HIV Infection and the Gut: Scarred for Life?

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(See the article by Estes et al., on pages 456–64.)

Over the past decade, the gut-associated lymphocytes have been shown to play a critical role in the early pathogenesis of HIV infection. Because of constant exposure to foreign antigens, the gut contains an abundance of activated effector memory CD4+ T cells that express CCR5 and are highly susceptible to HIV infection [1]. Primary HIV infections and simian immunodeficiency virus (SIV) infections lead to rapid and profound depletion of these cells [2–4], which is more pronounced than the depletion in peripheral blood or other lymphoid tissue and persists throughout the course of untreated infection. The administration of antiretroviral therapy during chronic infection is highly effective in increasing the number of CD4+ T cells and decreasing the proportion of activated T cells in peripheral blood. However, significant delay in CD4+ T cell restoration may be seen in the gut, particularly in the lamina propria [5]. Despite the slow or incomplete resolution of the profound abnormalities seen in the gut mucosa of HIV-infected patients, a clear connection to clinical outcome in humans is still missing.

The pathogenesis of HIV infection is characterized by CD4+ T cell immunodeficiency in the context of generalized immune activation and dysregulation. T cells with an activated phenotype have been associated with CD4+ T cell decline in peripheral blood, as well as with clinical disease progression [6, 7]. However, the exact mechanisms leading to this pathogenic immune activation remain unclear. One possible mechanism linking the effects of HIV in the gut to generalized immune activation has recently been postulated. Brenchley et al. [8] have shown that the bacterial cell wall component lipopolysaccharide (LPS) is elevated in the peripheral blood of individuals chronically infected with HIV, and the plasma level of LPS directly correlates with an increased proportion of circulating activated CD8+ T cells. These findings led to the hypothesis that dysfunction of the gastrointestinal mucosa leads to translocation of bacterial products and results in generalized immune activation. However, data from the nonpathogenic SIV–sooty mangabey model show that CD4+ T cell depletion is not sufficient to result in high LPS levels, which suggests that additional insults are required [9].

In this issue of the Journal, Estes et al. [10] report on collagen deposition in the gastrointestinal tract as another potential mechanism that contributes to T cell depletion and/or limits CD4+ T cell restoration in the gut. Previously, these authors reported that early fibrosis from collagen deposition resulted in disruption of the lymphatic tissue in the lymph nodes of HIV-infected individuals and was predictive of the magnitude of change in peripheral CD4+ T cell counts after up to 3 years of antiretroviral therapy [11–13]. They have postulated that the fibrosis found in lymph nodes is detrimental to survival, growth, and trafficking of CD4+ T cells through various mechanisms including physical constraint, cell-cell interactions, and access to cytokines. In the Estes et al. [10] article, they report on the extent of collagen deposition in Peyer patches and its potential association with immune restoration in this compartment, as compared with that in lymph nodes and peripheral blood.

In this study, uninfected individuals and HIV-infected individuals at various stages of disease underwent sampling of lymph nodes, ileum, and peripheral blood. A subset of infected participants began antiretroviral therapy and was sampled again, 6 months after initiation of therapy. At baseline, significant depletion of CD4+ T cells was observed for all compartments in HIV-infected participants, with a comparatively greater reduction in gut lymphoid tissue, although participants who did not initiate therapy were excluded from this analysis. Despite increases in the population of circulating CD4+ T cells after 6 months of antiretroviral therapy, there were no significant increases in the total population of CD4+ T cells in lymphoid tissue.
Flow cytometry and immunofluorescent imaging were used to examine subsets of CD4+ T cells before and after therapy, according to compartment. The naive and central memory CD4+ T cell populations in HIV-infected individuals increased in peripheral blood after therapy but remained lower than those of uninfected individuals. Similar increases were not seen in the lymph nodes, but an increase in the central memory CD4+ T cell population was seen in the Peyer patches of 2 patients who started therapy in the acute-early stage of infection.

