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Th17 Cell Dynamics in HIV Infection

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Abstract

Purpose of Review—Th17 cells are a newly identified subtype of CD4+ T cells that respond to bacterial and fungal antigens and are important in mucosal immunology. Because HIV infection results in loss of CD4+ T cells as well as disruption to the GI tract that causes microbial translocation and immune activation, Th17 cells potentially play an important role in HIV pathogenesis. Here we examine the relationship between Th17 cells and HIV disease pathogenesis.

Recent findings—Th17 cells are preferentially lost from the GI tract of HIV-infected individuals, which is not entirely due to direct infection, as Th17 cells can be infected *in vivo*, but are not preferentially infected. Long-term HAART can result in restoration of Th17 cells in the GI, which may be associated with better disease prognosis. Furthermore, other cells, such as Vδ1 T cells, can make IL-17 *in vivo* during HIV infection and may contribute to anti-bacterial immunity after loss of Th17 cells.

Summary—Recent studies have improved our understanding of the role for Th17 cells during HIV infection, however more studies are needed to discern better the detrimental consequences of loss of Th17 cells during HIV infection.

Keywords

HIV; Th17; T cell; microbial translocation; immune activation

Introduction

HIV infection is characterized by a progressive loss of CD4+ T cells and massive dysregulation of the immune system, which ultimately leads to AIDS. HIV pathogenesis is extraordinarily complex and begins its course of destruction during the acute phase of infection, which is characterized by robust viral replication concurrent with rapid infection and depletion of mucosal CD4+ T cells [1–4]. Since the primary co-receptor for HIV is CCR5, HIV specifically targets and replicates in CCR5+CD4+ memory T cells, which comprise the majority of CD4+ T cells in mucosal associated lymphoid tissues (MALT)[2,5–9]. Effector memory CCR5+ T cells mainly reside in extra-lymphoid and effector sites while CCR5– T cells reside in blood and lymph nodes; therefore peripheral CD4+ T cells are relatively spared of massive depletion during the acute phase [2,10–13]. During the chronic phase of infection, CD4+ T cells are slowly depleted in lymph nodes, effector tissues and blood, which persists until the majority of CD4+ T cells are depleted and patients develop opportunistic infections and succumb to AIDS.

During the chronic phase of infection, the strongest predictor of disease progression is the level of immune activation during HIV infection. Indeed systemic immune activation is a hallmark of the chronic phase and is characterized by increased cell turnover, high rates of lymphocyte apoptosis, cell cycle dysregulation, and increased levels of proinflammatory cytokines [14–16]. Massive infection of CD4⁺ T cells in MALT is directly associated with inflammation of the mucosal tissues and a breakdown of the mucosal integrity, resulting in microbial translocation from the lumen of the gut into peripheral blood [17]. Translocation of microbial products during HIV infection is demonstrated by an increase in plasma LPS levels and is associated with systemic immune activation [17–23]. Hence, regulation of T cell subsets in the mucosa of HIV-infected individuals is of extreme importance in both understanding HIV pathogenesis and developing potential therapies.

Interestingly, loss of CD4⁺ T cells alone is not sufficient to cause AIDS, as demonstrated by natural host models of simian immunodeficiency virus (SIV). Sooty mangabeys (SM) and African green monkeys (AGM) are natural hosts of SIV, and despite severe depletion of CD4⁺ T cells in the mucosal tissues during acute SIV infection, these animals do not succumb to AIDS, even in the face of high viral replication [24,25]. Furthermore, chronic depletion of CD4⁺ T cells in SM does not result in AIDS whether the depletion occurs naturally [26], is antibody-mediated experimentally [27], or by CCR5/CXCR4 dual tropic SIV infection [28]. In all of these studies, animals maintained high viremia, yet did not succumb to AIDS even though CD4⁺ T cells were lost, suggesting that other facets of disease pathogenesis may be responsible for progression to AIDS in HIV-infected humans and SIV-infected Asian macaques.

