

Th17 responses and host defense against microorganisms: an overview

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T helper (Th) 17 cells have recently been described as a third subset of T helper cells, and have provided new insights into the mechanisms that are important in the development of autoimmune diseases and the immune responses that are essential for effective antimicrobial host defense. Both protective and harmful effects of Th17 responses during infection have been described. In general, Th17 responses are critical for mucosal and epithelial host defense against extracellular bacteria and fungi. However, recent studies have reported that Th17 responses can also contribute to viral persistence and chronic inflammation associated with parasitic infection. It has become evident that the type of microorganisms and the setting in which they trigger the Th17 response determines the outcome of the delicate balance that exists between Th17 induced protection and immunopathogenesis. [BMB reports 2009; 42(12): 776-787]

INTRODUCTION

Mosmann and Coffman have introduced the concept of different sets of T helper (Th) cells, namely Th1 cells and Th2 cells (1). Th1 cells are characterized by the production of interferon- γ , which is essential for the defense against intracellular pathogens. Th2 cells are characterized by the production of interleukin (IL)-4 and are important in the host defense against parasitic infections. Recently, a new subset of T helper cells called Th17 cells has been described and these cells are characterized by the production of IL-17 (2), which is important for neutrophil recruitment and host defense against extracellular bacteria and fungi. Th17 cells produce a distinct cytokine profile, namely IL-17A (IL-17), IL-17F, IL-21 and IL-22. Like Th1 and Th2 cells, the development of Th17 cells from naïve T cells is dependent on antigen presentation by professional antigen presenting cells, co-stimulatory stimulation, and a specific cytokine milieu. In summary, the cytokines IL-1 β , IL-6, TGF β have been reported to induce the development of Th17 cells and IL-23 has been reported to be important for the maintenance of Th17 cells, whereas IL-12 is important for Th1 differentiation and IL-4 drives activated naïve T cells towards Th2 cells (3) (Fig. 1). It is important to mention that the cytokine IL-12 is composed of the subunits IL-12p40 and IL-12p35, and the cytokine IL-23 is composed of IL-12p40 and IL-23p19. Therefore IL-23p19 deficient mice are generally used as a model to study the role of IL-23, and IL-12p35 deficient mice are used to investigate IL-12 dependent mechanisms of disease. The functions of Th17 cells, called Th17 responses, in infectious diseases and autoimmune diseases have only recently started to be elucidated. It has become apparent that Th17 responses are associated with chronic inflammation and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis (4). Furthermore, Th17 responses have been shown to be important for the host defense against many microorganisms, although they can also contribute to immunopathology during infection. In this review we will provide an overview of the rapidly extending literature that has investigated the role of Th17 responses in relation to viral, bacterial, fungal and parasitic infections.

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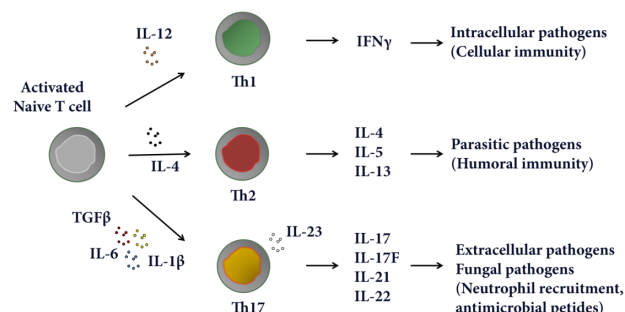


Fig. 1. Different types of T helper (Th) subsets. The cytokine profile which is responsible for the differentiation from activated naïve T cells into the three distinct Th subsets is shown. The main effector cytokines of and functions for each Th subset is shown.

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Th17 responses and infections in STAT3 deficient patients

STAT3 deficiency in humans, demonstrated to be the cause of hyperIgE syndrome, has provided crucial insights in the role of Th17 responses in the setting of antimicrobial host defense. STAT3 deficient patients suffer from *S. aureus* skin and pulmonary infections and mucocutaneous candidiasis (5). The cause of these complications has been linked to a defective Th17 response against *C. albicans* and gram positive bacteria, such as *S. aureus* and *S. pyogenes* (6). Intriguingly, defective Th17 responses were also seen with mitogenic stimulation of CD4 T helper cells from these patients, suggesting a severe defect in mounting an optimal Th17 response against many stimuli. These observations provide strong evidence that Th17 responses are needed to control fungal colonization at the mucosal level, and play an important role in host defense against extracellular bacteria, especially *S. aureus*, in the lung and skin.

