effectiveness against several experimental autoimmune diseases.[26–29]

Despite the ability of Th17 cells to mediate inflammatory pathology in numerous models of inflammatory auto-immunity, Th17 cells also confer immunity to extracellular bacterial and fungal infections. *Candida albicans* is a dimorphic fungus that primes CD4 T-cell Th17 differentiation after infection in mice.[30] Highlighting the requirement of IL-17A/IL-17A receptor for antifungal host defence, IL-17A receptor-deficient mice are highly susceptible to systemic *C. albicans* infection, and neutrophils are not recruited into the sites of infection in these mice.[31] Additionally, increased susceptibility to infection with either *Klebsiella pneumoniae* or *Citrobacter rodentium* in IL-17A receptor-deficient and IL-23p19-deficient animals indicates the importance of the IL-23/IL-17 axis in immunity to extracellular bacteria.[32–34] Although Th17 cells play a less direct role in protection against pathogens that primarily reside within the intracellular compartment of infected cells, several studies also indicate that Th17 cells contribute to protection against infection with *Mycobacteria* sp., *Listeria* sp., and *Salmonella* sp. In a vaccination model targeting a protective antigen from *Mycobacterium tuberculosis*, IL-17-producing CD4 T cells populate the lung, producing chemokines that recruit IFN-γ-producing antigen-specific Th1 cells to the site of infection.[35] Furthermore, IL-17 is induced during both the innate and the adaptive immune responses against *Mycobacterium bovis* bacille Calmette–Guérin (BCG) infection and is required for proper formation of granulomas during mycobacterial infection.[36]

This review will summarize recent accumulating data that directly link IL-17 with host defence and Th17 cells with pathogen-specific protective immunity during bacterial, mycobacterial and fungal infections. We will explore the potential mechanisms elicited by IL-17 that mediate these protective host responses, as well as discuss the beneficial and detrimental effects of IL-17 and Th17 CD4 T cells.

IL-17 in antibacterial host defence

The protective effects of IL-17 in host defence against bacterial pathogens was first demonstrated by Kolls and colleagues in studies that compared the susceptibility of IL-17 receptor-deficient and control mice to *K. pneumoniae*.[33] After intranasal infection, IL-17 receptor-deficient mice have increased numbers of recoverable bacteria in the lung, increased bacterial dissemination into the spleen, and reduced overall survival. The augmented susceptibility of IL-17 receptor-deficient mice to *K. pneumoniae* was directly associated with delayed neutrophil recruitment and reduced expression levels of granulocyte colony-stimulating factor and macrophage-inflammatory protein-2 in the lungs within the first 12–24 hr after infection.[33] In related experiments, the essential role of IL-23 in triggering IL-17 production during this infection was demonstrated. IL-23p19-deficient mice, like IL-17 receptor-deficient mice, are highly susceptible to *K. pneumoniae* and do not upregulate IL-17 in response to infection, whereas IL-17 production readily occurs after infection in resistant control mice.[34] Furthermore, recombinant IL-17 restores the early chemokine response and reduces the bacterial burden in IL-23-deficient mice after *K. pneumoniae* infection.[34] Together, these results demonstrate that IL-17 produced in an IL-23-dependent fashion plays important roles in early recruitment of neutrophils and other inflammatory cells to provide immunity to *K. pneumoniae* infection.

Following these initial studies with *K. pneumoniae*, the importance of IL-23 and IL-17 in host defence has been further established for a growing list of pathogens (Table 1). For example, increased bacterial dissemination and reduced survival after enteric *C. rodentium* infection occurs in IL-23p19-deficient mice compared with control mice.[32] Similarly, IL-23p19 neutralization before *Mycoplasma pneumoniae* infection reduces IL-17 production and impedes bacterial clearance.[37] Furthermore, IL-17 receptor-deficient mice are highly susceptible to

Table 1. Role of interleukin-17 (IL-17)/IL-23 in protection against specific bacterial, mycobacterial and fungal pathogens

