Review Article
Loss and Dysregulation of Th17 Cells during HIV Infection

Sandra L. Bixler and Joseph J. Mattapallil

Department of Microbiology & Immunology, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA

Correspondence should be addressed to Sandra L. Bixler; sandra.bixler@usuhs.edu and
Joseph J. Mattapallil; joseph.mattapallil@usuhs.edu

Bacterial translocation across the damaged mucosal epithelium has emerged as a major paradigm for chronic immune activation observed during HIV infection. T helper 17 (Th17) cells are a unique lineage of T helper cells that are enriched in mucosal tissues and are thought to play a central role in protecting the integrity of the mucosal barrier and maintaining immune homeostasis at mucosal sites. Th17 cells are lost very early during the course of HIV infection, and their loss has been shown to correlate with bacterial translocation. Interestingly, Th17 cells are unable to completely recover from the early destruction even after successful antiretroviral therapy (ART). Here, we review some of the potential mechanisms for the loss and dysregulation of Th17 cells during HIV infection.

1. Introduction

T helper 17 (Th17) cells have emerged as a key player in host-pathogen interplay at the mucosal surface. The lack of Th17 cells has been associated with recurring bacterial and fungal infections that are a hallmark of hyper-IgE syndrome [1, 2]. Th17 cells are enriched at mucosal sites [3–5] where they are thought to play a role in maintenance of immune homeostasis in response to commensal organisms and protect against pathogens that may gain entry via these surfaces [6]. Studies have shown that a paucity of Th17 cells in mucosal tissues is associated with systemic translocation of bacteria across the intestinal epithelial barrier [7].

Th17 cells are a unique lineage of T helper cells that are induced under anti-Th1/Th2 polarizing conditions and preferentially produce interleukin-17 (IL-17) [8–12] and express markers such as CD26, CD161, and interleukin-4-inducible gene [11, 13–15]. This newly identified subset of Th17 cells was later found to be the key effector T-cell subset mediating experimental autoimmune encephalitis (EAE) in mice [16, 17]. Deletion of Th1 cells was found to exacerbate the symptoms of EAE, and this finally led to identification of Th17 cells as the primary cells mediating the development of EAE [18–20].

IL-17 produced by Th17 cells serves as a chemoattractant for neutrophils to sites of infection and inflammation [21, 22]. IL-17 also promotes tight junction formation at mucosal surfaces through the upregulation of claudin-1, claudin-2, and zona occludens-1 expression, which are all key proteins essential for maintenance of epithelial barrier integrity [23, 24]. Studies have demonstrated that IL-17 increases the production of antimicrobial peptides such as β-defensins that play critical roles in defense against microbial pathogens [25–28]. Th17 cells also produce a number of other cytokines such as IL-22 and IL-21 that have been shown to synergize with IL-17 and enhance the expression of antimicrobial peptides in mucosal tissues [26]. Additionally, IL-22 has been demonstrated to be critical for enterocyte homeostasis [29]. Numerous studies have shown that Th17 cells express CCR4, CCR6, CCR9, and $\alpha4\beta7$ [30–33] suggesting that these cells preferentially migrate to mucosal tissues.

Th17 cells play a critical role in protection against pathogens though they have been implicated in several autoimmune and inflammatory disorders, including asthma and allergy [34], psoriasis [35, 36], and inflammatory bowel disease [37, 38]. Interestingly, recent studies have shown that other cells such as CD8 T cells called T-cytotoxic-17 (Tc17) cells were capable of producing IL-17. Huber et al. [39]

showed that IL-17 secretion by CD8 T cells supported Th17-mediated autoimmune encephalomyelitis, whereas Saxena et al. [40] demonstrated that Tc17 cells potentiated Th1-mediated diabetes in the mouse model. Other studies have implicated Tc17 cells in vaccine-mediated immunity against fungal pathogens [41].

2. Th17 Cells during HIV Infection

HIV and SIV infections are characterized by massive loss of T helper cells, particularly at mucosal sites that persists during the course of infection, with little or no repopulation even after long periods of antiretroviral therapy [32, 42–53]. Destruction of mucosal CD4+ T cells is accompanied by dramatic alterations of the mucosal microenvironment, and is characterized by a preferential loss of Th17 cells, intestinal dysfunction and malabsorption, loss of mucosal epithelial barrier integrity, and severe enteropathy [54].

The exact mechanisms for the loss of Th17 cells are still under investigation. Brenchley et al. [4] reported that Th17 cells in the mucosa express high levels of CCR5, the coreceptor for HIV, and appear to be preferentially depleted despite the fact that they were not preferentially infected. On the other hand, Hed et al. using phenotypic markers such as CCR6 expression to delineate Th17 cells reported that direct infection by HIV likely played a central role in their depletion [55]. Ndhlovu et al. [56] demonstrated that IL-17 expression was dependent on the extent of infection in HIV-1+ children whereas HIV-infected patients with a plasma viral load below 50 copies/mL had detectable IL-17 expression. Other studies [57] have shown that HIV-1 specific Th17 cells were present in the acute stage of HIV infection yet were undetectable during chronic infection. The exact role that virus-specific Th17 cells play in HIV infection is still under investigation. Interestingly, however, HIV long-term nonprogressors appear to preserve their Th17 subsets [58]. In spite of ongoing debate about the exact mechanisms for the loss of Th17 cells, it is clear from a large number of studies in HIV-infected subjects and nonhuman primates with pathogenic SIV infections that Th17 cells are depleted to some degree during infection and their depletion contributes to the pathogenesis of HIV infection. Recent studies have shown that the Tc17 cells like their counterparts are also depleted during chronic HIV and SIV infections [59, 60].

In a landmark study, Brenchley et al. [61] showed that HIV infection was accompanied by translocation of microbial products across the lumen of the intestinal mucosa into systemic circulation. These translocated microbial products are believed to be a major cause for chronic immune activation and disease progression characterized by increased cell turnover [61–63]. A number of studies in HIV-infected patients and nonhuman primate models have demonstrated that the loss of Th17 cells from the mucosa most likely plays a major role in microbial translocation. Raffatellu et al. [7] showed that Th17 cell deficiency during SIV infection was associated with systemic translocation of *Salmonella*. Likewise, pathogenic SIV infections are accompanied by a severe loss of Th17 cells at mucosal sites within the first

few weeks of infection that persists in chronic infection [64]. In contrast to pathogenic infections, natural hosts of SIV infection such as sooty mangabeys and African green monkeys were found to preserve their Th17 cells following infection and display little or no immune activation even when viral replication is high [4].