Biological relevance of Th17 cells

An important role of mucosal T cells in health has been recently highlighted by numerous studies dedicated to a newly identified subset of CD4⁺ T cells, Th17 cells, which predominate in the gastrointestinal (GI) tract [29–33]. These T cells produce IL-17, which is important in adaptive immunity against extracellular bacteria and fungi [34,35]. Th17 cells are functionally distinct from either Th1 or Th2 cells, and have a crucial role in mucosal immunology, as these cells are potent inducers of tissue inflammation. Th17 cells not only produce IL-17, but they also can secrete TNF α , IL-1, IL-2, IL-21 and IL-22, all strong pro-inflammatory cytokines. These cells have the ability to recruit neutrophils and myeloid cells to effector sites by inducing granulocyte-colony stimulating factor [36], and are involved in epithelial regeneration in mucosal tissues [37]. This regeneration of epithelial cells may be driven by Th17 cells' ability to induce the expression of claudins, which are components of epithelial tight junctions, and stimulation of defensins and mucin production, all vital for mucosal integrity [38,39]. The importance of Th17 cells in human immunology was recently highlighted by Milner et al., when they showed that individuals with hyper-IgE syndrome (HIES or "Jobs" syndrome) lack IL-17 production by T cells, which leads to susceptibility to certain bacterial and fungal infections [40**].

Indeed, Th17 cells play a crucial role in protection against infections. Ye et al. first demonstrated this, when they infected IL-17 receptor-deficient mice with *K. pneumoniae* and found that the IL-17 receptor deficient mice had increased susceptibility to *K. pneumoniae* [36]. Furthermore, Ye et al. demonstrated that this phenotype was directly associated with delayed neutrophil recruitment and reduced expression levels of granulocyte colony-stimulating factor in the lungs of IL-17 receptor-deficient mice [36]. Since these studies, multiple reports have demonstrated the importance of Th17 cells in infection, including multiple bacterial infections, mycobacterium, and fungal infections (summarized in [41] and Table 1). Of note, anti-microbial effects of IL-17 have been independently demonstrated in nearly every bacterial and fungal infection associated with opportunistic infections observed in AIDS patients, albeit these studies have not been performed in the context of HIV/AIDS.

Briefly, the effects of IL-17 and/or IL-23 have been associated with reduced bacteria or fungus numbers and/or increased survival for *Mycobacterium spp.*, *Salmonella sp.*, *Aspergillus sp.*, *Cryptococcus sp.*, *Pneumocystis sp.*, *Streptococcus*, *Mycoplasma* and *Klebsiella pneumoniae*, as well as *Candida spp.* [34,36,42–52].

Th17 cells and autoimmunity

Th17 cells, however, can be a double-edged sword. On the one hand, the potent inflammatory properties of these cells are vital to immunity against extracellular bacteria and maintenance of mucosal integrity, while on the other hand unchecked proliferation of these cells can result in autoimmunity and inflammatory conditions leading to pathogenesis. A role for IL-17 was recently described in diseases such as Crohn's disease, psoriasis, pneumonia and atopic dermatitis even before Th17 cells were characterized [36,53–55]. In the case of inflammatory conditions such as Crohn's disease, ulcerative colitis, and inflammatory bowel disease, there is an association between inflamed mucosa and an increased number of IL-17 producing cells in the gut as compared to healthy controls [37,56,57*–59]. Furthermore, it was shown that in inflammatory GI tract diseases such as these, IL-17 is readily measured in patient serum while it is undetectable in healthy patients [56]. The same phenomena have also been observed in other inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis [60–63]. Though these studies highlight a negative role for Th17 cells in the context of autoimmunity, lack of Th17 cells results is also detrimental. The possible implications of the anti-microbial role of Th17 cells and the role of these cells during progression to AIDS during HIV infection have been the subject of recent investigations.