Class	Pathogen	Protective	Effects of IL-17 and/or IL-23	References
Bacteria	*Bacteroides fragilis*	No	Contributes to intra-abdominal abscess formation	54
	Bordetella pertussis	Yes	Required for vaccine-primed protection	45
	Borrelia sp.	No	Contributes to development of arthritis	55
	Citrobacter rodentium	Yes	Increases survival	32
	Escherichia coli	Yes	Reduces bacterial burden	39
	Helicobacter pylori	No	Associated with chronic gastric inflammation	58,59
	Klebsiella pneumoniae	Yes	Reduces bacterial burden, increases survival	33,34
	Listeria monocytogenes	Yes	Reduces bacterial burden in liver, contributes to granuloma formation	42,43
	Mycoplasma pneumoniae	Yes	Enhances the kinetics of bacterial clearance	37
	Porphyromonas gingivalis	Yes	Prevents periodontal bone destruction	38
	Pseudomonas aeruginosa	No	Associated with pulmonary exacerbations in patients with cystic fibrosis	56,57
	Streptococcus pneumoniae	Yes	Prevents colonization	40
	Salmonella enterica	Yes	Reduces bacterial burden	41
Mycobacteria	*Mycobacterium tuberculosis*	Yes	Enhances T helper type 1 memory response, reduces mycobacterial burden after vaccination	35,63,64
	Mycobacterium bovis bacille Calmette–Guérin (BCG)	Yes	Contributes to acute neutrophil-mediated inflammation and granuloma formation	35,63,64
Fungi	*Aspergillus fumigatus*	No	Increases fungal burden (intranasal inoculation)	76
	Candida albicans	Yes	Reduces fungal burden, increases survival (intravenous inoculation or natural cutaneous infection)	31,73
	Candida albicans	No	Increases fungal burden (intragastric inoculation)	76
	Cryptococcus neoformans	Yes	Reduces fungal burden, increases survival	74
	Pneumocystis carinii	Yes	Reduces fungal burden	75

periodontal disease induced by the oral pathogen *Porphyromonas gingivalis*,[38] while neutralization of IL-17 impairs the clearance of *Escherichia coli* after intraperitoneal inoculation.[39] Importantly for each of these infection models, increased susceptibility resulting from either IL-23 or IL-17 deficiency is associated with reduced early neutrophil infiltration into the infected tissue. Collectively these results demonstrate that IL-17 plays an essential role in protective immunity to 'extracellular' bacterial pathogens by co-ordinating early neutrophil recruitment into local sites of infection. Moreover, a recent study suggests that IL-17, in addition to orchestrating the chemokine cascades required for early neutrophil mobilization, may also augment neutrophil bactericidal activity.[40]

Interestingly, numerous recent studies also indicate that IL-17 augments host defence against more classically described 'intracellular' bacterial pathogens, although the magnitude of IL-17-mediated protective effects is more modest for 'intracellular' compared with 'extracellular' bacterial pathogens. For example, although IL-17-deficient and control mice both survive infection with sublethal doses of *Salmonella enterica*, consistently higher bacterial burdens are found in the spleen and liver of IL-17-deficient mice compared with control mice.[41] Similarly, after primary *Listeria monocytogenes* infection, increased numbers of bacterial colony-fomring units and defects in organized granuloma formation within the liver arise in the absence of IL-17.[42] Comparatively, lymphocyte function-associated antigen-1-deficient mice compared with control mice have increased neutrophil infiltration into the liver and elevated serum IL-17 levels and are accordingly more resistant to primary *L. monocytogenes* infection.[43] In contrast, under similar conditions for *L. monocytogenes* infection, IL-17 receptor-deficient mice do not exhibit significant differences in bacterial burden within the spleen compared with control mice.[44] Together these results suggest that during *L. monocytogenes* infection, IL-17 plays a more important role in bacterial clearance from the liver than from the spleen. Similar to the mechanism of protection to 'extracellular' bacterial pathogens, early neutrophil mobilization directly associates with IL-17-mediated protection after both *Salmonella* and *Listeria* infections. However, whether IL-17 mediates its protective effects against intracellular bacterial pathogens solely by early neutrophil recruitment or through other mechanisms is currently unclear. The source of IL-17 may also contribute to differences in immunity or act during different phases of the immune response, and whether this relates to general differences between how IL-17 mediates protection to intracellular and extracellular bacteria warrants further investigation. In support of this idea, $\gamma\delta^+$ T cells are a major cellular source of early IL-17

production during *Salmonella* and *Listeria* infection, as opposed to $\alpha\beta^+$ T cells during *C. rodentium* infection.[32,41,42]