The effect of HIV and SIV infections on the loss of Th17 cells has been well documented. Not much is, however, known about the ability of Th17 cells to effectively repopulate either during the course of infection or after therapy. Ciccone et al. demonstrated that long-term highly active antiretroviral therapy (HAART) was somewhat successful in achieving Th17 repopulation in both peripheral blood and the mucosa [58]. On the other hand, Macal et al. [65] suggested that Th17 repopulation was dependent on overall levels of CD4+ T cell restoration in the gastrointestinal-associated lymphoid tissue (GALT). Gaardbo et al. [66] reported that ~20% of the HIV patients on antiretroviral therapy failed to completely reconstitute their CD4+ T cells which was accompanied by an incomplete repopulation of Th17 cells. Mavigner et al. [33] showed that incomplete mucosal immune reconstitution was associated with defective gut homing of CCR9+β7+ CD4+ T cells, a population that harbored Th17 cells. This was likely due to the altered expression of the CCR9 ligand CCL25 in the small intestinal mucosa of HIV-infected individuals. He et al. [67] reported that HIV-infected patients had significantly low levels of Th17 cells that were partially restored after 6 months of HAART though higher levels were observed after 1 year of therapy. Likewise, elite control of HIV infection has been associated with higher levels of Th17 cells [68]. However, others have demonstrated that HAART failed to restore Th17 cells in HIV-infected patients undergoing therapy [55, 69]. The inability to effectively repopulate Th17 cells unlike other subsets such as Th1 or Tregs suggests that mechanisms that likely affect either the induction or differentiation of Th17 cells may be involved in the poor repopulation of Th17 cells.

Even though HAART has had limited effect on Th17 repopulation, recent studies suggest that using probiotics can potentially enhance gastrointestinal immunity, enhance CD4+ T cell numbers, and lead to the restoration of Th17 cells in the mucosa [70]. Klatt et al. [71] showed that treatment of SIV infected pigtail macaques with probiotics/prebiotics for 60 days along with antiretroviral therapy was accompanied by an increase in IL-23 producing cells and higher levels of multifunctional Th17 cells in the mucosa as compared to animals that only received antiretroviral therapy. Like-wise, Gonzalez-Hernandez et al. [72] showed that symbiotic treatment of HIV-infected subjects with a combination of pre- and probiotics significantly decreased microbial translocation and inflammation and improved the immunological status of patients leading to a better long-term outcome. However, another randomized clinical trial [73] reported no major changes in either microbial translocation or markers of immune activation. It is not clear if a better outcome would have been observed with either longer periods of symbiotic treatment or if patients were on antiretroviral therapy at the time of symbiotic therapy. Additional studies are needed to assess the beneficial role of symbiotic therapy on Th17 reconstitution.

3. Regulation of Th17 Cells and HIV Infection

Like the other T helper subsets, Th17 cells are memory CD4+ T cells [30, 69] that differentiate from naïve CD4+ T cells after TCR stimulation and costimulation by antigen presenting cells (APC) in the presence of Th17 promoting cytokines [74–76].

Development of Th17 cells requires key cytokine signals, several of which are produced by APCs following activation of toll-like receptors (TLRs) by pathogen-associated motifs. Activation of TLR 1/2, TLR 3, TLR 4, TLR7/8, and TLR9 have been shown to promote development of Th17 cells [74–78]. Fukata et al. [79] also demonstrated a role for MyD88 induction in Th17 differentiation. Reynolds et al. [80] showed that Th17 cells express high levels of TLR2 and stimulation with TLR2 agonists in the presence of Th17-promoting cytokines led to increased IL-17 production and expression of Th17-associated gene products. Signaling through other molecules such as dectin-1 and DC-SIGN has also been shown to promote Th17 development [81–85].

Initial studies identified IL-6, IL-21, IL-23, and TGFβ as critical cytokines essential for the induction of Th17 cells. A number of studies using mouse models suggested that IL-6 and TGFβ were essential for the initial differentiation of Th17 cells. Unlike mouse, however, the studies in humans have suggested that any of the four cytokines along with IL-1β in different combinations were sufficient to induce Th17 cells [85–87]. Of the four Th17 promoting cytokines, IL-6 and TGFβ appear to be critical for the polarization of Th17 cells as Th17 cells produce IL-17 and IFNγ in the absence of TGFβ.

IL-6 binding to the IL-6 receptor initiates signaling through STAT3 and RORγt transcription factors leading to the STAT3-mediated activation of the IL-17 promoter and the induction of IL-21 and IL-23 receptor expression, two factors that are important for subsequent stages of Th17 development [88]. The essential requirement of IL-6 for the generation of Th17 cells came from studies showing that expression of mutant gp130 IL-6R [89] or treatment with an anti-IL-6 antibody prevented Th17 polarization [76, 90].

Unlike IL-6, the ability of TGFβ to polarize Th17 cells appears to be dependent on the concentration of TGFβ in the environment; low concentrations of TGFβ in the presence of other Th17-promoting cytokines drives RORγt expression and induces Th17 cells. On the other hand, high concentrations of TGFβ in the absence of other Th17 inducing cytokines promote the development of T regulatory (Treg) cells and inhibit Th17 development through an effect on the Treg transcription factor FoxP3. TGFβ1 deficient mice have low levels of Th17 cells and circulating IL-17 [91] whereas treatment with anti-TGFβ1 antibodies were found to inhibit the generation of Th17 cells [92].

The second stage of Th17 differentiation is mediated by IL-21, a member of the common gamma chain family of cytokines. IL-21 is an autocrine cytokine that provides a positive feedback mechanism for the induction of Th17 cells [93, 94] and has been shown to inhibit FoxP3, thereby skewing the development away from Tregs. IL-21 has been shown to promote the induction of IL-17 and block IFNγ production [93–96] whereas other studies have shown that IL-21 knockout mice or IL-21R-deficient mice fail to develop Th17 cells when stimulated with IL-6 [93–97]. Interestingly, one study reported that IL-21 can subvert the requirement for IL-6-mediated stimulation for inducing Th17 cells by promoting an alternative pathway; a combination of IL-21 and TGFβ was found to induce Th17 cells in IL-6 deficient mice [98].

Like IL-21, IL-23 appears to be critical for the differentiation of Th17 cells during later stages of development. IL-23 is a heterodimeric cytokine comprised of the IL-12p40 and p19 subunits that is induced by stimulation of dendritic cells and macrophages with different TLR2 and dectin-1 ligands [84, 85, 99]. IL-23 binds to the IL-23 receptor which is primarily expressed by activated memory T cells [100]. Initial studies suggested that IL-23 was essential for the Th17 polarization. Later studies, however, demonstrated that it was not required for initial differentiation of Th17 cells but was essential for the survival and expansion of Th17 cells [8, 9, 101]. Importantly, naïve CD4+ T cells were found to lack the IL-23 receptor. This further supports a role for IL-23 in the later stages of Th17 differentiation.

Interestingly, both HIV and SIV infections are characterized by high levels of IL-6 and TGFβ [102–104]. Conversely, IL-21 producing CD4+ T cells are lost very early in infection [105–107] though other cellular subsets such as CD8 T cells have been shown to upregulate IL-21 production [107–111]. The presence of high levels of Th17 promoting cytokines during HIV and SIV infections suggests that the failure to induce Th17 cells during infection is likely mediated by mechanisms unrelated to availability of these cytokines.

