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Curr Opin HIV AIDS. Author manuscript; available in PMC 2011 June 15.

Published in final edited form as:
Curr Opin HIV AIDS. 2010 March ; 5(2): 146–150. doi:10.1097/COH.0b013e32833647a8.

Th17 cells and HIV infection

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Abstract

Purpose of review—This review summarizes the recent literature about the potential perturbation and role of Th17 cells in HIV pathogenesis. We discuss the recent findings on Th17 deficiency in HIV/SIV infection and how this may impact the mucosal host defenses, potentially contributing to chronic immune activation.

Recent findings—Th17 cells have been implicated in host defense against a variety of pathogens and are involved in the pathogenesis of autoimmune diseases. Recently Th17 cells were shown to be perturbed during HIV infection in humans and SIV infection in non-human primates. Th17 cells were found to be infected *in vitro* by HIV and SIV and are significantly depleted in the gastrointestinal (GI) tract of HIV-infected individuals. In monkeys, Th17 cells are only depleted in the pathogenic SIV infection of rhesus macaques, which correlates with the progression to AIDS in these primates, while they remain intact in the non-pathogenic SIV infection of African Green Monkeys or Sooty Mangabeys.

Summary—Th17 cells appear to be perturbed during HIV and SIV infection. This finding could have important implications in understanding the disruption of mucosal defenses in the GI tract and potentially in predicting opportunistic infections during the course of HIV disease.

Keywords

Th17; HIV; SIV; immune activation

Introduction

Th17 cells are a subset of effector T cells that promote inflammation through stimulating inflammatory cytokine release, chemokine expression and recruitment of neutrophils (1-6). Th17 cells mediate protective inflammatory reactions to a variety of bacterial and fungal pathogens (7-10) especially in the mucosal tissues and skin (11-14). However they are also implicated in causing pathogenic autoimmune diseases (15-20). Perturbation of Th17 cells during HIV infection at musocal sites, could therefore contribute to the pathogenesis of HIV either through increased susceptibility to bacterial and fungal infections or by disrupting the mucosal immune defenses. Here we review the recent findings on the role of Th17 cells during HIV and SIV infection and their potential contribution in HIV pathogenesis.

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Phenotype and Function of Th17 cells

Th17 cells are defined by the secretion of IL-17, a proinflammatory cytokine mediating some of the effector functions of Th17 cells (6,18,21-25), and by the expression of the transcription factor Retinoic Orphan Receptor γt (RORγt), which is required for their differentiation, both in mice and humans (26-28). In humans, all Th17 cells express CCR6, which directs homing of these cells to skin and mucosal tissues (9,29,30), (31). Most Th17 cells are also thought to express IL-23R (32), which signals through IL-23, a proinflammatory cytokine that is required for the expansion and survival of these cells (33) (34). A portion of Th17 cells also express either Th2 associated chemokine receptor CCR4, or mutually exclusive Th1 associated CXCR3 (9). In addition, a sizeable portion of Th17 cells express HIV-coreceptor CCR5 (35,36) and gut homing receptor α4β7 (37), which presumably allow them to migrate throughout mucosal tissues (38). Indeed, Th17 cells are enriched in the lamina propria of the GI tract and may play an important role in the defense against microbes at mucosal surfaces (12,13,26).

Functionally, Th17 cells were shown to be involved in defense against extracellular bacteria such as *Klebsiella pneumoniae* (7), *Mycobacterium Tuberculosis* (39) and fungi such as *Candida albicans* in a murine model of systemic candidiasis (8). A role in host defense against *Pneumocystis carinii* was also suggested since as IL23p19$^{-/-}$ mice had impaired clearance of infection and did not contain any Th17 cells. In humans, it was recently reported that patients with hyper immunoglobulin E syndrome, characterized by recurrent staphylococcal and candida infections (40,41) have impaired Th17 development (42,43), further highlighting the role of Th17 responses in normal host defense against these pathogens.

Th17 cells are also implicated in variety of autoimmune inflammatory conditions. For example, the skin samples of psoriasis patients were found to contain high levels of IL-17A, IL-17F, and RORγt expression, and numerous IL-23 producing dendritic cells (DCs) were also present (32). Th17 cells have also been linked to several mouse models of inflammatory diseases, such as experimental autoimmune encephalomyelitis and collagen-induced arthritis (17,44,45). An increased expression of IL-17 was also reported in multiple sclerosis patients (46) and in the inflamed mucosa or the serum of patients with inflammatory bowel disease (47).

While there is ample evidence implicating Th17 cells in both protective and harmful immune responses, their function in HIV infection is not yet fully characterized. Existence of HIV-specific Th17 cells were recently reported (48), suggesting a potential role for these cells in host defense against HIV. However, another study did not support this finding (49), thus it remains to be determined whether Th17 cells have direct anti-viral effector functions during HIV infection. Conversely, loss of Th17 cells in HIV infected individuals could have indirect consequences such as rendering them more prone to opportunistic bacterial and fungal infections (Figure 1). The concentration of Th17 cells at the mucosal tissues and their selective loss in these regions could also result in permeation of natural flora through mucosal linings, which in turn could result in unwanted immune activation, thus contributing to HIV pathogenesis (Figure 1).