Fungal infections

Candida

Involvement of Th17 responses in protective antifungal host defense was first demonstrated in IL-17RA deficient mice that showed increased susceptibility to disseminated *C. albicans* infection (7). In addition, a model for oropharyngeal candidiasis in mice showed that IL-23p19 or IL-17 deficiency resulted in severe oropharyngeal candidiasis, while mice deficient for IL-12p35 did not show this (8). However, negative effects of Th17 mediated inflammatory responses to intragastric *C. albicans* and intranasal *Aspergillus fumigatus* infection in mice have also been reported. IL-23p19 deficiency was shown to reduce fungal burden and IL-17 inhibited Th1 responses to *C. albicans* (9). Furthermore, mice with defects in Toll IL1R8 (TIR8), a negative regulator of Th17 responses, showed higher susceptibility to *Candida* and *Aspergillus* and more immunopathology (10). Differences in the animal model, *Candida* strains and mouse strains could account for these contradictory observations. However, patients with impaired *Candida* specific Th17 responses such as patients with hyper IgE syndrome or chronic mucocutaneous candidiasis (CMC), are highly susceptible to mucosal *C. albicans* infections (5, 11). These observations strongly indicate that Th17 responses are important for human anti-*Candida* mucosal host defense. Th17 induction in response to *Candida* infection is strongly dependent on C type lectin receptors (CLRs), since it has been shown that the CLR: mannose receptor, dectin-1 and dectin-2 are important in the IL-17 production in response to *Candida* (12-14). Furthermore, dectin-1 and dectin-2 signal through the Syk-CARD9 pathway, and CARD9 was shown to be involved in *Candida*-induced Th17 responses (13). Recently, it has been reported that patients with genetic defects in dectin-1 or CARD9 suffer from chronic orychoomycosis and mucosal fungal infection (15, 16). Both dectin-1 and CARD9 deficiency was shown to result in

deficient fungal induced IL-17 responses. These data further strengthen the crucial role of Th17 cells in human antifungal mucosal defense.

Other fungi

Patients with chronic granulomatous disease (CGD) lack NADPH oxidase activity and do not generate reactive oxygen species, which results in recurrent bacterial and fungal infections, especially fungal infections with *Aspergillus*. It has been reported that in the setting of deficient reactive oxygen species generation in a mouse model of CGD, the tryptophan metabolism in mice is deficient, which eventually resulted in increased IL-17 responses (17). These increased IL-17 responses were suggested to be detrimental to the host when CGD mice were infected with *Aspergillus*. It has been suggested that the IL-17 pathway also plays a role in *Pneumocystis carinii* infections. Stimulation of alveolar macrophages with *Pneumocystis carinii* induces IL-23 mRNA. Furthermore, neutralization of IL-23 or IL-17 increased disease severity during *P. carinii* infection in WT mice (18). Another important fungal pathogen is *Cryptococcus neoformans*, which is associated with HIV infection and causes lethal fungal meningoencephalitis in patients suffering from AIDS. Mice deficient of IL-12p40 show much higher mortality and had impaired IL-17 expression when compared to IL-12p35 deficient mice (19). This indicates a role for IL-23 and thus Th17 responses in protection against *C. neoformans* infection. Another study that investigated the role of the Th17 response in antifungal host defense reported that in a mice model of *Paracoccidioides brasiliensis* infection, TLR2 deficiency resulted in increased Th17 responses which were associated with protection (20). Overall, these data indicate that Th17 responses can be induced by fungi and that the IL-17 pathway plays an important role in the protective antifungal host defense.

Th17 responses in bacterial infections

Borrelia

One of the first studies that reported pathogen specific induced IL-17 production showed that *Borrelia burgdorferi* and *Mycobacterium bovis* BCG lipopeptides were able to induce IL-17 in addition to IFN γ in CD4 positive T helper cells (21). Furthermore, it was shown that these responses were dependent on antigen presentation (21). Another study reported that *B. burgdorferi* triggers bone marrow derived DC's to produce IL-23, causing stimulation of IL-17 producing T-cells (22). Codolo et al. presented that *B. burgdorferi* neutrophil-activating protein A (NapA) is capable of generating increased IL-6, IL-1 β , IL-23, and TGF- β expression by cells of the innate immune system, thereby inducing Th17 responses in human synovial fluid (23). Notably, in an animal model of *Borrelia*-induced destructive arthritis, anti-IL-17 and anti-IL-17R treatment resulted in prevention of severe destructive arthritis (24). In addition, it was shown that IL-23, which is a survival factor for Th17 cells, was associated with Lyme arthritis, and depletion of IL-23p19 or

blockade of IL-23 resulted in the absence of *Borrelia* induced arthritis in mice (25). These studies provide evidence that while Th17 effector functions are likely to be involved in the host defense against *Borrelia* spp., they also play an important role in mediating the strong immunopathology associated with chronic *Borrelia* infection.

Helicobacter pylori

IL-17 has been shown to be increased in *H. pylori*-infected gastric mucosa and stimulated the synthesis of IL-8 which is a strong chemoattractant for neutrophils (26). Another study provided evidence that STAT3 activation in lamina propria mononuclear cells could lead to sustained IL-17 production, resulting in persistent inflammation (27). In an experimental mouse model, IL-17 neutralization resulted in an increased Th1 response with elevated IL-12, TNF- α and IFN- γ mRNAs levels, while replenishing IL-17 showed reduction of the Th1 response (28). This underscores that counter-regulation between Th1 and Th17 responses is present during infection. As with many other infections, it remains to be determined which response is protective for host defense against *H. pylori* and which response will lead to persistent infection that could be detrimental to the host. Notably, it has been shown in a recent publication that IL-17RA signaling regulates gastric B cell recruitment (29). This indicates that IL-17 has an important role in the orchestration of immune cells such as neutrophils and B cells at the site of infection during *H. pylori* infection.