Recent studies have shown that the loss of Th17 cells was accompanied by an expansion of Treg cells. These studies have suggested that the accumulation of byproducts of tryptophan metabolism promotes the development of Treg's and inhibits Th17 cells. Indoleamine deoxygenase (IDO), a rate-limiting enzyme that mediates the catabolism of tryptophan, has been shown to be significantly upregulated during HIV and SIV infections [68, 112–115]. Likewise the frequency of Tregs was reported to be altered during HIV infection and during HAART [116–120] whereas effector IL-17 absolute cell numbers were significantly lower in all HIV(+) subjects tested and were not restored after therapy. On the other hand, Brandt et al. [68] showed that the ratio of Th17/Treg in elite controllers did not differ from that of uninfected controls, whereas the ratio was lower in viremic patients and patients on HAART.

It is not clear if HIV infection alters the signaling pathways that promote the induction of Th17 cells. RORγt is a lineage specific transcription factor associated with Th17 differentiation [88, 121, 122] whose expression is regulated by signal transducers and activators of transcription-3 (STAT3) [123, 124]. They bind to ROR-dependent enhancer elements in conserved noncoding sequence (CNS)-2, which is located upstream of the IL17A promoter [124]. Rueda et al. [125] examined expression of T helper lineage-specific transcription factors in the GALT from healthy uninfected volunteers, HIV-infected untreated, and patients undergoing HAART and found that the ratio of RORγt to FoxP3 expression

shifted in favor of FoxP3 in untreated patients, though RORγt expression itself was not changed among the groups.

Numerous studies have demonstrated the importance of the Janus-associated kinases (JAK)/STAT3 signaling pathway in the development of Th17 cells [126, 127]. Binding of Th17 promoting cytokines to their cognate receptors initiates the signaling cascade that leads to receptor dimerization and recruitment of JAK culminating in the activation and phosphorylation of STAT3. Activated pSTAT3 dimerizes and translocates to the nucleus where it binds to the IL-17 promoter and drives the induction of IL-17. Studies have shown that STAT3 knockout mice failed to develop Th17 cells [123, 128], whereas patients with Jobs' syndrome lack functional STAT3 and display impaired Th17 development [2].

STAT3 is negatively regulated by a number of factors such as the suppressor of cytokine signaling-3 (SOCS3), protein inhibitor of activated STAT3 (PIAS3), and protein tyrosine phosphatase (SHP-2). Overexpression of SOCS3 has been shown to inhibit Th17 development while SOCS3 conditional knockouts were shown to have higher levels of Th17 cells [129]. Interestingly while SOCS3 is activated by Th17 promoting cytokines IL-6, IL-21, and IL-23 [92, 129], TGFβ has been shown to inhibit SOCS3 induction by IL-6 and IL-23, thereby promoting the activation of STAT3 and subsequent induction of Th17 cells [92].

CD4+ T cells from HIV-infected patients have been shown to express high levels of SOCS3 mRNA [130] though SOCS3 protein levels were lower. Higher levels of SOCS3 mRNA have been reported in the gastrointestinal tissues of SIV-infected rhesus macaques [131]. Interestingly, increased levels of SOC3 have been shown to aid in HIV replication [132] whereas high levels of SOCS3 in hepatic cells have been associated with nonresponsiveness to therapy in HIV/HCV infected individuals [133]. Moutsopoulos et al. [134] reported that high levels of SOCS3 protein in mucosa-associated lymphoid organ such as the tonsils are associated with increased susceptibility to HIV infection.

Unlike SOCS3, PIAS3 has been shown to directly interact with pSTAT3 and inhibit its binding to target DNA thereby interfering with the STAT3-mediated activation of target genes [135, 136]. Others have shown that PIAS3 directly inhibits the transactivation of STAT3 [137]. PIAS3 transcript levels were found to be absent in Th17 cells as compared to Th1 or Th2 cells in mice, and knockdown of PIAS3 with siRNA resulted in severe EAE suggesting an important role for PIAS3 in Th17 regulation [138]. Recent studies have shown that PIAS3 mRNA levels were significantly upregulated in CD4 T cells from SIV-infected rhesus macaques and high levels of PIAS3 was found to significantly correlate with immune activation and markers of microbial translocation [139]. Not much is known about the effect of HIV infection on PIAS3 and if PIAS3 plays a role in dysregulating the induction of Th17 cells.

Like SOCS3 and PIAS3, SHP2 negatively regulates IL-17 production. However, unlike the other two, SHP2 interferes with IL-6 signaling-mediated activation of STAT3. SHP2 is recruited to receptors following cytokine signaling and JAK activation. Studies have shown that SHP2 is recruited to gp130 domain of the IL6 receptor following IL-6 signaling and dephosphorylates pSTAT3, preventing its dimerization and translocation to the nucleus [140, 141]. The exact role of SHP2 in preventing the induction of Th17 cells during HIV infection is not clear. However, studies have shown that HIV-mediated signaling through CCR5 and C-type lectin domain-4 (DCIR) results in recruitment of SHP-2 whereas HIV gp120 binding has been shown to increase SHP2-mediated signaling [142].

4. Summary

Th17 cells play an essential role in host immunity and are key players in protecting the mucosal integrity. Their loss during HIV infection is associated with translocation of microbial products across the damaged mucosal epithelium leading to immune activation and poor long-term outcome in HIV-infected patients. While progress has been made in understanding the role of Th17 cells in HIV infection, there are significant gaps in the field regarding the exact mechanisms that prevent full Th17 reconstitution during therapy. A better understanding of how these key molecular mechanisms are altered during HIV infection and the role these altered mechanisms play is essential to develop better therapeutic approaches to repopulate Th17 cells and overcome the deleterious effects associated with the loss of Th17 cells during HIV infection.

Acknowledgments

References

[1] B. Grimbacher, S. M. Holland, J. I. Gallin et al., "Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder," *New England Journal of Medicine*, vol. 340, no. 9, pp. 692–702, 1999.

[2] J. D. Milner, J. M. Brenchley, A. Laurence et al., "Impaired TH17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome," *Nature*, vol. 452, no. 7188, pp. 773–776, 2008.

[3] K. Atarashi, J. Nishimura, T. Shima et al., "ATP drives lamina propria TH17 cell differentiation," *Nature*, vol. 455, no. 7214, pp. 808–812, 2008.

[4] J. M. Brenchley, M. Paiardini, K. S. Knox et al., "Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections," *Blood*, vol. 112, no. 7, pp. 2826–2835, 2008.

[5] I. I. Ivanov, R. D. L. Frutos, N. Manel et al., "Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine," *Cell Host and Microbe*, vol. 4, no. 4, pp. 337–349, 2008.

[6] D. Mucida and S. Salek-Ardakani, "Regulation of TH17 cells in the mucosal surfaces," *Journal of Allergy and Clinical Immunology*, vol. 123, no. 5, pp. 997–1003, 2009.

[7] M. Raffatellu, R. L. Santos, D. E. Verhoeven et al., "Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination from the gut," *Nature Medicine*, vol. 14, no. 4, pp. 421–428, 2008.

[8] L. E. Harrington, R. D. Hatton, P. R. Mangan et al., "Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages," *Nature Immunology*, vol. 6, no. 11, pp. 1123–1132, 2005.

[9] H. Park, Z. Li, X. O. Yang et al., "A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17," *Nature Immunology*, vol. 6, no. 11, pp. 1133–1141, 2005.