HIV and SIV infection of Th17 cells

Recently it was found that the number of Th17 cells is reduced in the mucosa of HIV-infected individuals and SIV-infected macaques. In *in vitro* experiments it was found that sorted CD4+ Th17 cells from healthy macaques were infected by SIV_{mac251} by measuring p27 Gag in the supernatant of infected cultures (50). In adult blood from healthy individuals, we found that a sizeable portion of adult CD4+ Th17 cells express the HIV co-receptor

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CCR5 and produce very low levels of CCR5 ligands MIP-1α and MIP-1β (36). Accordingly, CCR5+ Th17 cells were efficiently infected with CCR5-tropic HIV and were depleted during viral replication *in vitro* (36). While both SIV and HIV appears to infect Th17 cells *in vitro*, it remains to be determined whether this is the main reason for their disruption *in vivo* (Figure 1).

Perturbation of Th17 cells in HIV-infected individuals

Currently, little is known about whether Th17 cells are disrupted or expanded during HIV infection. A recent study comparing a group of HIV-1 infected children to uninfected pediatric subjects found a marked reduction in Th17 cells in PBMCs only from infected children with a plasma viral load higher than 50 copies/ml (51), showing a positive correlation between the reduction in Th17 cell number and plasma viral load. It is of interest to note that the frequency of IFNγ cells was unchanged in these groups and that Th17 cells did not express CCR5. The authors of this study speculated that Th17 cells are not directly targeted by HIV but instead their differentiation is not sustained *in vivo* in HIV-1 positive children with a high viral load.

It is now well established that mucosal tissues are the major regions of HIV-replication, which results in drastic depletion of CD4+ effector T cells in the GI tract, possibly compromising mucosal defenses. Recent findings provide compelling evidence that the frequency of IL-17 producing CD4+ T cells is also significantly reduced in the GI tract of treatment naïve HIV-infected adults (49). Furthermore, only few of the remaining Th17 cells express CCR5, indicating a preferential loss of CCR5+ Th17 cells, and possibly arguing for a direct role of the virus-mediated depletion of this subset (49). Th17 cells are possibly important in host defense against extracellular bacteria in mucosal tissues through recruitment of neutrophils and production of antimicrobial peptides in the mucosa (12). The loss of Th17 cells in the gut of HIV-infected individuals might therefore compromise this mucosal line of defense, which normally limits bacterial dissemination from the intestinal mucosa (Figure 1). This is supported by the observation that IL-17 receptor-deficient mice developed increased systemic dissemination of *Salmonella typhimurium* from the gut to the mesenteric lymph nodes and spleen, which could explain the high occurrence of nontyphoidal Salmonella serotypes in HIV-infected individuals (52). Th17 responses, which dominate the gene expression profile from the ileal mucosa of S.typhimurium-infected rhesus macaques, were blunted when these macaques were also infected with SIV suggesting a Th17 deficiency during S.typhimurium infection in SIV-infected macaques compared to uninfected controls (52). How Th17 cells limit S.typhimurium dissemination from the intestinal mucosa is not yet known. Th17 depletion in the mucosa of HIV-infected individuals could also result in higher levels of lipopolysaccharide (LPS), derived from the bacteria translocated in the gut mucosa, in the blood of chronically HIV-infected individuals and SIV-infected rhesus macaques. The higher levels of LPS could in turn stimulate the innate immunity and result in systemic immune activation observed in pathogenic HIV and SIV infections (53).

An important question is whether Th17 cell loss during HIV infection cae restored. Macal et al. reported that the loss of Th17 cells appears to be reconstituted upon treatment (54). They showed that the highest level of CD4+ restoration during HAART correlated with a substantial increase in mucosal Th17 cells and a decreased level of inflammation as evidenced by gene profiling of inflammatory responses from jejunal biopsies. However, a low level of immune activation persisted in GALT despite long-term therapy.

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Perturbation of Th17 cells in SIV-infected macaques

African green monkeys (AGMs) and Sooty mangabeys (SMs) are natural SIV hosts that share many similarities with HIV infection of humans and SIV infection of Asian macaques; however they usually do not progress to AIDS (55,56). During the acute phase of infection in both natural and non-natural SIV hosts, there is a peak in viral replication accompanied by high viral loads and depletion of mucosal CD4+ T cells (57). But during later stages, viral loads decline, which indicates a partial control of virus replication along with an active immune response. The difference, however, between natural and non–natural SIV hosts is in the chronic phase of infection where natural SIV hosts such as AGMs do not manifest a progressive depletion of mucosal or peripheral blood CD4+ T cells and the elevated immune activation they develop in the acute phase rapidly subsides (55,56). Remarkably, despite not progressing to AIDS, these monkeys maintain relatively high viral load. The AGMs or SMs infected with SIV also do not manifest signs of microbial translocation from the intestinal lumen to the systemic circulation during chronic infection (53,55,56). In contrast, SIV-infected macaques experience a rapid and drastic loss of mucosal CD4+ T cells during acute infection, which continues throughout the chronic phase along with depletion of circulating CD4+ T cells. The SIV-infected macaques also have immunostimulatory microbial products in their blood and display a generalized chronic immune activation (53,55,56).