Klebsiella pneumoniae

IL-17 deficient mice suffer from lethal *K. pneumoniae* infection in contrast to control mice (30). In addition, overexpression of IL-17 leads to increased IL-1 β , TNF- α and MIP-2 and G-CSF, which results in higher leukocyte numbers and increased clearance of infection (30). Experimental *K. pneumoniae* infection in mice was reported to induce IL-23p19 and subsequently IL-17 production (31). Furthermore, the importance of the Th17 cytokines for protection against *K. pneumoniae* infection was shown in mice deficient in IL-12p40, IL-23p19 or IL-17R, which suffer from higher susceptibility and mortality (32). Furthermore, IL-17 administration was able to restore the normal host defense against *K. pneumoniae* in IL-23 deficient mice (32). Both IL-17 and IL-22 were shown to be crucial for protective local host defense against *K. pneumoniae*. However, only IL-22 was crucial for defense against transepithelial damage, since in contrast to IL-17, IL-22 was able to enhance repair of transepithelial resistance. Interestingly, it was shown that blocking IL-22 in mice infected with *K. pneumoniae* resulted in 100% mortality within one day, which was significantly earlier than control mice or IL-17 deficient mice. Furthermore, IL-22 blockade resulted in increased dissemination of bacteria in both control mice and IL-17 deficient mice. These data argue that IL-22 plays a more important role than IL-17 in mucosal host defense against *K. pneumoniae*. A recent study has reported that lipocalin-2 is important for mucosal host defense against *K. pneumoniae*. Although IL-17 can induce

Lcn2 *in vitro*, it was not necessary for *in vivo* induction (33, 34). IL-22 is also able to induce Lcn2 *in vitro* (33). However, to what extent IL-22 plays a role in the induction of Lcn2 *in vivo* remains to be determined. In conclusion, Th17 responses provide protective host defense against *K. pneumoniae*.

Citrobacter rodentium

Infection of IL-23p19 deficient mice with *Citrobacter rodentium* showed reduced survival rates due to increased bacterial dissemination as a result of impaired Th17 responses (35). Also, a role for IL-17A and IL-17F induced β -defensin expression in the defense against *C. rodentium* has been described (36). In addition, by using the *C. rodentium* as a mouse model for human intestinal infection, Zheng et al. hypothesized that the Th17 cytokine IL-22 also plays an important role in human intestinal infection (37). Interestingly, it has recently been shown that Th17 differentiation in the small intestine is dependent on specific commensal flora (38). A single microbe, namely a segmented filamentous bacterium, was responsible for inducing Th17 responses in the lamina propria of the small intestine (39). Colonization with this specific commensal resulted in increased Th17 responses, which were protective during experimental infection with *C. rodentium* (39).

***Salmonella* spp.**

Salmonella enterica serotype Typhimurium can induce Th17 responses in the intestinal mucosa in mice (40). Another study showed that *Salmonella enterica* serotype Typhimurium infection resulted in increased levels of IL-17, IL-22 and IL-23, and induction of MIP-2 and Lcn2 genes in the intestine (41). These responses were mainly driven by IL-23 (41). In the setting of IL-12 deficiency, IL-23 dependent IL-22 was shown to be crucial in protection against disseminated infection with *Salmonella enterica* serotype Enteritidis, while IL-17 was redundant in this model (42). However, it has also been shown that IL-17 deficient mice had slightly higher bacterial load in liver and spleen when compared to control mice in this model of disseminated *Salmonella* infection (42). During *Salmonella enterica* serotype Typhimurium infection, IL-17 deficiency in mice resulted in impaired neutrophil recruitment to the intestinal mucosa (43). It has been reported that HIV-infected patients are more susceptible to non-typhoid *Salmonella* bacteremia (44). IL-17 deficiency caused by Simian immunodeficiency virus (SIV) in macaques, which is the primate variant of HIV, resulted in increased translocation of *Salmonella enterica* serotype Typhimurium (43). Interestingly, *S. typhimurium* infection in SIV positive macaques caused significant less IL-17 and IL-22, whereas IFN γ production was normal. These data indicate that Th17 responses play an important role in controlling mucosal host defense against non-typhoid *Salmonella* and protection against disseminated salmonellosis. In addition, *S. enterica* serotype Typhi can inhibit Th17 responses, which probably contributes to the higher virulence associated with this *Salmonella* spp. (40).