[10] L. Steinman, "A brief history of TH17, the first major revision in the T H1/TH2 hypothesis of T cell-mediated tissue damage," *Nature Medicine*, vol. 13, no. 2, pp. 139–145, 2007.

[11] B. Bengsch, B. Seigel, T. Flecken, J. Wolanski, H. E. Blum, and R. Thimme, "Human Th17 cells express high levels of enzymatically active dipeptidylpeptidase IV (CD26)," *Journal of Immunology*, vol. 188, pp. 5438–5447, 2012.

[12] S. Romagnani, E. Maggi, F. Liotta, L. Cosmi, and F. Annunziato, "Properties and origin of human Th17 cells," *Molecular Immunology*, vol. 47, no. 1, pp. 3–7, 2009.

[13] F. Annunziato, L. Cosmi, F. Liotta, E. Maggi, and S. Romagnani, "Defining the human T helper 17 cell phenotype," *Trends in Immunology*, vol. 33, pp. 505–512, 2012.

[14] L. Maggi, V. Santarlasci, M. Capone et al., "CD161 is a marker of all human IL-17-producing T-cell subsets and is induced by RORC," *European Journal of Immunology*, vol. 40, no. 8, pp. 2174–2181, 2010.

[15] K. Nistala, S. Adams, H. Cambrook et al., "Th17 plasticity in human autoimmune arthritis is driven by the inflammatory environment," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 33, pp. 14751–14756, 2010.

[16] E. Bettelli, Y. Carrier, W. Gao et al., "Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells," *Nature*, vol. 441, no. 7090, pp. 235–238, 2006.

[17] C. L. Langrish, Y. Chen, W. M. Blumenschein et al., "IL-23 drives a pathogenic T cell population that induces autoimmune inflammation," *Journal of Experimental Medicine*, vol. 201, no. 2, pp. 233–240, 2005.

[18] I. A. Ferber, S. Brocke, C. Taylor-Edwards et al., "Mice with a disrupted IFN-γ gene are susceptible to the induction of experimental autoimmune encephalomyelitis (EAE)," *Journal of Immunology*, vol. 156, no. 1, pp. 5–7, 1996.

[19] B. Gran, G. X. Zhang, S. Yu et al., "IL-12p35-deficient mice are susceptible to experimental autoimmune encephalomyelitis: evidence for redundancy in the IL-12 system in the induction of central nervous system autoimmune demyelination," *Journal of Immunology*, vol. 169, no. 12, pp. 7104–7110, 2002.

[20] G. X. Zhang, B. Gran, S. Yu et al., "Induction of experimental autoimmune encephalomyelitis in IL-12 receptor-β2-deficient mice: IL-12 responsiveness is not required in the pathogenesis of inflammatory demyelination in the central nervous system," *Journal of Immunology*, vol. 170, no. 4, pp. 2153–2160, 2003.

[21] M. Laan, Z. H. Cui, H. Hoshino et al., "Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways," *Journal of Immunology*, vol. 162, no. 4, pp. 2347–2352, 1999.

[22] M. Miyamoto, O. Prause, M. Sjöstrand, M. Laan, J. Lötvall, and A. Lindén, "Endogenous IL-17 as a mediator of neutrophil recruitment caused by endotoxin exposure in mouse airways," *Journal of Immunology*, vol. 170, no. 9, pp. 4665–4672, 2003.

[23] T. Kinugasa, T. Sakaguchi, X. Gu, and H. Reinecker, "Claudins regulate the intestinal barrier in response to immune mediators," *Gastroenterology*, vol. 118, no. 6, pp. 1001–1011, 2000.

[24] D. J. Cua and C. M. Tato, "Innate IL-17-producing cells: the sentinels of the immune system," *Nature Reviews Immunology*, vol. 10, no. 7, pp. 479–489, 2010.

[25] C. Y. Kao, Y. Chen, P. Thai et al., "IL-17 markedly up-regulates β-defensin-2 expression in human airway epithelium via JAK and NF-κB signaling pathways," *Journal of Immunology*, vol. 173, no. 5, pp. 3482–3491, 2004.

[26] S. C. Liang, X. Y. Tan, D. P. Luxenberg et al., "Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides," *Journal of Experimental Medicine*, vol. 203, no. 10, pp. 2271–2279, 2006.

[27] S. J. Aujla, P. J. Dubin, and J. K. Kolls, "Th17 cells and mucosal host defense," *Seminars in Immunology*, vol. 19, no. 6, pp. 377–382, 2007.

[28] C. Dong, "TH17 cells in development: an updated view of their molecular identity and genetic programming," *Nature Reviews Immunology*, vol. 8, no. 5, pp. 337–348, 2008.

[29] G. Pickert, C. Neufert, M. Leppkes et al., "STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing," *Journal of Experimental Medicine*, vol. 206, no. 7, pp. 1465–1472, 2009.

[30] E. V. Acosta-Rodriguez, G. Napolitani, A. Lanzavecchia, and F. Sallusto, "Interleukins 1β and 6 but not transforming growth factor-β are essential for the differentiation of interleukin 17-producing human T helper cells," *Nature Immunology*, vol. 8, no. 9, pp. 942–949, 2007.

[31] F. Annunziato, L. Cosmi, V. Santarlasci et al., "Phenotypic and functional features of human Th17 cells," *Journal of Experimental Medicine*, vol. 204, no. 8, pp. 1849–1861, 2007.

[32] M. Kader, S. Bixler, M. Roederer, R. Veazey, and J. J. Mattapallil, "CD4 T cell subsets in the mucosa are CD28+Ki-67−HLA-DR−CD69+ but show differential infection based on α4β7 receptor expression during acute SIV infection," *Journal of Medical Primatology*, vol. 38, supplement 1, pp. 24–31, 2009.

[33] M. Mavigner, M. Cazabat, M. Dubois et al., "Altered CD4+ T cell homing to the gut impairs mucosal immune reconstitution in treated HIV-infected individuals," *Journal of Clinical Investigation*, vol. 122, pp. 62–69, 2012.

[34] K. Oboki, T. Ohno, H. Saito, and S. Nakae, "Th17 and allergy," *Allergology International*, vol. 57, no. 2, pp. 121–134, 2008.

[35] J. Li, X. Chen, Z. Liu, Q. Yue, and H. Liu, "Expression of Th17 cytokines in skin lesions of patients with psoriasis," *Journal of Huazhong University of Science and Technology*, vol. 27, no. 3, pp. 330–332, 2007.

[36] M. A. Lowes, T. Kikuchi, J. Fuentes-Duculan et al., "Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells," *Journal of Investigative Dermatology*, vol. 128, no. 5, pp. 1207–1211, 2008.

[37] S. Fujino, A. Andoh, S. Bamba et al., "Increased expression of interleukin 17 in inflammatory bowel disease," *Gut*, vol. 52, no. 1, pp. 65–70, 2003.

[38] T. Kobayashi, S. Okamoto, T. Hisamatsu et al., "IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease," *Gut*, vol. 57, no. 12, pp. 1682–1689, 2008.