Recently, several papers determined the levels of Th17 cells in SIV infection. Brenchley et al compared SIV-infected SMs to uninfected controls and found that infected SMs maintained normal frequencies of Th17 cells in the GI tract, with a lower frequency of Th17 cells in the peripheral blood compared with uninfected SMs (49). However, the infection of macaques with pathogenic SIV_{mac251} reduced the frequency of Th17 cells only at mucosal sites within a few weeks from infection (primary infection) and was not restored to normal levels in the chronic phase except in elite controller macaques (50). In healthy macaques, the frequency of Th17 cells is normally higher at the mucosal sites than the systemic tissues, whereas Th1 cells are equally distributed in all compartments. Th altered the balance of Th1 and Th17 cells during SIV infection, thus rendered Th1 to predominate over Th17 at the mucosal sites. SIV plasma viral load also negatively correlated with the percent of IL-17-producing cells in this group of macaques (50).

In light of the difference in SIV pathogenesis between macaques and AGMs, a recent report compared SIV infection in pigtailed macaques (PTs) to that in AGMs (58). They found that infected PTs rapidly developed systemic immune activation with a high level of HLADR+ and Ki67+ cells in the blood, lymph node, colon and bone marrow; a marked and selective depletion of Th17 cells; and a loss of balance between Th17 and T regulatory (Treg) cells in the blood, mucosa, and lymphoid tissue. AGMs, on the other hand, maintained high and balanced levels of Th17 and Treg cells. A micro array analysis comparing PTs to AGMs at the time of infection and 45 days post infection found that the depletion of Th17 cells in PT macaques was selective because IFNγ and IL-4 were maintained at the same levels in both species post infection (58).

It seems from the above studies that Th17 cells are an important contributor to SIV pathogenesis in macaques. Therefore, finding ways to maintain their frequencies at normal levels might slow down SIV disease progression.

Role of Th17 cells in immune response against HIV infection

Th17 depletion during HIV infection could also impact the natural immunity to HIV (Figure 1). A recent study did not find HIV-specific T cells that produce IL-17 in peripheral blood lymphocytes from HIV-infected individuals stimulated *ex vivo* with HIV antigens (49). However, another group reported the presence of HIV-specific Th17 cells in the blood of

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HIV-infected individuals during early infection that were undetectable during chronic or non progressive stages (defined as HIV-1 infected for less than 1 year, greater than 1 year, or greater than 10 years with no evidence of decline in the number of CD4+ T cells below 500/mm^3 respectively) (48). Therefore, it remains to be determined whether Th17 cells that recognize HIV antigens are present in HIV-infected individuals during different stages of the infection, and whether Th17 cell products, such as IL-17, promote or suppress HIV replication in target CD4+ T cells. Alternatively, Th17 cells could play a role in amplifying the innate responses to HIV infection, such as enhancing the expression of anti-microbial peptides (59,60). It is also conceivable that Th17 cells have a detrimental role on the immune response to HIV infection. This possibility has become more plausible in light of a recent report that showed that Th17 cells could potentially enhance viral persistence and inhibit T cell cytotoxicity in murine encephalomyelitis virus infection model (61).

Conclusion

Recent studies suggest that Th17 cells are reduced in the gut of HIV-infected individuals, which could lead to bacterial translocation from the gut lumen to the systemic circulation and chronic immune activation. Depletion of Th17 cells in macaques but not in natural hosts like AGMs and SMs, could serve as an important contributing factor to the disease progression in SIV-infected macaques. While major gaps remain in our understanding of the role of Th17 cells during HIV infection, their potential perturbation during HIV/SIV infection could have important implications in understanding HIV disease progression.

Acknowledgments

We thank Frances Mercer, Stephen Rawlings, Angela Zou, and Alka Khaitan for critical reading and helpful suggestions on the review.

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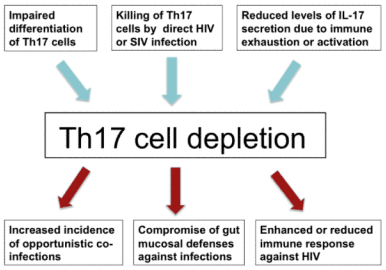

Figure 1.
Potential mechanisms and immunological consequences of Th17 depletion during HIV or SIV infection