HIV and peripheral Th17 cells

The first description of a role for Th17 cells during HIV infection was reported by Maek-anantawat et al. in 2007 [64]. Here, the authors stimulated peripheral blood mononuclear cells (PBMC) with phorbol myristate acetate and ionomycin and found that in HIV+ individuals from Thailand, there was a significant increase in IL-17 producing CD4+ T cells compared to seronegative controls. However, it is still unclear as to the role of Th17 cells in peripheral tissues after lentiviral infection, as other studies have shown differing results as to whether Th17 cells are increased, decreased, or not affected in peripheral blood after HIV infection or SIV infection of Asian macaques [65**–68]. For instance, Lishomwa et al. assessed the frequency of IL-17 producing CD4+ T cells in HIV-1 infected children, as compared to healthy controls or exposed uninfected individuals [69]. The authors found that in HIV-infected children with plasma viral loads >50 copies/mL there was a significant loss of IL-17 producing PBMC. Furthermore, the authors found a significant negative correlation between the frequency of Th17 cells and HIV plasma viremia, indicating that loss of IL-17 production may be either a cause or effect of high HIV viremia in plasma [69]. The contradictory data on peripheral Th17 cells in HIV, however, may be explained by issues in the quantitative and qualitative assessment of these cells, or possibly timing after infection. Since HIV-infected individuals have a greater frequency of memory T cells compared to uninfected individuals, measuring IL-17 responses in bulk CD4+ T cells vs. memory CD4+ T cells may explain differing results. Another possibility is that at different points after HIV infection, Th17 cells re-circulate, or proliferate in response to a homeostatic drain, which may lead to differing results depending on what phase of infection patients were sampled. A longitudinal assessment of Th17 cells in the periphery during SIV and/or HIV infection is needed in order to better determine the magnitude and tempo of Th17 cell dynamics in peripheral blood.

HIV and mucosal Th17 cells

In order to define better the dynamics and anatomical restrictions of Th17 cells during HIV infection, Brenchley et al. carried out a comprehensive analysis of Th17 cells from the blood,

gastrointestinal (GI) tract and bronchoalveolar lavage (BAL) [65**]. In this study, the authors first determined that Th17 cells are found in peripheral blood of healthy individuals, but these cells are comparatively enriched in the GI tract. The authors demonstrated that in both HIV-infected and uninfected individuals, Th17 cells respond to bacterial and fungal antigens such as *Staphylococcus aureus*, *Streptococcal* kinase, Tetanus toxoid, and *Candida albicans*, however Th17 cells were not specific for viral antigens, such as HIV, adenovirus, Cytomegalovirus (CMV), Epstein-Barr virus, and influenza. These data were further confirmed by Yue et al., who demonstrated that in uninfected and chronically HIV-infected individuals, IL-17 was not produced in response to either HIV or CMV antigens [70]. Brenchley et al. went on to show that Th17 cells are preferentially lost from the GI tracts of chronically HIV-infected individuals as compared to uninfected individuals, but this loss of Th17 cells was not observed in BAL or peripheral blood, indicating that this phenomena is specific to the mucosal tissues of the GI tract. The authors furthered their analysis by demonstrating that CD4+ T cells in blood of HIV-infected patients are skewed toward a Th1 phenotype. In order to determine whether HIV preferentially infected Th17 cells, Brenchley et al. sorted IL-17⁺IFN γ ⁻, IL-1⁻IFN γ ⁺, and IL-1⁻IFN γ ⁻ cells from peripheral blood and determined the infection frequency of each subset using quantitative real-time PCR for HIV DNA. They found that Th17 cells were infected *in vivo*, however there was no significant differences between the infection frequencies of any functional subset, suggesting that in peripheral blood Th17 cells are not preferentially infected. However, due to limitations with the number of cells available from GI tract biopsies, the infection frequency of Th17 cells in the GI tract was not determined. In order to ascertain if Th17 cells are lost in the GI tract after HIV infection due to direct virus infection or bystander effects such as inflammation and immune activation, further studies are required.