[39] M. Huber, S. Heink, A. Pagenstecher et al., "IL-17A secretion by CD8+ T cells supports Th17-mediated autoimmune encephalomyelitis," *Journal of Clinical Investigation*, vol. 123, pp. 247–260, 2013.

[40] A. Saxena, S. Desbois, N. Carrie, M. Lawand, L. T. Mars, and R. S. Liblau, "Tc17 CD8$^+$ T cells potentiate Th1-mediated autoimmune diabetes in a mouse model," *Journal of Immunology*, vol. 189, pp. 3140–3149, 2012.

[41] S. G. Nanjappa, E. Heninger, M. Wuthrich, D. J. Gasper, and B. S. Klein, "Tc17 cells mediate vaccine immunity against lethal fungal pneumonia in immune deficient hosts lacking CD4$^+$ T cells," *PLoS Pathogens*, vol. 8, Article ID e1002771, 2012.

[42] J. M. Brenchley, T. W. Schacker, L. E. Ruff et al., "CD4$^+$ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract," *Journal of Experimental Medicine*, vol. 200, no. 6, pp. 749–759, 2004.

[43] M. Guadalupe, E. Reay, S. Sankaran et al., "Severe CD4$^+$ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy," *Journal of Virology*, vol. 77, no. 21, pp. 11708–11717, 2003.

[44] M. Kader, S. Bixler, M. Piatak, J. Lifson, and J. J. Mattapallil, "Anti-retroviral therapy fails to restore the severe Th-17: Tc-17 imbalance observed in peripheral blood during simian immunodeficiency virus infection," *Journal of Medical Primatology*, vol. 38, no. 1, pp. 32–38, 2009.

[45] M. Kader, W. M. Hassan, M. Eberly et al., "Antiretroviral therapy prior to acute viral replication preserves CD4 T cells in the periphery but not in rectal mucosa during acute simian immunodeficiency virus infection," *Journal of Virology*, vol. 82, no. 22, pp. 11467–11471, 2008.

[46] M. Kader, X. Wang, M. Piatak et al., "$\alpha4^+\beta7$hiCD4$^+$ memory T cells harbor most Th-17 cells and are preferentially infected during acute SIV infection," *Mucosal Immunology*, vol. 2, no. 5, pp. 439–449, 2009.

[47] Q. Li, L. Dua, J. D. Estes et al., "Peak SIV replication in resting memory CD4$^+$ T cells depletes gut lamina propria CD4$^+$ T cells," *Nature*, vol. 434, no. 7037, pp. 1148–1152, 2005.

[48] J. J. Mattapallil, D. C. Douek, B. Hill, Y. Nishimura, M. Martin, and M. Roederer, "Massive infection and loss of memory CD4$^+$ T cells in multiple tissues during acute SIV infection," *Nature*, vol. 434, no. 7037, pp. 1093–1097, 2005.

[49] S. Mehandru, M. A. Poles, K. Tenner-Racz et al., "Primary HIV-1 infection is associated with preferential depletion of CD4$^+$ T lymphocytes from effector sites in the gastrointestinal tract," *Journal of Experimental Medicine*, vol. 200, no. 6, pp. 761–770, 2004.

[50] S. Mehandru, M. A. Poles, K. Tenner-Racz et al., "Lack of mucosal immune reconstitution during prolonged treatment of acute and early HIV-1 infection," *PLoS Medicine*, vol. 3, no. 12, pp. 2335–2348, 2006.

[51] R. S. Veazey, M. DeMaria, L. V. Chalifoux et al., "Gastrointestinal tract as a major site of CD4$^+$ T cell depletion and viral replication in SIV infection," *Science*, vol. 280, no. 5362, pp. 427–431, 1998.

[52] A. Prendergast, J. G. Prado, Y. H. Kang et al., "HIV-1 infection is characterized by profound depletion of CD161$^+$ Th17 cells and gradual decline in regulatory T cells," *AIDS*, vol. 24, no. 4, pp. 491–502, 2010.

[53] M. Salem, A. Ronit, J. C. Gaardbo et al., "Altered balance between IL-17A- and IL-17F-producing Th17 cells in HIV-infected patients," *Journal of Acquired Immune Deficiency Syndromes*, vol. 63, pp. e28–e30, 2013.

[54] S. Dandekar, "Pathogenesis of HIV in the gastrointestinal tract," *Current HIV/AIDS Reports*, vol. 4, no. 1, pp. 10–15, 2007.

[55] A. E. Hed, A. Khaitan, L. Kozhaya et al., "Susceptibility of human Th17 cells to human immunodeficiency virus and their perturbation during infection," *Journal of Infectious Diseases*, vol. 201, no. 6, pp. 843–854, 2010.

[56] L. C. Ndhlovu, J. M. Chapman, A. R. Jha et al., "Suppression of HIV-1 plasma viral load below detection preserves IL-17 producing T cells in HIV-1 infection," *AIDS*, vol. 22, no. 8, pp. 990–992, 2008.

[57] Y. Y. Feng, A. Merchant, C. M. Kovacs, M. Loutfy, D. Persad, and M. A. Ostrowski, "Virus-specific interleukin-17-producing CD4$^+$ T cells are detectable in early human immunodeficiency virus type 1 infection," *Journal of Virology*, vol. 82, no. 13, pp. 6767–6771, 2008.

[58] E. J. Ciccone, J. H. Greenwald, P. I. Lee et al., "CD4$^+$ T cells, including Th17 and cycling subsets, are intact in the gut mucosa of HIV-1-infected long-term nonprogressors," *Journal of Virology*, vol. 85, no. 12, pp. 5880–5888, 2011.

[59] J. C. Gaardbo, H. J. Hartling, K. Thorsteinsson, H. Ullum, and S. D. Nielsen, "CD3$^+$CD8$^+$CD161high Tc17 cells are depleted in HIV-infection," *AIDS*, vol. 27, pp. 659–662, 2013.

[60] P. Nigam, S. Kwa, V. Velu, and R. R. Amara, "Loss of IL-17-producing CD8 T cells during late chronic stage of pathogenic simian immunodeficiency virus infection," *Journal of Immunology*, vol. 186, no. 2, pp. 745–753, 2011.

[61] J. M. Brenchley, D. A. Price, T. W. Schacker et al., "Microbial translocation is a cause of systemic immune activation in chronic HIV infection," *Nature Medicine*, vol. 12, no. 12, pp. 1365–1371, 2006.

[62] D. C. Douek, L. J. Picker, and R. A. Koup, "T cell dynamics in HIV-1 infection," *Annual Review of Immunology*, vol. 21, pp. 265–304, 2003.

[63] D. C. Douek, M. Roederer, and R. A. Koup, "Emerging concepts in the immunopathogenesis of AIDS," *Annual Review of Medicine*, vol. 60, pp. 471–484, 2009.

[64] V. Cecchinato, C. J. Trindade, A. Laurence et al., "Altered balance between Th17 and Th1 cells at mucosal sites predicts AIDS progression in simian immunodeficiency virus-infected macaques," *Mucosal Immunology*, vol. 1, no. 4, pp. 279–288, 2008.