Mycobacteria

M. bovis was one of the first microorganisms reported to induce IL-17 production in CD4 positive T cells (21). In addition, dendritic cells that are stimulated with *M. tuberculosis* produce IL-12 and IL-23 (45). IL-23 was shown to be crucial for the induction of Th17 responses against *M. tuberculosis* and *M. Bovis* (46). IL-23 has also been shown to be important for *M. tuberculosis*-induced Th1 responses (45). Interestingly, it has been reported that when the IL-17A receptor is absent in mice, no difference in clearance of *M. tuberculosis* infection was observed compared to control mice (47). Th1 cells seem to be more important in the protection against primary *M. tuberculosis* infection, while the absence of Th17 cells does not alter protection against primary infection (48). These data are supported by the absence of mycobacterial infections in patients with hyperIgE syndrome. Although IL-17 does not appear to play a role in primary TB infection, it may play a role in the maintenance of the inflammatory response. In line with this, granuloma formation in the lungs of IL-17 deficient mice infected with BCG was reported to be impaired and IL-17 was shown to play a role in the trafficking of Th1 cells to the site of infection (49). These data suggest that Th17 responses play an important role in providing long lasting immunity against *M. tuberculosis*, and could therefore be crucial for vaccine development against *M. tuberculosis*.

Bordetella spp.

Although earlier studies have reported that *B. pertussis* infection promotes the Th1 response (50), more recent studies have shown that *B. pertussis* is also able to skew the host response towards a Th17 profile (51). Blocking of IL-17 during *B. pertussis* infection in mice resulted in reduced neutrophil recruitment and modestly increased bacterial burden (51). In addition, *B. pertussis* toxin is able to induce IL-17 responses (52). *B. bronchiseptica* is also able to skew the immune response towards a Th17 response (53). Interestingly, lung tissue from mice infected with *B. bronchiseptica* expressed a strong Th17 response. It remains however to be established if Th17 responses contribute to host defense against *Bordetella* spp.

Other bacteria

Porphyromonas gingivalis is an anaerobic bacterium which causes periodontal disease (PD). This is associated with periodontal bone destruction. It has been reported that patients with severe PD have elevated IL-17 responses (54). Despite this observation and the observations that Th17 responses have been associated with bone destruction and the induction of Lyme arthritis, it has been reported that the Th17 response induced by *P. gingivalis* infection prevented bone destruction in mice (55).

In case of *Mycoplasma pneumoniae* it has been reported that this pathogen triggered alveolar macrophages to produce IL-23, which subsequently contributed to an increase of IL-17 production (56). Depletion of IL-23 resulted in less IL-17 pro-

duction and reduced lung neutrophil recruitment (56).

However, Th17 responses during bacterial infection are not always beneficial for the host. Patients with cystic fibrosis (CF), which have defects in a chlorine channel which contributes to thick mucus production in the lungs (57), are more susceptible to *Pseudomonas aeruginosa* infection. CF patients with *P. aeruginosa* infection had higher levels of the Th17 cytokines IL-23 and IL-17 (58). An important observation made by others was that mice deficient in IL-23 showed decreased inflammation compared to wild type mice, although they had the same amount of *P. aeruginosa* dissemination (59). These data suggest that the Th17 response against *P. aeruginosa* does not play a crucial role in the host defense against this pathogen, but that it contributes to the pathology of the airways which leads to bronchiectasis seen in CF patients. It must however also be mentioned that IL-17 was recently shown to be a critical factor in a vaccine that induced protection to *P. aeruginosa* (60). Another study has shown that mice injected intraperitoneal with *B. fragilis* formed abscesses in an IL-17 dependant way, and that co-localization of IL-17 producing CD4 positive cells within the abscess wall was shown (61). Furthermore, when these mice were treated with an IL-17 neutralizing antibody, the formation of these abscesses was blocked. These studies suggest that Th17 responses during certain types of bacterial infections can result in deleterious host effects.

Patients with hyperIgE syndrome are especially susceptible to *S. aureus* (6, 62-64). It has recently been reported that human keratinocytes and bronchial epithelial cells were especially dependent on Th17 cytokines for their anti-staphylococcal host defense, such as secretion of chemokines that recruit neutrophils and the production of antimicrobial peptides (64). In addition, an association between the severity of the defective Th17 response against *S. aureus* and the susceptibility to *S. aureus* pneumonia has been reported (van de Veerdonk et al. in press). Three patients with a STAT3 mutation and hyperIgE syndrome that had a partial *S. aureus*-induced IL-17 deficiency, never developed *S. aureus* pneumonia in contrast to patients with a complete deficiency in *S. aureus* induced IL-17.