The protective effects of IL-17 in host defence after primary infection also extend to numerous models of vaccination-primed adaptive T-cell-mediated immunity to specific bacterial pathogens. For example, while a whole bacterial cell vaccine preparation readily primes protection against pneumococcal colonization in normal mice, these vaccine-primed protective effects are eliminated in IL-17-deficient mice.[40] Moreover, the degree of pneumococcal colonization after immunization is directly correlated with the potential of leucocytes to produce IL-17 after antigen restimulation. Interestingly, similar reductions in IL-17 production are found in leucocytes from newborns compared with adults, suggesting that the decreased rate of pneumococcal colonization in adults compared with infants and children may be explained by the increased numbers of pneumococcal-specific T cells primed for IL-17 production found in adults.[40] Demonstrating similar requirements for IL-17 in vaccine-primed protective immunity, administration of whole cell pertussis vaccine primes a population of both IL-17-producing Th17 cells and IFN-γ-producing Th1 cells, and IL-17 neutralization significantly reduces vaccine-conferred protection.[45] Furthermore, in other vaccine-primed models of protective immunity where pathogen-specific CD8 T cells are the primary mediators of protective immunity and CD4 T cells play a secondary role for maintaining these protective CD8 T cells into memory time points, deviation of the pathogen-specific CD4 T-cell response from Th1 to Th17 does not significantly impact the protective effects of vaccine-primed pathogen-specific CD8 T cells.[46]

The protective effects for IL-17 are also readily demonstrated in patients with hyper-immunoglobulin E (IgE) syndrome who are highly susceptible to chronic, recurrent and severe infections with *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and pathogenic fungal pathogens. Recent studies have identified the molecular defect that causes hyper-IgE syndrome to naturally-occurring mutations in signal transducer and activator of transcription 3 (STAT3).[47] Both IL-6 and IL-23, key factors in the development of Th17 cells, activate STAT3.[48,49] Moreover, retinoic acid-related orphan receptor (ROR)-γt, a critical transcription factor for Th17 differentiation, is induced by IL-6 and IL-23 in a STAT3-dependent manner.[50] Accordingly the profound defects in IL-17 production and Th17 CD4 T-cell differentiation found in these patients underscore the important role that IL-17 signalling plays in protective immunity against these specific pathogens.[51,52] Therefore, natural mutations in Th17 differentiation confirm the importance of these cells in host defence against bacterial infection.

Interleukin-17 potently triggers inflammation and recruitment of inflammatory cells early after infection, resulting in rapid pathogen eradication; however, in other infection-related illnesses where inflammation plays a major pathological role, increased levels of IL-17 can also exacerbate inflammation-mediated disease. For example, in sepsis triggered by caecal ligation and puncture, IL-17 neutralization improves survival and is associated with significant reductions in bacteraemia and systemic cytokine production.[53] Consistently, IL-17 neutralization prevented intra-abdominal abscess formation after *S. aureus* and *Bacteroides fragilis* infection.[54] In a direct implication of immunopathology, IL-23 neutralization in a murine model for human Lyme disease prevented the development of arthritis caused by *Borrelia bissettii* infection.[55] Furthermore, in cystic fibrosis patients who have defects in airway clearance that result in chronic *Pseudomonas aeruginosa* infection, significantly elevated levels of IL-17 and IL-23 are found in the sputum during pulmonary exacerbations, and the levels of these cytokines decline after antimicrobial therapy targeted against *P. aeruginosa*.[56] Comparatively after intratracheal inoculation, inert beads containing a clinical mucoid isolate of *P. aeruginosa* readily triggers a local inflammatory response characterized by elevated IL-17 levels and infiltration of neutrophils into the airway.[57] Similarly patients with chronic gastric inflammation caused by *Helicobacter pylori* infection show similar findings, with increased levels of IL-23 and IL-17 in gastric biopsy samples.[58,59] Moreover, in response to IL-23 stimulation, gastric lamina propria mononuclear cells from biopsy specimens readily produce IL-17, while blockade of IL-23 or STAT3 reduces IL-17 production.[58] These findings demonstrate that IL-17, while important in host defence against bacteria, also has the potential to elicit detrimental responses during specific infection-related inflammatory conditions.

IL-17 in antimycobacterial host defence

In mycobacterial infection, production of IL-17 and the Th17 CD4 T-cell response largely depend on IL-23. Cooper *et al.* first noted that the combinatorial loss of both IL-12 and IL-23 during *Mycobacterium tuberculosis* infection leads to increased bacterial burden, reduced IFN-γ production and higher mortality as compared with the loss of IL-12 alone.[60] Supporting a protective role for IL-23 in host defence to against *M. tuberculosis*, expression of the IL-23p19 subunit is enhanced in the lungs of infected mice.[60] Although IL-23 expression increases during *M. tuberculosis* infection, several studies indicate that IL-23 and IL-17 are dispensable for protection against primary *M. tuberculosis* infection. Mice deficient in the IL-23p19 subunit exhibit normal IFN-γ production and unaltered disease progression; however, these mice have a dramatic reduction in IL-17-producing antigen-specific CD4 T cells and decreased IL-17 transcripts within the lung.[61] Additionally, the absence of IL-17RA signalling

does not diminish the kinetics of *M. tuberculosis* clearance in comparison with control mice, indicating that Th17 cells play a much less direct role in host immunity to intracellular mycobacterial infections than in extracellular bacterial infections.[62]

While protection against *M. tuberculosis* infection does not require IL-23 or IL-17, the administration of IL-23 as a vaccine adjuvant enhances the *M. tuberculosis*-specific CD4 T-cell response,[63,64] and IL-17 contributes to the maintenance of the inflammatory response.[35,36] Pulmonary IL-23 gene delivery reduces both the mycobacterial burden and inflammation in the lungs and augments the expansion of mycobacteria-specific IFN-γ-producing and IL-17-producing CD4 T cells.[64] Additionally, when codelivered with the coding sequence for the protective *M. tuberculosis*-specific Ag85B antigen, IL-23 induces a strong IFN-γ response in mice deficient for the IL-12/23p40 subunit, indicating the ability of IL-23 to induce a protective IFN-γ response through IL-12-independent means.[63] In addition to a robust Th1 response, healthy adults that were vaccinated with BCG as babies exhibit a strong mycobacteria-specific Th17 CD4 T-cell response characterized by robust production of IL-17 and IL-22 after restimulation with *M. tuberculosis* purified protein derivative. Interestingly, these Th17 cells display a 'central memory' phenotype ($CCR7^+$ $CD45RA^-$) distinct from the Th1 population's 'effector memory' phenotype, indicating that mycobacteria-specific Th17 cells may provide long-lasting immunity while Th1 cells more rapidly target the site of infection but may not expand or survive long-term.[65]

During *Mycobacteria bovis* BCG infection, IL-17 is expressed during both the early innate and the later adaptive immune phases. In BCG-infected animals, $\gamma\delta^+$ T cells are the primary cellular source of IL-17, accounting for more than 60% of the IL-17-producing population.[36] In turn, IL-17 contributes to acute neutrophil-mediated inflammation, and in the absence of IL-17, a significantly lower number of neutrophils are recruited into the bronchoalveolar lavage fluid because of the decreased expression of neutrophil-inducing cytokines and chemokines.[36] In a human study comparing *M. tuberculosis*-infected patients with healthy donors, the proportion of IL-17-producing $\gamma\delta^+$ T cells increased while the proportion of IFN-γ-producing $\gamma\delta^+$ T cells decreased in patients with tuberculosis compared with healthy donors.[66] Furthermore, the bacterial burden between T-cell receptor-$\gamma\delta$ knockout and wild-type control mice does not differ significantly, but granuloma structures are less organized with a decreased composition of lymphocytes and monocytes in T-cell receptor-$\gamma\delta$-deficient mice compared with control mice after *M. tuberculosis* infection.[67] Impaired granuloma formation is also observed in the lungs of IL-17-deficient mice infected with BCG, highlighting the importance of IL-17 in proper formation of tubercular granulomas.[36]