[65] M. Macal, S. Sankaran, T. W. Chun et al., "Effective CD4$^+$ T-cell restoration in gut-associated lymphoid tissue of HIV-infected patients is associated with enhanced Th17 cells and polyfunctional HIV-specific T-cell responses," *Mucosal Immunology*, vol. 1, no. 6, pp. 475–488, 2008.

[66] J. C. Gaardbo, H. J. Hartling, J. Gerstoft, and S. D. Nielsen, "Incomplete immune recovery in HIV infection: mechanisms, relevance for clinical care, and possible solutions," *Clinical and Developmental Immunology*, vol. 2012, Article ID 670957, 17 pages, 2012.

[67] Y. He, J. Li, Y. Zheng et al., "A randomized case-control study of dynamic changes in peripheral blood Th17/Treg cell balance and interleukin-17 levels in highly active antiretroviral-treated HIV type 1/AIDS patients," *AIDS Research and Human Retroviruses*, vol. 28, pp. 339–345, 2012.

[68] L. Brandt, T. Benfield, H. Mens et al., "Low level of regulatory T cells and maintenance of balance between regulatory T cells and TH17 cells in HIV-1-infected elite controllers," *Journal of Acquired Immune Deficiency Syndromes*, vol. 57, no. 2, pp. 101–108, 2011.

[69] A. Gosselin, P. Monteiro, N. Chomont et al., "Peripheral blood CCR4$^+$CCR6$^+$ and CXCR3$^+$CCR6$^+$CD4$^+$ T cells are highly

permissive to HIV-1 infection," *Journal of Immunology*, vol. 184, no. 3, pp. 1604–1616, 2010.

[70] S. Cunningham-Rundles, S. Ahrne, R. Johann-Liang et al., "Effect of probiotic bacteria on microbial host defense, growth, and immune function in human immunodeficiency virus type-1 infection," *Nutrients*, vol. 3, pp. 1042–1070, 2011.

[71] N. R. Klatt, N. T. Funderburg, and J. M. Brenchley, "Microbial translocation, immune activation, and HIV disease," *Trends in Microbiology*, vol. 21, pp. 6–13, 2013.

[72] L. A. Gonzalez-Hernandez, L. F. Jave-Suarez, M. Fafutis-Morris et al., "Synbiotic therapy decreases microbial translocation and inflammation and improves immunological status in HIV-infected patients: a double-blind randomized controlled pilot trial," *Nutrition Journal*, vol. 11, article 90, 2012.

[73] M. Schunter, H. Chu, T. L. Hayes et al., "Randomized pilot trial of a synbiotic dietary supplement in chronic HIV-1 infection," *BMC Complementary and Alternative Medicine*, vol. 12, article 84, 2012.

[74] K. Hirota, B. Martin, and M. Veldhoen, "Development, regulation and functional capacities of Th17 cells," *Seminars in Immunopathology*, vol. 32, no. 1, pp. 3–16, 2010.

[75] M. Veldhoen, K. Hirota, A. M. Westendorf et al., "The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins," *Nature*, vol. 453, no. 7191, pp. 106–109, 2008.

[76] B. Stockinger and M. Veldhoen, "Differentiation and function of Th17 T cells," *Current Opinion in Immunology*, vol. 19, no. 3, pp. 281–286, 2007.

[77] R. K. Benwell and D. R. Lee, "Essential and synergistic roles of IL1 and IL6 in human Th17 differentiation directed by TLR ligand-activated dendritic cells," *Clinical Immunology*, vol. 134, no. 2, pp. 178–187, 2010.

[78] M. G. Kattah, M. T. Wong, M. D. Yocum, and P. J. Utz, "Cytokines secreted in response to toll-like receptor ligand stimulation modulate differentiation of human Th17 cells," *Arthritis and Rheumatism*, vol. 58, no. 6, pp. 1619–1629, 2008.

[79] M. Fukata, K. Breglio, A. Chen et al., "The myeloid differentiation factor 88 (MyD88) is required for CD4+ T cell effector function in a murine model of inflammatory bowel disease," *Journal of Immunology*, vol. 180, no. 3, pp. 1886–1894, 2008.

[80] A. D. Reynolds, D. K. Stone, J. A. L. Hutter, E. J. Benner, R. L. Mosley, and H. E. Gendelman, "Regulatory T cells attenuate Th17 cell-mediated nigrostriatal dopaminergic neurodegeneration in a model of Parkinson's disease," *Journal of Immunology*, vol. 184, no. 5, pp. 2261–2271, 2010.

[81] S. I. Gringhuis, J. den Dunnen, M. Litjens, M. van der Vlist, and T. B. H. Geijtenbeek, "Carbohydrate-specific signaling through the DC-SIGN signalosome tailors immunity to *Mycobacterium tuberculosis*, HIV-1 and Helicobacter pylori," *Nature Immunology*, vol. 10, no. 10, pp. 1081–1088, 2009.

[82] S. I. Gringhuis, J. den Dunnen, M. Litjens, B. van het Hof, Y. van Kooyk, and T. H. Geijtenbeek, "C-type lectin DC-SIGN modulates Toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB," *Immunity*, vol. 26, no. 5, pp. 605–616, 2007.

[83] S. I. Gringhuis and T. B. H. Geijtenbeek, "Carbohydrate signaling by C-type lectin DC-SIGN affects NF-κB activity," *Methods in Enzymology*, vol. 480, pp. 151–164, 2010.

[84] F. L. van de Veerdonk, R. J. Marijnissen, B. J. Kullberg et al., "The macrophage mannose receptor induces IL-17 in response to *Candida albicans*," *Cell Host and Microbe*, vol. 5, no. 4, pp. 329–340, 2009.

[85] E. V. Acosta-Rodriguez, L. Rivino, J. Geginat et al., "Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells," *Nature Immunology*, vol. 8, no. 6, pp. 639–646, 2007.

[86] N. Manel, D. Unutmaz, and D. R. Littman, "The differentiation of human TH-17 cells requires transforming growth factor-β and induction of the nuclear receptor RORγt," *Nature Immunology*, vol. 9, no. 6, pp. 641–649, 2008.

[87] N. J. Wilson, K. Boniface, J. R. Chan et al., "Development, cytokine profile and function of human interleukin 17-producing helper T cells," *Nature Immunology*, vol. 8, no. 9, pp. 950–957, 2007.

[88] L. Zhou, I. I. Ivanov, R. Spolski et al., "IL-6 programs TH-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways," *Nature Immunology*, vol. 8, no. 9, pp. 967–974, 2007.

[89] M. Nishihara, H. Ogura, N. Ueda et al., "IL-6-gp130-STAT3 in T cells directs the development of IL-17+ Th with a minimum effect on that of Treg in the steady state," *International Immunology*, vol. 19, no. 6, pp. 695–702, 2007.

[90] M. Veldhoen, R. J. Hocking, C. J. Atkins, R. M. Locksley, and B. Stockinger, "TGFβ in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells," *Immunity*, vol. 24, no. 2, pp. 179–189, 2006.