Finally, studies that investigated the role of IL-17 in anti-bacterial host defense have also provided insights in the role of IL-17 production by innate immune cells such as $\gamma\delta$ T-cells. $\gamma\delta$ T-cells rather than CD4 T helper cells were found to be the main source of IL-17 during mycobacteria infection in mice (65). This was further supported by the observation that patients with TB had higher proportions of $\gamma\delta$ T-cells that were able to produce IL-17 in their peripheral blood compared to healthy controls (66). In addition, it has been shown that IL-17 mediates protection against *Listeria monocytogenes* in the liver (67, 68) and this IL-17 production was mainly derived from $\gamma\delta$ T-cells (67, 68). Similar findings were reported for *Escherichia coli* in a mouse model of intraperitoneal infection (69), where neutrophils were shown to infiltrate in an IL-17 dependant manner and interestingly $\gamma\delta$ T-cells were the major source

for IL-17 (69). These observations suggest that innate immune cells are also an important source of IL-17 during bacterial infections and supports the hypothesis that IL-17 producing $\gamma\delta$ T-cells are able to provide an efficient first line of defense against bacterial invasion (70).

Th17 responses in viral infections

Viruses

It is generally accepted that antiviral host defense is mainly mediated through the production of type 1 IFN and IFN γ . Th1 responses have clearly been associated with protective host defense against viruses. Since there were no suggestions that STAT3 deficient patients were more susceptible to viral infections, it may be hypothesized that Th17 responses played a minor role in antiviral host defense and that Th1 and type I interferon responses are the main protective adaptive immune response against viral infection. However, recent evidence suggests that viruses can also induce Th17 cells, although their role in antiviral host defense still remains to be elucidated.

Vaccinia virus

Smallpox, which represents a serious threat as a possible agent for bioterrorism, has been eradicated by the smallpox vaccine that consists of live vaccinia virus (VV). One of the first reports that studied the role of IL-17 in viral infection was from Patera et al. They inserted murine IL-17 into vaccinia virus (VV-IL-17) and showed that VV-IL-17 was much more virulent than wild type VV (71). Mice infected with VV-IL-17 had higher viral burdens and had impaired NK cell cytotoxicity. In contrast, another study reported that VV-IL-17 was less virulent than VV-WT in mice, and IL-17-deficient mice were more sensitive to VV-WT than control mice (72). In addition, VV expressing IL-23 were shown to be less virulent than wild type VV (72). This controversy still has to be addressed in additional studies.

In patients with atopic dermatitis, VV vaccination can result in eczema vaccinatum, which is a disseminated form of vaccinia infection and can be lethal. Recently, two reports showed an immunopathological role for IL-17 in eczema vaccinatum (73, 74). IL-17 was shown to reduce NK activity in mice with atopic dermatitis, resulting in higher susceptibility to eczema vaccinatum (73). Similar results were obtained by eliciting Th2 responses using ovalbumin, thereby simulating allergic skin inflammation (74). After VV inoculation, mice with sensitized skin showed localized IL-17 expression, increased IL-23, IL-6 levels and neutrophil influx, which resulted in increased viral loads in the skin and organs when compared with mice that had unsensitized skin (74). Moreover, IL-17 neutralization using anti-IL-17 showed decrease of lesions and viral load while IL-17 administration promoted viral replication. In conclusion, these data suggest that IL-17 contributes to viral replication in a model of disseminated vaccinia infection rather than providing host defense against viral infection, and suggests that IL-17 is a potential target during disseminated vaccinia virus infection.

Theilers murine encephalomyelitis virus

Theilers murine encephalomyelitis virus (TMEV) infects microglial cells, oligodendrocytes, astrocytes and macrophages in the central nervous system of mice, thereby inducing demyelinating disease. In response to TMEV, macrophages are able to produce IL-23p19 and IL-12p40 (75). Recently, it has been shown that Th17 cells promote chronic viral infection in an experimental TMEV infection model, and play an important role in demyelinating disease. IL-17 was responsible for the induction of anti-apoptotic mechanisms that resulted in the survival of cells infected with TMEV (76). Blocking IL-17 resulted in more efficient clearance of TMEV and cytotoxic T cell responses and could prevent disease development. It has been proposed that IL-17 could be a potential therapeutic target in chronic diseases associated with viral infections.

Herpes simplex virus

An important complication of Herpes simplex virus infection (HSV) is damage to the cornea, also called herpetic stromal keratitis. It has been shown that patients with corneal HSV infection have increased levels of local IL-17, which can bind to IL-17R on corneal fibroblasts (77). This triggers expression of the neutrophil attracting chemokines IL-8 (CXCL8) and MMP-1, which can subsequently result in neutrophil influx and inflammation that causes damage to the cornea and eventually blindness. In addition, mice lacking the IL-17R have decreased neutrophilic migration in the cornea and corneal pathology, although this effect was transient and control of viral growth in the cornea was not affected in IL-17R $^{-/-}$ mice (78). However, it has also been proposed that the immunopathology in herpetic stromal keratitis is mainly driven by Th1 responses and not Th17 responses (79).