Interferon-γ counter-regulates IL-17 and, in the absence of IFN-γ during BCG infection, the number of IL-17-producing mycobacteria-specific CD4 T cells increases. While the overall accumulation of effector T cells and neutrophils within lesions is greater in IFN-γ knockout mice compared with control mice infected with BCG, IFN-γ knockout mice do not control bacterial growth as well as control mice.[68] These results suggest that Th1 and Th17 cells are both required and contribute to different steps in host defence against mycobacterial infection. Interleukin-17 induces the expression of the CXCR3 ligands CXCL9, CXCL10 and CXCL11 in the lungs of vaccinated animals after *M. tuberculosis* challenge, thereby critically regulating the trafficking of Th1 cells to the site of infection. Additionally, an accelerated Th1 memory response in the lungs of vaccinated mice challenged with *M. tuberculosis* depends on IL-23 and IL-17.[35] Therefore in the setting of mycobacterial infection, pathogen-specific Th17 and Th1 cells most likely work in a synergistic fashion for optimal protection.

Although less well understood, the proinflammatory cytokine IL-27 performs dual roles in mycobacterial infection. IL-27 prevents optimal immunity against *M. tuberculosis*, as IL-27 receptor (IL-27R) knockout mice have a significantly reduced mycobacterial burden in the lungs, liver and spleen compared with control mice during the later stages of infection.[69,70] Additionally, the absence of IL-27R signalling increases recruitment and activation of T cells to the site of infection, as well as enhances the proinflammatory cytokine response in the infected lungs.[69] Ultimately, however, IL-27R knockout mice succumb to death earlier than their wild-type counterparts because of increased immunopathology.[69] Implicated in this immunopathology is an uncontrolled Th17 response. These results are consistent with the ability of IL-27 to potently inhibit CD4 T-cell Th17 differentiation and are further demonstrated by the unrestrained Th17 response and severe neuroinflammation that develops in IL-27R knockout mice chronically infected with *Toxoplasma gondii*.[71] Accordingly early in the response to mycobacterial infection, IL-27 may be limiting the recruitment of immune cells to the site of infection and restricting the overall host response via inhibition of IL-17, but without regulation of the Th17 response by IL-27, immunopathology will develop.

IL-17 in antifungal host defence

In humans, IL-17 produced by pathogen-specific Th17 CD4 T cells provides protection to fungal pathogens by triggering inflammation and activating other immune mediators with fungicidal activity. Among memory $CD4^+$ T cells from healthy volunteers, *C. albicans*-specific cells are predominantly found in the Th17 subset while *M. tuberculosis*-specific cells are primarily found in the

Th1 subset.[72] Moreover, IL-17 production is significantly augmented in peripheral leucocytes from patients during *Candida* infection compared with healthy non-infected controls after stimulation with *Candida* antigen.[73] By contrast, peripheral leucocytes from patients with chronic mucocutaneous candidiasis compared with either healthy controls or patients with acute *Candida* infection produce significantly reduced levels of IL-17. These findings, together with the well-characterized susceptibility to *Candida* and other fungal infections in patients with hyper-IgE syndrome who have impaired Th17 CD4 T-cell differentiation as the result of spontaneous mutations in STAT3,[51,52] demonstrate that *Candida*-specific CD4 T cells are selectively comprised by Th17 CD4 T cells and that the absence of these cells directly correlates with increased susceptibility to more chronic and often invasive infection.