[91] P. R. Mangan, L. E. Harrington, D. B. O'Quinn et al., "Transforming growth factor-β induces development of the T H17 lineage," *Nature*, vol. 441, no. 7090, pp. 231–234, 2006.

[92] H. Qin, L. Wang, T. Feng et al., "TGF-β promotes Th17 cell development through inhibition of SOCS3," *Journal of Immunology*, vol. 183, no. 1, pp. 97–105, 2009.

[93] R. Nurieva, X. O. Yang, Y. Chung, and C. Dong, "Cutting edge: in vitro generated Th17 cells maintain their cytokine expression program in normal but not lymphopenic hosts," *Journal of Immunology*, vol. 182, no. 5, pp. 2565–2568, 2009.

[94] G. J. Martinez, R. I. Nurieva, X. O. Yang, and C. Dong, "Regulation and function of proinflammatory TH17 cells," *Annals of the New York Academy of Sciences*, vol. 1143, pp. 188–211, 2008.

[95] M. A. Hoeve, N. D. L. Savage, T. de Boer et al., "Divergent effects of IL-12 and IL-23 on the production of IL-17 by human T cells," *European Journal of Immunology*, vol. 36, no. 3, pp. 661–670, 2006.

[96] L. Wei, A. Laurence, K. M. Elias, and J. J. O'Shea, "IL-21 is produced by Th17 cells and drives IL-17 production in a STAT3-dependent manner," *Journal of Biological Chemistry*, vol. 282, no. 48, pp. 34605–34610, 2007.

[97] R. I. Nurieva and C. Dong, "Keeping autoimmunity in check: how to control a Th17 cell controller," *Immunity*, vol. 29, no. 6, pp. 841–843, 2008.

[98] T. Korn, M. Mitsdoerffer, A. L. Croxford et al., "IL-6 controls Th17 immunity in vivo by inhibiting the conversion of conventional T cells into Foxp3+ regulatory T cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 47, pp. 18460–18465, 2008.

[99] F. Gerosa, B. Baldani-Guerra, L. A. Lyakh et al., "Differential regulation of interleukin 12 and interleukin 23 production in human dendritic cells," *Journal of Experimental Medicine*, vol. 205, no. 6, pp. 1447–1461, 2008.

[100] C. Parham, M. Chirica, J. Timans et al., "A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rβ1 and a novel cytokine receptor subunit, IL-23R," *Journal of Immunology*, vol. 168, no. 11, pp. 5699–5708, 2002.

[101] S. Aggarwal, N. Ghilardi, M. H. Xie, F. J. De Sauvage, and A. L. Gurney, "Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17," *Journal of Biological Chemistry*, vol. 278, no. 3, pp. 1910–1914, 2003.

[102] D. Emilie, M. Peuchmaur, M. C. Maillot et al., "Production of interleukins in human immunodeficiency virus-1-replicating lymph nodes," *Journal of Clinical Investigation*, vol. 86, no. 1, pp. 148–159, 1990.

[103] D. L. Birx, R. R. Redfield, K. Tencer, A. Fowler, D. S. Burke, and G. I. Tosato, "Induction of interleukin-6 during human immunodeficiency virus infection," *Blood*, vol. 76, no. 11, pp. 2303–2310, 1990.

[104] T. P. Stein, B. Koerner, M. D. Schluter et al., "Weight loss, the gut and the inflammatory response in AIDS patients," *Cytokine*, vol. 9, no. 2, pp. 143–147, 1997.

[105] A. Iannello, M. R. Boulassel, S. Samarani et al., "Dynamics and consequences of IL-21 production in HIV-infected individuals: a longitudinal and cross-sectional study," *Journal of Immunology*, vol. 184, no. 1, pp. 114–126, 2010.

[106] A. Iannello, C. Tremblay, J. P. Routy, M. R. Boulassel, E. Toma, and A. Ahmad, "Decreased levels of circulating IL-21 in HIV-infected AIDS patients: correlation with CD4$^+$ T-cell counts," *Viral Immunology*, vol. 21, no. 3, pp. 385–388, 2008.

[107] L. Micci, B. Cervasi, Z. S. Ende et al., "Paucity of IL-21-producing CD4$^+$ T cells is associated with Th17 cell depletion in SIV infection of rhesus macaques," *Blood*, vol. 120, pp. 3925–3935, 2012.

[108] S. Pallikkuth, A. Parmigiani, and S. Pahwa, "Role of IL-21 and IL-21 receptor on B cells in HIV infection," *Critical Reviews in Immunology*, vol. 32, pp. 173–195, 2012.

[109] S. Pallikkuth, S. P. Kanthikeel, S. Y. Silva, M. Fischl, R. Pahwa, and S. Pahwa, "Upregulation of IL-21 receptor on B cells and IL-21 secretion distinguishes novel 2009 H1N1 vaccine responders from nonresponders among HIV-infected persons on combination antiretroviral therapy," *Journal of Immunology*, vol. 186, no. 11, pp. 6173–6181, 2011.

[110] N. Strbo, L. De Armas, H. Liu, M. A. Kolber, M. Lichtenheld, and S. Pahwa, "IL-21 augments natural killer effector functions in chronically HIV-infected individuals," *AIDS*, vol. 22, no. 13, pp. 1551–1560, 2008.

[111] L. White, S. Krishnan, N. Strbo et al., "Differential effects of IL-21 and IL-15 on perforin expression, lysosomal degranulation, and proliferation in CD8 T cells of patients with human immunodeficiency virus-1 (HIV)," *Blood*, vol. 109, no. 9, pp. 3873–3880, 2007.

[112] D. Favre, S. Lederer, B. Kanwar et al., "Critical loss of the balance between Th17 and T regulatory cell populations in pathogenic SIV infection," *PLoS Pathogens*, vol. 5, no. 2, Article ID e1000295, 2009.

[113] D. Favre, J. Mold, P. W. Hunt et al., "Tryptophan catabolism by indoleamine 2, 3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease," *Science Translational Medicine*, vol. 2, no. 32, p. 32, 2010.

[114] D. J. Hartigan-O'Connor, K. Abel, and J. M. McCune, "Suppression of SIV-specific CD4$^+$ T cells by infant but not adult macaque regulatory T cells: implications for SIV disease progression," *Journal of Experimental Medicine*, vol. 204, no. 11, pp. 2679–2692, 2007.

[115] R. K. Reeves, P. A. Rajakumar, T. I. Evans et al., "Gut inflammation and indoleamine deoxygenase inhibit IL-17 production and promote cytotoxic potential in NKp44+ mucosal NK cells during SIV infection," *Blood*, vol. 118, pp. 3321–3330, 2011.

[116] J. C. Gaardbo, S. D. Nielsen, S. J. Vedel et al., "Regulatory T cells in human immunodeficiency virus-infected patients are elevated and independent of immunological and virological status, as well as initiation of highly active anti-retroviral therapy," *Clinical and Experimental Immunology*, vol. 154, no. 1, pp. 80–86, 2008.