Human immunodeficiency virus

Interestingly, early HIV infection is associated with an increase of IL-17 production by CD4 positive and CD4 negative cells in peripheral blood (80). Misse et al. have proposed that IL-22 contributed to antiviral defense by activating acute-phase proteins and induction of IL-22 might be a protective mechanism during HIV infection (81). Although Th17 responses could have a protective role against HIV infection, HIV infection has mainly provided supporting evidence of the role of CD4 positive T cells during specific infections. This is due to the fact that HIV specifically infects CD4 positive T helper cells, which results in a depletion of CD4 positive IL-17 producing cells in humans *in vivo*. The observation that HIV patients are especially susceptible to oropharyngeal *C. albicans* infection supports the important role for CD4 positive cells that secrete IL-17 in anti-*Candida* host defense. Furthermore, the increased susceptibility to non-typhoid salmonella infections underscores the important role for Th17 cells in the protection against non-typhoid *Salmonella* spp.

Hepatitis viruses

It has been shown that during hepatitis C infection virus specific Th17 cells are induced (82). However, hepatitis C also induces immunosuppressive cytokines IL-10 and TGF- β , which are able to inhibit Th17 and Th1. Neutralization of TGF- β has been shown to increase IL-17 production in response to hepatitis C nonstructural protein 4 (82). In patients with chronic hepatitis B, Th1 cells were decreased and Th17 cells were increased (83). The Th17 cytokine IL-22 was shown to be protective, however a protective function for IL-17 was not observed (84). The balance between Th1 and Th17 seems to play an important role in viral hepatitis, although it remains to be elucidated if Th17 responses favor protective host defense.

Other viruses

Several other studies have shown that IL-17 is elevated during viral infection: when mice that are deficient in Th1 responses are infected with lymphocytic choriomeningitis viral infection, they display elevated IL-17 producing CD8 T cells and develop progressive inflammation (85). Human T-cell leukemia virus (HTLV) was shown to up-regulate IL-17 expression in CD4 T-cells (86). In studies where epithelial cells were exposed to human rhinovirus, increased induction of IL-17 was shown, together with specific infiltration of neutrophils in the lungs (87). It was however not clear in these studies whether IL-17 provides a protective antiviral role or whether it contributes to inflammation that is detrimental for the host. Notably, Th17 responses were shown to be protective in IL-10 deficient mice infected with Influenza virus (88).

Th17 responses in parasite infections

Protozoa

Evidence regarding the role of Th17 responses in the host defense against protozoa is relatively limited. IL-4 which is the prototypical effector cytokine of Th2 cells can negatively regulate Th17 responses (2), and therefore it may be hypothesized that Th17 responses would not be strongly involved in host defense against parasites. However, new studies have suggested a more subtle view. Oral *Toxoplasma gondii* infection in IL-17 deficient mice leads to higher mortality than in control mice (89). These mice were shown to have less parasite burden and normal neutrophil infiltration during *T. gondii* infection (89). Despite the beneficial effect of IL-17 mediated inflammation which effectively cleared *T. gondii* infection, increased liver and intestinal pathology was observed. Stumhofer et al, have shown that IL-27 deficient mice show a profound Th17 response and severe neuroinflammation (90). These data indicate that Th17 responses can contribute to persistent inflammation in the organs affected by *Toxoplasma*. Furthermore, IL-27 which suppresses Th17 responses was found to be beneficial in infections with the protozoan *Trypanosoma cruzi* (91). In an experimental model of *Leishmania* infection, IL-17 and IL-22

were shown to be important in the protection against *L. donovani* (92), but in *L. major* infection IL-27 was shown to inhibit Th17 responses and this prevented immunopathology (93). These data suggest that the inhibiting effect of IL-27 during infection with protozoa is of utmost importance to control the Th17 responses that contribute to persistent inflammation.

Mice deficient in bradykinin receptor 2 were shown to have higher Th1 responses at the cost of lower Th17 responses, and were better protected against intraperitoneal *T. cruzi* infection than control mice, which provides further evidence that Th17 responses can be detrimental for the host during protozoal infection (94). However, it must be mentioned that a study on *Leishmania braziliensis* showed protection that was mediated by IFN- γ and IL-17 producing T-cells (95).

Helminths

Infection with *Schistosoma mansoni* in mice causes development of hepatic granuloma around the *S. mansoni* eggs (96). Antigens from these parasite eggs have been shown to cause CD4 positive T-cell mediated immunopathology. IL-12p40 deficient mice not able to make IL-12 and IL-23 were completely resistant to immunopathology (96), while mice with IL-12p35 deficiency that are not capable of making IL-12 still showed severe immunopathology. In addition, IL-17 neutralization significantly reduced immunopathology observed in *S. mansoni* infection (96, 97). Despite this immunopathological role for Th17 responses in *S. mansoni* infection, it has also been shown that TGF- β can up-regulate Th17 responses which result in increased resistance against lung-stage schistosomula (98). Evidence for a negative role for Th17 was also described during infection with *Trichuris muris*, which is the murine variant of *Trichuris trichuria*. Down-regulation of the Th2 promoting cytokine IL-25 caused severe inflammation associated with high levels of IFN- γ and IL-17, although it still remains to be elucidated which cytokine contributed most substantially to these effects (99). In general, these observations suggest that Th17 responses in the setting of parasitic infections can contribute to host defense, but they have to be controlled, for example by cytokines such as IL-27, in order to prevent immunopathology.