These protective roles for IL-17 and Th17 cells in antifungal host defence have also been characterized more precisely after experimental infection with *Candida* and numerous other fungal pathogens. For example, after intravenous *C. albicans* infection, IL-17 expression is readily induced, and mice unable to respond to IL-17 because of targeted defects in the IL-17 receptor have increased tissue fungal burdens and decreased survival that is associated with impaired mobilization of peripheral neutrophils into infected organs.[31] Moreover, augmented IL-17 expression in IL-17-sufficient mice confers increased levels of protection to systemic *C. albicans* infection.[31] Similarly for mice with targeted defects in IL-23p19, reduced concentration of IL-17 is produced after *Cryptococcus neoformans* infection that is associated with reduced survival, delayed fungal clearance in the liver, and defective recruitment of mononuclear cells into the brain.[74] Furthermore after *Pneumocystis carinii* infection, both IL-23p19-deficient mice and mice depleted of IL-17 have increased fungal burdens compared with control mice.[75] Consistent with the means of protection against other fungal pathogens, increased susceptibility to *P. carinii* in the absence of IL-17 is associated with reduced levels of chemokines such as macrophage inflammatory proteins 1a and 1b, monokine induced by IFN-γ and CXCL-10 which are normally required for lymphocyte infiltration into infected tissue.

Interestingly, in addition to these protective roles attributable to Th17 cells and IL-17-mediated inflammation in both human and mouse models of fungal infection, other studies suggest that Th17 cells can act as a detriment in antifungal host defence. For example, reduced fungal burdens are found after intragastric *C. albicans* infection or intranasal *Aspergillus fumigatus* infection in mice with IL-23 defects either from targeted deficiency or antibody neutralization.[76] This group further demonstrated that these effects might be the result of the ability of IL-17 to inhibit the fungicidal activity of neutrophils in a dose-dependent manner.[76] Additionally, a more recent study from this same group found increased inflammatory pathology and susceptibility to *Candida* and *Aspergillus* infections in mice with targeted defects in Toll IL-1R8, a negative regulator of Toll-like receptor/IL-1R signalling, a molecule causally linked to the activation of the Th17 pathway.[77] The key differences in infection conditions between studies that show a detrimental role for IL-17 in antifungal immunity and studies that show a protective role for IL-17 are not clearly defined but may relate to differences in the infection route and inocula used.[31,76] Further investigation is needed to more clearly define the requirements to elicit a beneficial Th17 antifungal response while avoiding the potential detrimental effects associated with Th17 immunity.

Concluding remarks

Since the initial identification of Th17 CD4 T cells as a separate and distinct CD4 T-cell lineage, numerous studies have characterized the functional role of these cells. Collectively, these results indicate that Th17 cells play important roles in host defence against infection with extracellular bacterial and fungal pathogens by recruiting acute inflammatory cells into local sites of infection. Accordingly, the discovery that Th17 cells provide protection against extracellular bacterial and fungal infection fills a deficit in immunity to a niche of pathogens not previously covered by the Th1 or Th2 lineages and furthers our understanding of host defence. In addition to host defence, ample experimental evidence supports a pathological role for Th17 cells during numerous systemic and organ-specific autoimmune diseases. These diseases probably result from Th17 cells directed against self-antigen. Therefore the challenge for immunologists and physicians is to uncover strategies to maximize the protective effects of these cells, especially in patients with underlying increased susceptibility to bacterial, mycobacterial and fungal pathogens while simultaneously preventing these cells from causing immune-mediated host damage.

Especially intriguing is the demonstration that while Th17 CD4 cells represent a separate and distinct CD4 T-cell lineage, pathogen-specific Th17 cells can play cooperative roles with pathogen-specific Th1 cells in host defence during some infections. Moreover, accumulating evidence demonstrates that Th17 cells also provide protective effects during infection with more traditional intracellular pathogens. This is particularly interesting because most studies *in vitro* indicate that cytokines that promote CD4 T-cell differentiation into each lineage not only strongly reinforce other cells to differentiate into the same lineage but also potently inhibit differentiation into other CD4 lineages. These results suggest that additional signals with the capacity to override lineage-differentiating signals are triggered during *in vivo* infection to allow the

immune system to 'fine-tune' the kinetics and balance the relative degree of CD4 T-cell differentiation into multiple effector lineages during infection. Additional studies characterizing the role of pathogen-specific Th17 cells during specific infections and how these cells regulate CD4 T-cell differentiation and mediate their protective effects are important areas for future investigation.

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