[117] L. Kolte, J. C. Gaardbo, K. Skogstrand, L. P. Ryder, A. K. Ersbøll, and S. D. Nielsen, "Increased levels of regulatory T cells (Tregs) in human immunodeficiency virus-infected patients after 5 years of highly active anti-retroviral therapy may be due to increased thymic production of naive Tregs," *Clinical and Experimental Immunology*, vol. 155, no. 1, pp. 44–52, 2009.

[118] A. Lim, D. Tan, P. Price et al., "Proportions of circulating T cells with a regulatory cell phenotype increase with HIV-associated immune activation and remain high on antiretroviral therapy," *AIDS*, vol. 21, no. 12, pp. 1525–1534, 2007.

[119] S. Tsunemi, T. Iwasaki, T. Imado et al., "Relationship of CD4$^+$CD25$^+$ regulatory T cells to immune status in HIV-infected patients," *AIDS*, vol. 19, no. 9, pp. 879–886, 2005.

[120] J. Schulze Zur Wiesch, A. Thomssen, P. Hartjen et al., "Comprehensive analysis of frequency and phenotype of T regulatory cells in HIV infection: CD39 expression of FoxP3+ T regulatory cells correlates with progressive disease," *Journal of Virology*, vol. 85, no. 3, pp. 1287–1297, 2011.

[121] I. I. Ivanov, B. S. McKenzie, L. Zhou et al., "The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells," *Cell*, vol. 126, no. 6, pp. 1121–1133, 2006.

[122] R. Nurieva, X. O. Yang, G. Martinez et al., "Essential autocrine regulation by IL-21 in the generation of inflammatory T cells," *Nature*, vol. 448, no. 7152, pp. 480–483, 2007.

[123] X. O. Yang, A. D. Panopoulos, R. Nurieva et al., "STAT3 regulates cytokine-mediated generation of inflammatory helper T cells," *Journal of Biological Chemistry*, vol. 282, no. 13, pp. 9358–9363, 2007.

[124] X. O. Yang, B. P. Pappu, R. Nurieva et al., "T helper 17 lineage differentiation is programmed by orphan nuclear receptors ROR alpha and ROR gamma," *Immunity*, vol. 28, no. 1, pp. 29–39, 2008.

[125] C. M. Rueda, P. A. Velilla, C. A. Chougnet, C. J. Montoya, and M. T. Rugeles, "HIV-induced T-cell activation/exhaustion in rectal mucosa is controlled only partially by antiretroviral treatment," *PLoS One*, vol. 7, Article ID e30307, 2012.

[126] K. Hirahara, K. Ghoreschi, A. Laurence, X. P. Yang, Y. Kanno, and J. J. O'Shea, "Signal transduction pathways and transcriptional regulation in Th17 cell differentiation," *Cytokine and Growth Factor Reviews*, vol. 21, no. 6, pp. 425–434, 2010.

[127] J. J. O'Shea, S. M. Steward-Tharp, A. Laurence et al., "Signal transduction and Th17 cell differentiation," *Microbes and Infection*, vol. 11, no. 5, pp. 599–611, 2009.

[128] T. J. Harris, J. F. Grosso, H. R. Yen et al., "An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity," *Journal of Immunology*, vol. 179, no. 7, pp. 4313–4317, 2007.

[129] Z. Chen, A. Laurence, Y. Kanno et al., "Selective regulatory function of Socs3 in the formation of IL-17-secreting T cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 21, pp. 8137–8142, 2006.

[130] R. C. Miller, E. Schlaepfer, S. Baenziger et al., "HIV interferes with SOCS-1 and -3 expression levels driving immune activation," *European Journal of Immunology*, vol. 41, no. 4, pp. 1058–1069, 2011.

[131] M. Mohan, P. P. Aye, J. T. Borda, X. Alvarez, and A. A. Lackner, "CCAAT/enhancer binding protein β is a major mediator of inflammation and viral replication in the gastrointestinal tract of simian immunodeficiency virus-infected rhesus macaques," *American Journal of Pathology*, vol. 173, no. 1, pp. 106–118, 2008.

[132] L. N. Akhtar, H. Qin, M. T. Muldowney et al., "Suppressor of cytokine signaling 3 inhibits antiviral IFN-β signaling to enhance HIV-1 replication in macrophages," *Journal of Immunology*, vol. 185, no. 4, pp. 2393–2404, 2010.

[133] K. A. Kim, W. Lin, A. W. Tai et al., "Hepatic SOCS3 expression is strongly associated with non-response to therapy and race in HCV and HCV/HIV infection," *Journal of Hepatology*, vol. 50, no. 4, pp. 705–711, 2009.

[134] N. M. Moutsopoulos, N. Vázquez, T. Greenwell-Wild et al., "Regulation of the tonsil cytokine milieu favors HIV susceptibility," *Journal of Leukocyte Biology*, vol. 80, no. 5, pp. 1145–1155, 2006.

[135] C. D. Chung, J. Liao, B. Liu et al., "Specific inhibition of Stat3 signal transduction by PIAS3," *Science*, vol. 278, no. 5344, pp. 1803–1805, 1997.

[136] Z. Yagil, H. Nechushtan, G. Kay, C. M. Yang, D. M. Kemeny, and E. Razin, "The enigma of the role of Protein inhibitor of Activated STAT3 (PIAS3) in the immune response," *Trends in Immunology*, vol. 31, no. 5, pp. 199–204, 2010.

[137] C. Borghouts, H. Tittmann, N. Delis, M. Kirchenbauer, B. Brill, and B. Groner, "The intracellular delivery of a recombinant peptide derived from the acidic domain of PIAS3 inhibits STAT3 transactivation and induces tumor cell death," *Molecular Cancer Research*, vol. 8, no. 4, pp. 539–553, 2010.

[138] M. P. Mycko, M. Cichalewska, A. Machlanska, H. Cwiklinska, M. Mariasiewicz, and K. W. Selmaj, "MicroRNA-301a regulation of a T-helper 17 immune response controls autoimmune demyelination," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, pp. E1248–E1257, 2012.

[139] S. L. Bixler, N. G. Sandler, D. C. Douek, and J. J. Mattapallil, "Suppressed Th17 levels correlate with elevated PIAS3, SHP2, and SOCS3 expression in CD4 T cells during acute simian immunodeficiency virus infection," *Journal of virology*. In press.

[140] H. Kim, T. S. Hawley, R. G. Hawley, and H. Baumann, "Protein tyrosine phosphatase 2 (SHP-2) moderates signaling by gp130 but is not required for the induction of acute-phase plasma protein genes in hepatic cells," *Molecular and Cellular Biology*, vol. 18, no. 3, pp. 1525–1533, 1998.

[141] T. Ohtani, K. Ishihara, T. Atsumi et al., "Dissection of signaling cascades through gp130 in vivo: reciprocal roles for STAT3- and SHP2-mediated signals in immune responses," *Immunity*, vol. 12, no. 1, pp. 95–105, 2000.

[142] A. Balasubramanian, R. K. Ganju, and J. E. Groopman, "Hepatitis C virus and HIV envelope proteins collaboratively mediate interleukin-8 secretion through activation of p38 MAP kinase and SHP2 in hepatocytes," *Journal of Biological Chemistry*, vol. 278, no. 37, pp. 35755–35766, 2003.