Th17 responses in infection: the balance between protection and immunopathogenesis

Both pathological and protective roles have been described with respect to the Th17 lineage in infectious diseases (Table 1). In infections caused by bacteria and fungi, the pathogen induced Th17 response has been reported as an important mediator of protective mucosal host defense. Th17 cells improve mucosal barrier function during infection by secretion of anti-microbial peptides and additional chemokine signaling for neutrophil reinforcements. The importance of the Th17 subset in mucosal host defense is underscored by the observation that patients with hyperIgE syndrome and chronic mucocutaneous

Table 1. Overview regarding the role of Th17 responses in relation to viral, bacterial, fungal and parasitic infections

	Pathogen	Infection	Th17 response
Fungi	<i>Candida albicans</i>	Systemic Mucosal	Increased susceptibility in IL-17RA deficient mice (7) Deficient Th17 response in humans and mice leads to increased susceptibility to candidiasis (6, 11, 63, 64) IL-17 deficiency increases susceptibility to oropharyngeal candidiasis in mice (8)
	<i>Aspergillus fumigatus</i>	Intra gastric Intranasal Pulmonary	Th17 responses are detrimental to the host (10) IL-23 deficiency reduces fungal burden, IL-17 inhibits protective Th1 responses (9) Deficient ROS results in increased Th17 responses detrimental for the host (17)
	<i>Pneumocystis carinii</i>	Pulmonary	IL-17 neutralization increases disease severity (18)
	<i>Cryptococcus neoformans</i>	Brain	IL-23 deficiency leads to impaired IL-17 expression and higher mortality in mice (19)
	<i>Paracoccidioides brasiliensis</i>	Pulmonary	Mice deficient for TLR2 show increased protective Th17 responses (20)
Bacteria	<i>Borrelia burgdorferi</i>	Synovium	Neutralization of Th17 responses prevents <i>Borrelia</i> induced arthritis (25)
	<i>Helicobacter pylori</i>	Gastric	STAT3 induction resulting in sustained IL-17 expression and persistent inflammation (27)
	<i>Klebsiella pneumoniae</i>	Pulmonary	Th17 deficiency leads to lethal infection in mice, IL-17 administration restores normal host defence (30, 32) Induction of AMPs by Th17 cytokines IL-17 and IL-22 (33, 34) IL-17 deficiency results in impaired neutrophil recruitment (43)
	<i>Salmonella enterica</i> <i>Typhimurium</i>	Intestinal mucosa	IL-22 crucial in protection against dissemination of infection (42) IL-17 deficiency causes higher bacterial load in liver and spleen (42)
	<i>Salmonella enterica</i> Enteritidis	Intestinal mucosa	viaB capsule encoding locus inhibits IL-17 expression (40)
	<i>Salmonella enterica</i> Typhi	Intestinal mucosa	Induction of IL-17 expression in CD4 T cells (21)
	<i>Mycobacterium bovis</i> BCG	Pulmonary	IL-23 crucial for Th17 response (46) IL-17RA deficiency gives no difference in bacterial clearance (47) Host response is skewed towards Th17 response and neutralization of IL-17 before challenge showed reduced vaccine protection (51) Pertussis toxin induces IL-17 responses (52)
	<i>Mycobacterium tuberculosis</i>	Pulmonary	IL-17 is associated with abscess formation (61)
	<i>Bordetella pertussis</i>	Pulmonary	Elevated IL-17 in patients with severe PD (54) Th17 responses prevent bone destruction in mice (55) High levels of IL-23 and IL-17 associated with severe inflammation during infection in CF patients (58) IL-23 deficiency causes decreased inflammation but unchanged bacterial dissemination in CF mice (59) IL-17 critical in vaccine induced protectivity (60)
	<i>Bacteroides fragilis</i>	Abdominal	IL-23 depletion results in reduced neutrophil recruitment in mice (56)
	<i>Porphyromonas givivalis</i>	Periodontal	Reduced survival rates in IL-23 deficient mice (35) Induction of AMPs by Th17 responses in mice (36, 37)
	<i>Pseudomonas aeruginosa</i>	Pulmonary	IL-17 contributes to protection, mainly derived from $\gamma \delta$ T-cells (67, 68) IL-17 contributes to protection, mainly derived from $\gamma \delta$ T-cells (69) Deficient Th17 response in humans and mice leads to increased susceptibility infection (6, 62-64) Induction of AMPs by Th17 responses in mice (36) Deficient Th17 response in humans and mice leads to increased susceptibility infection (62)
	<i>Mycoplasma pneumoniae</i>	Pulmonary	
	<i>Citrobacter rodentium</i>	Intestinal mucosa	
	<i>Listeria monocytogenes</i>	Liver	
<i>Escherichia coli</i>	Intra peritoneal		
<i>Staphylococcus aureus</i>	Epithelium (lung, skin)		
<i>Haemophilus influenzae</i>	Pulmonary		
Viruses	Vaccinia virus	Skin	localized Th17 responses are associated with increased viral loads (74)
	Theilers murine encephalomyelitis virus	Brain	IL-17 contributed to viral persistence (76)
	Herpes simplex virus	Eye	IL-17R deficient mice have less corneal pathology but unaffected viral growth (78)
	Human immunodeficiency virus	Systemic	Increased IL-17 production in early HIV infection (80) Induction of acute-phase proteins by IL-22 (81)
	Hepatitis B virus	Liver	Chronic hepatitis show increased Th17 and decreased Th1 responses (83) IL-22 is protective in conA induced hepatitis (84) Increased induction of Th17 and pulmonary neutrophil infiltration (87) Protective Th17 responses in IL-10 deficient mice (88)
<i>Rhino virus</i>	Pulmonary		
<i>Influenza virus</i>			
Parasites	<i>Toxoplasma gondii</i>	Intestinal Brain	IL-17 contributes to host defense, but also inflammatory damage (89) IL-27 deficiency results in higher Th17 responses and neuroinflammation (90)
	<i>Trypanosoma cruzi</i>	Systemic	IL-27 mediated suppression of Th17 responses is beneficial (91)
	<i>Cryptosporidium parvum</i>	Intestinal	IL-23 and IFN- γ reduced parasite shedding (100)
	<i>Leishmania braziliensis</i>	Systemic	Protection by IFN- γ and Th17 producing T-cells (95)
	<i>Leishmania donovani</i>	Systemic	IL-22 and IL-17 shown to be protective (92)
	<i>Leishmania major</i>	Systemic	Less pathology when Th17 response is inhibited by IL-27 (93)
	<i>Schistosoma mansoni</i>	Liver	Less Th17 responses resulted in absence of pathology (96, 97) TGF- β mediated upregulation of Th17 responses resulted in protection (98) Downregulation of Th2 responses resulted in immunopathology through Th1 and Th17 responses (99)
<i>Trichuris muris</i>	Lung Intestine		