Interestingly, in this study the authors also determined the frequency of Th17 cells in the GI tracts of SIV-infected SM. Brenchley et al. found that there was no preferential loss of Th17 cells, which may suggest a possible mechanism by which SM maintain a healthy GI tract despite overall loss of GI tract CD4+ T cells. Further studies to determine whether Th17 cells are lost from the GI tracts of HIV-infected long-term non-progressors are needed to determine if this may be a mechanism of protection against microbial translocation and immune activation during non-progressive HIV infection.

Indeed, a study by Macal et al. demonstrated that some HIV-infected individuals that were given long term (>5 years) highly active antiretroviral therapy (HAART) were able to reconstitute both Th17 cells and overall frequencies of CD4+ T cells in the GI tract and periphery to healthy levels [71]. In the individuals who received HAART and reconstituted CD4+ T cells, the levels of immune activation, as measured by gene expression levels, were decreased compared to HAART treated, HIV-infected, individuals who did not reconstitute CD4+ T cells. Instead, a low level of immune activation persisted in these individuals when compared to healthy controls. Thus the questions remain whether reconstitution of overall CD4+ T cells and Th17 in the GI tract translates into increased survival, and what happens to viremia after patients stop receiving HAART.

HIV and IL-17 producing $\gamma\delta$ T cells

Other T cell subsets may also be contributing to IL-17 production *in vivo*, and these cells may be important during HIV pathogenesis, as demonstrated by Fenoglio et al. In this study, the authors assessed a role for V δ 1 T cells during HIV infection [72]. V δ 1 T cells are one of two predominant subsets of $\gamma\delta$ T cells, which are important for mucosal immunity. During HIV infection, V δ 1 T cells are increased in the peripheral blood, which is suggested to result from mucosal depletion and recirculation [73,74**]. V δ 1 T cells are important to mucosal immunity as they are found in the intraepithelial lymphoid tissue of the mucosa, and mediate immunity

against antigens such as *Listeria monocytogenes* and CMV [75,76]. In this study, Fenoglio et al. found that V δ 1 T cells isolated from HIV-infected patients co-express IL-17 and IFN γ , as well as the Th17 transcription factor ROR γ t and the Th1 transcription factor TBX21, and are expanded *in vivo* as compared to healthy patients. Furthermore, they found that these V δ 1 T cells proliferate and produce cytokines in response to *Candida albicans* and express CCR4 and CCR6, which suggests their ability to home to the GI tract. Of interest, the 30 HIV-infected, HAART-naïve, individuals in this study with >200 CD4⁺ T cells/mL blood, had varying levels of viremia. The authors suggest that the V δ 1 T cells found in these individuals may be compensating for Th17 function, and that these V δ 1 T cells, expanded in these patients, may play an important role in the control of HIV spreading and defense against opportunistic infections. However, the frequency of these V δ 1 T cells in individuals with AIDS was not studied for comparison. Indeed, a thorough assessment of the association between V δ 1 T cells and IL-17 production and better disease prognosis would be warranted.

Undoubtedly, many further studies are needed to dissect the role of IL-17 producing cells during HIV infection. Favre et al. recently demonstrated that during pathogenic SIV infection of pigtail macaques (PTM), there is a loss of balance between Th17 and regulatory T cell (Treg) populations, whereas the balance is maintained during nonpathogenic SIV infection of AGM [77]. Here the authors found that the loss of balance between Th17 cells and Tregs in PTM was predictive of increased immune activation and disease progression. Indeed, regulation of different CD4⁺ T cell subsets is likely crucial for homeostasis, albeit discerning different phenotypes is complex. Data on Tregs during HIV infection has been conflicting due to lack of effective markers to adequately identify Tregs. An intriguing study by Wang et al. recently defined GARP, a transmembrane protein that is expressed by Tregs [78]. The authors were able to correlate expression of GARP on activated Tregs with their suppressive capacity, but this did not correlate with FoxP3 expression. Here the authors show that CD25⁺GARP⁺ T cells produced 3–5 fold higher levels of IL-17 compared to CD25⁺GARP⁺ or CD25⁺GARP[−], indicating that GARP may discriminate Tregs from Th17 cells. Furthermore, when the authors assessed FoxP3⁺ T cells from HIV-infected individuals, they did not find a proportionate increase in GARP⁺ T cells, suggesting that increases in FoxP3 expression in HIV-infected patients may simply reflect increased immune activation and potentially an increase in IL-17 producing cells, rather than an increase in Tregs. It is clear that both Th17 cells and Tregs play an important role in maintaining a healthy immune system, however studies that define better these cell subsets are needed.

