HOT TOPICS

IL-17 and HIV pathogenesis

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There is an increasing body of evidence showing that T_H17 cells constitute a novel T_H cell lineage [1, 2]. In 2005, T_H17 cells were shown to arise from a lineage separate from that of T_H1 and T_H2 cells [1, 3], and to be associated with autoimmunity [4]. They produce IL-17 (also called CTLA-8), that shares homology with an open reading frame in *Herpesvirus saimiri* [5]. T_H17 cells are also characterized by the production of IL-21, IL-22 and IL-26 and express chemokine receptors such as CCR4 and CCR6 [6]. CCR6, in particular, is the homing receptor important for T_H17 cell migration to certain tissue microenvironments of the intestine such as Peyer's patches, where its ligand, CC-chemokine ligand 20 (CCL20, also known Mip-3α), is expressed [7, 8]. TGF-β, an immunosuppressive cytokine that has a major role in T_{reg} differentiation [9], combined with the pro-inflammatory cytokine IL-6 are required for naive T cell differentiation into IL-17-producing T cells in mice [10-12]. TGF-β expression in Peyer's patches has already been recognized for its role in directing B cell switching to IgA [13]. Additionally, cytokines such as IL-23 and IL-21 promote the generation or proliferation of T_H17 cells, whereas others, such as IFN-γ, IL-4, and IL-27, suppress their generation [14, 15]. The role of IL-21 in the differentiation of T_H17 is an important factor for up-regulating IL-23R expression, which is not expressed by naive cells. Thus, IL-21 promotes the expansion of T_H17 cells by increasing their responsiveness to IL-23. IL-23 is required to expand and stabilize the cell population. Although it was initially proposed that human T_H17 cells were different from mouse T_H17 cells in that TGF-β and IL-6 are not required for the generation of T_H17 cells [6, 16], other reports have shown that TGF-β and inflammatory cytokines such as IL-1β, IL-6, and IL-23 are the most effective cytokines for enhancing the generation or expansion of human T_H17 cells [17]. Among the transcription factors, it has been shown that the transcription factor retinoic-acid-related orphan receptor-γt (ROR-γt; also known as RORC) is important for the generation of T_H17 cells *in vitro* and *in vivo* [18]. In addition to ROR-γt, T_H17 cell differentiation is regulated by the transcription factor signal transducer and activator of transcription 3 (STAT3), and aryl hydrocarbon receptor [19, 20]. Recently, it was shown that a dominant, negative form of STAT3, found in hyper-IgE syndrome patients, caused a primary immunodeficiency of T_H17 cells, associated with an inability to control *Candida* and *S.aureus* infections of skin and mucosal surfaces [21, 22].

IL-17 comprises a family of cytokines composed of IL-17A through F [23]. Receptors belonging to the IL-17R family have a unique structural feature that mediates a signaling pathway through NF-κB activator 1 (ACT1, also known CIKS for its connection to IKK and SAPK/JNK) [24, 25], which is clearly distinct from the signatures involved in the T_H1 and T_H2 response, particularly Janus kinase (JAK)-STAT pathways. Thus, IL-17 culminates in the activation of pro-inflammatory mediators and is usually associated with innate immune signaling. Thus, IL-17 promotes neutrophil mobilization and the expression of antimicrobial factors. Interestingly, IL-17 family homologues have been found in various species including sea lamprey, rainbow trout and *Caenorhabditis elegans*, highlighting the potential role of this cytokine.

T_H17 cells are widely found in non-lymphoid tissues (*e.g.* intestine) and secondary lymphoid tissues (mesenteric lymph nodes, peripheral lymph nodes, spleen, and Peyer's patches). T_H17 cell differentiation in the lamina propria of the small intestine requires specific, commensal microbiota, and is inhibited by antibiotics. Differentiation of T_H17 cells correlates with the presence of Cytophaga-Flavobacterium-Bacteroides bacteria in the intestine and is dependent on TGF-β activation. Thus, it has been proposed that the composition of intestinal microbiota regulates the T_H17/Treg balance in the lamina propria, and may thus influence intestinal immunity, tolerance, and susceptibility to inflammatory bowel diseases [26, 27]. Interestingly, Pigtail macaques (PTMs), which are highly sensitive to Simian-immunodeficiency Virus (SIV) infection, had high frequencies of interleukin-17-producing T cells associated with high levels of

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microbial translocation that correlated with significant damage to the structural barrier of the gastrointestinal tract [28]. Finally, IL-17 and T_H17 cells have been reported to be involved in the induction of autoimmune inflammation in several animal models, such as allergic encephalomyelitis [3, 4, 29], collagen induced arthritis [30], and colitis [31]. Consistently, T_H17 cells are also increased in the inflamed tissue sites of patients with multiple sclerosis, rheumatoid arthritis, and inflammatory bowel diseases [32]. There is also considerable evidence, in mice, that IL-17 is important in host responses to infection by Gram-negative bacteria, specifically *Klebsiella*, *Pseudomonas*, *Escherichia coli*, *Salmonella*, and *Bordetella* species [33].