candidiasis suffer from a severe form of mucosal candidiasis and they display specific defects in their Th17 response against *C. albicans*.

However, in viral infections and parasitic infections the role of Th17 responses is less clear and IL-17 has even been reported to be detrimental for the host. Interestingly, Th17 responses inhibit apoptosis of virus infected cells and contribute to persistence of the virus. In parasitic infections IL-17 was shown to contribute to persistent inflammation. Since Th17 cells are associated with autoimmune diseases and hence chronic inflammation, it seems logical that persistent and chronic induction of Th17 responses, triggered by pathogens that are not sufficiently cleared, can result in immunopathology that is detrimental for the host.

Th17 responses can effectively recruit and orchestrate neutrophil activation, and therefore are probably very efficient in inducing the killing of extracellular invading pathogens, while the killing and clearance of intracellular pathogens such as viruses may be more efficient in the setting of a strong Th1 response, and host defense against parasitic infection requires an optimal Th2 response. Since skewing towards Th17 responses can result in downregulation of Th1 and possibly Th2 responses, Th17 cells might in this way contribute to a sub-optimal host defense against viruses and parasites (Fig. 2). Although Th17 cells have only recently been discovered, they have already provided crucial insights into the host defense against microorganisms. Understanding the Th17 responses and their interactions with the immune repertoire will likely

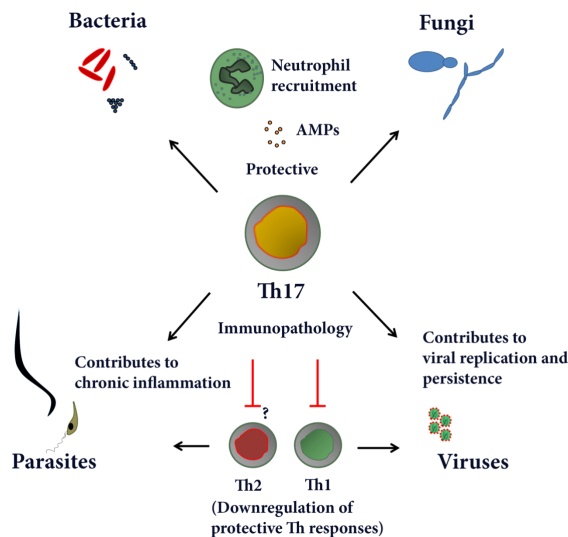


Fig. 2. Th17 responses in infection: the balance between protection and immunopathogenesis. Th17 responses are important for the host defense against extracellular bacteria and fungi by orchestrating neutrophil recruitment and stimulating antimicrobial peptides (AMPs). However, Th17 responses can also contribute to chronic inflammation and can be favorable for the pathogen, as has been shown for parasites and viruses.

provide crucial insights in the host defense and immune responses, and this will provide new tools for the development of effective immunomodulatory treatment strategies in the setting of infectious diseases.

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