Conclusion

HIV disease pathogenesis is extraordinarily complex and involves both immunodeficiency that leads to opportunistic infections and AIDS as well as excessive inflammation and systemic immune activation. It is not, therefore, surprising that IL-17 producing T cells play a role in HIV pathogenesis (summarized in Table 2). Though there are varying data regarding Th17 cell dynamics in peripheral blood during HIV infection, it is clear that Th17 cells are substantially depleted from the GI tract. Loss of mucosal integrity during HIV and pathogenic SIV infection leads to microbial translocation, which in turn further drives systemic immune activation. Hence Th17 cells may be an excellent target for therapeutic interventions. The extent to which loss of Th17 cells causes dysregulation of mucosal immunity in HIV is still unclear, however Th17 cells are clearly vital in maintaining a healthy mucosa, and loss of these cells is undoubtedly detrimental. However, there are many unanswered questions. First, is it possible to expand Th17 cells in the GI tract after HIV infection? If so, could this expansion increase targets for HIV infection *in vivo*? Furthermore, could excessive proliferation of Th17 cells potentially lead to uncontrolled inflammation in mucosal tissues as observed in chronic inflammatory diseases such as Crohn's disease and ulcerative colitis? Such inflammation could result in increased destruction to the epithelial barrier of mucosal tissues, enhancing microbial

translocation and immune activation. One possibility would be to expand alternative IL-17 producing cells, such as CD8+ T cells, V δ 1 T cells, or to find supplemental cytokines and or chemokines that induce restoration of mucosal tissues without causing systemic inflammation. Given the role for Th17 cells and anti-microbial immunity in mucosal tissues, it is undeniable that loss of these cells impacts immunity during HIV infection, and contribute to opportunistic infections, and a better understanding of the role of Th17 cells during HIV pathogenesis will be critical as new therapeutic interventions are designed.

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Table 1

Pathogenic microbes whose containment involves Th17 cells

Type	Pathogen	Effect	Reference
Bacteria	<i>Citrobacter rodentium</i>	Increases survival	31
	<i>Escherichia coli</i>	Decreases bacterial burden	41
	<i>Klebsiella pneumoniae</i>	Decreases bacterial burden	42
	<i>Listeria monocytogenes</i>	Decreases bacterial burden, neutrophil recruitment	41
	<i>Mycoplasma pneumoniae</i>	Reduces bacterial burden	43
	<i>Streptococcus pneumoniae</i>	Prevents colonization	44
	<i>Salmonella enterica</i>	Decreases bacterial burden	45
Mycobacteria	<i>Mycobacterium tuberculosis</i>	Decreases mycobacterial burden	46
	<i>Mycobacterium bovis</i>	Neutrophil recruitment	46
Fungi	<i>Candida albicans</i>	Decreases fungal burden, increases survival	34
	<i>Cryptococcus neoformans</i>	Decreases fungal burden, increases survival	47
	<i>Pneumocystis carinii</i>	Decreases fungal burden	48

Table 2

Effects of lentiviral infection on IL-17 producing cell subsets

Cell type	HIV-infected human	SIV-infected macaque	SIV-infected natural host
Mucosal CD4 T cells	Preferentially depleted	Preferentially depleted	No preferential depletion
PeripheralCD4 T cells	No preferential depletion	No preferential depletion	No preferential depletion
Mucosal $\gamma\delta$ T cells	Unknown	Unknown	Unknown
Peripheral $\gamma\delta$ T cells	Preferentially depleted	Unknown	Unknown