The central role of TGF-β in the differentiation of T_H17 suggests that pathologies associated with an over-production of TGF-β might promote the differentiation of T_H17 cells. In the 1990s, several reports showed increase expression of TGF-β in the context of HIV-infected individuals [34-36], although other reports did not find this [37]. A possible over-production of TGF-β may be associated with increased collagen deposition in lymph nodes of HIV-infected patients, and alterations in lymph node architecture [38, 39]. More recently, using non-human primate models of lentiviral infection, we and other groups have reported higher levels of TGF-β [39-41] in SIV-infected rhesus macaques (RM). Moreover, it has been reported that the increased inflammation in HIV patients is associated with the presence of lipopolysaccharide (LPS), a potent inflammatory product, in the plasma of HIV-infected individuals and in SIV-infected RM [42]. Thus, the elevation of TGF-β, plus an inflammatory environment, support the possible induction of IL-17 populations during AIDS. However, several groups have shown a decline in T_H17 $CD4^+$ T cells during HIV and SIV infections [43-46]. Conversely, no depletion in T_H17 cells was reported in SIV-infected African green monkey, a model of lentiviral infection that does not progress to disease [45, 47]. This result was consistent with the results from another group who found unchanged numbers of IL-17 cells in the peripheral blood of the Sooty mangabey, a non-pathogenic model of SIV infection [43]. Thus, despite a favorable environment for T_H17 cell expansion, a decline of this subset was observed in AIDS, which was restored under HAART [48]. It has been proposed that a reduction in this subset may lead to the disruption of mucosal barrier integrity, loss of control of commensal bacteria, and a subsequent wasting syndrome. During the acute phase, despite a drastic decline both in $CD4^+$ T cells and T_H17 cells in the peripheral blood and the intestine, animals did not develop this wasting syndrome and were devoid of bacterial translocation [42]. Our recent results demonstrated the early expansion of IL-17-expressing cells in SIV-infected RM that correlated with TGF-β expression [47], suggesting the existence of IL-17-producing cells compensating for the defect in T_H17 cells that is essential for controlling bacterial translocation.

In addition to T_H17, it has been shown that CD8 T cells [49], γδ T cells [50, 51], $CD4^-CD8^-TCR^+$ T cells [52], and NKT cells [53, 54] are also able to produce IL-17. In early HIV-1 infection, Vδ1 T lymphocytes are increased in peripheral blood and display concurrent IFN-γ and IL-17 expression [55]. We found an innate IL-17 production by NKT cells that is rapid, and precedes the adaptive T_H17 response. Thus, the emergence of this $IL\text{-}17^+NKT^+$ population in SIV-infected RM as well as of $IL\text{-}17^+$Vδ1 T cells, therefore, could compensate for the defect in T_H17 $CD4^+$ T cells, preventing microbial translocation (no LPS was detected during the acute phase) [42], and the occurrence of a wasting syndrome early after infection. Thus, microbial translocation might be a symptom of the defect in IL-17 populations, and not a direct cause of HIV-1 disease.

The mechanism by which T_H17 may be depleted remains unclear, since they exhibit a $CCR4^+CCR6^+$ phenotype [56], whereas the HIV co-receptor is not expressed on $CCR4^+CD4^+$ T cells (Zaunders *et al.*, unpublished data). Nevertheless, it has been reported that there is a selective infection of T_H17 $CD4^+$ T cells [57, 58], although not in all reports [43]. Most importantly, in non-pathogenic primate models of lentiviral infection, despite intense viral replication, there is no depletion of T_H17 $CD4^+$ T cells. Therefore, indirect mechanisms to explain this defect are probably more plausible. In this sense, it has been shown that iNKT cells, during T-cell priming, impede the commitment of naïve T cells to the T_H17 lineage [59]. Moreover, cytokines such as type I IFN, are critical in negatively regulating T_H17 $CD4^+$ T cells through IL-27 [60, 61]. This should be particularly relevant for HIV and SIV-infection in which higher levels of type I IFN early after infection is associated with poor prognosis [62-65].

All these data demonstrate the critical balance between pro- and anti-inflammatory cytokines occurring during HIV infection that may have a major impact on the differentiation of T cell subsets as well as on the expansion of cells such as NKT cells, that bridge innate and adaptive immunity.

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