To test the hypothesis that, compared with uninfected individuals, fibrosis occurred more rapidly and extensively in the gut of HIV-infected individuals, thus contributing to the greater depletion of CD4+ T cells and more limited immune restoration as compared to lymph nodes, the authors stained gut tissue samples with trichrome and used quantitative image analysis to determine the extent of fibrosis in Peyer patches and the lamina propria. HIV-infected individuals had significantly more collagen in Peyer patches, compared with uninfected individuals, and 6 months of antiretroviral therapy had no effect on the amount of collagen seen in participants who underwent treatment. In individuals with acute-early infection, the level of collagen in Peyer patches was higher than that seen in the lymph nodes, indicating more rapid deposition in the gut. In addition, the extent of collagen deposition was inversely correlated with the size of the total and naive CD4+ T cell populations in Peyer patches, yet the size of the naive CD4+ T cell population did not differ between HIV-infected and uninfected participants.

Estes et al. have previously postulated that the fibrosis that occurs in lymphoid tissue results from immune activation and inflammation, driven in part by ongoing viral replication in these tissues. In nonhuman primate studies, the authors were able to implicate transforming growth factor (TGF)–β+ regulatory T cells as the mechanistic cause of collagen deposition in lymph nodes and showed that sooty mangabeys had lower levels of collagen deposition in lymph nodes, compared with infected rhesus macaques [14]. These findings raise many interesting questions that deserve further exploration. It is unclear how the disease stage, as estimated by peripheral CD4+ T cell count, is associated with the degree of fibrosis in the gut. It is also of interest to know whether there is a mechanistic link between the amount of collagen deposition and the presence of high plasma levels of LPS. SIV-infected sooty mangabeys demonstrate high plasma viral loads and experience extensive loss of CD4+ T cells in the gut, but they do not exhibit generalized immune activation, do not have elevated plasma levels of LPS, and do not experience progressive disease [9]. Thus, it would be important to determine the extent of collagen deposition in the gut of infected sooty mangabeys, compared with that observed in rhesus macaques and that of elite controllers who have elevated LPS levels [15] with overall preserved peripheral and possibly gut CD4+ T cell populations. Given the roles of TGF-β in both fibrogenesis and the development of Th-17 cells that have recently been reported to be preferentially lost in the gut [16], there also may be interplay between these processes. Loss of epithelial cells due to apoptosis, as seen in the SIV–rhesus macaque model [17], may be another important link, because the subsequent damage to the gut epithelial barrier may stimulate collagen deposition; loss of colonic epithelial cells may also lead to decreases in local interleukin (IL)–10 production, which can further enhance inflammation and TGF-β production in the presence of LPS [18]. Finally, macrophages that are activated via the alternative pathway by Th2-type cytokines can also lead to increased collagen deposition [19]. The potential role of these mechanisms in fibrogenesis during HIV infection should be explored in both lymphoid and nonlymphoid organs, such as the liver, kidneys, and bone marrow.

The findings of Estes et al. [10] provide another piece in the puzzle of early pathogenesis in HIV infection. Given the rapid onset of CD4+ T cell depletion and collagen deposition in the gut inductive sites and the potential to reverse or prevent these processes depending on when therapy is initiated, the authors offer this as an argument in favor of earlier initiation of antiretroviral therapy. These findings are intriguing and the call for earlier therapy in HIV infection is supported by other evidence [20]; however, further studies with longitudinal sampling of subjects who start therapy at various pretherapy CD4+ T cell counts will be required to confirm these observations and to better understand their clinical implications. It also remains to be seen whether prolonged antiretroviral therapy (beyond 6 months) leads to reduction of fibrosis in the lymphoid tissue. Provided that fibrosis may be a more widespread insult in lymphoid and nonlymphoid organs resulting from HIV infection, therapeutic interventions directed at immune activation and fibrosis itself, such as interventions that inhibit TGF-β signaling, should be investigated to determine whether collagen deposition can be prevented or reduced.

References


6. Deeks SG, Kitchen CM, Liu L, et al. Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell...