CD4+ lymphopenia is a common hallmark of both idiopathic CD4+ lymphopenia (ICL) and human immunodeficiency virus (HIV) infection, leading to opportunistic infections. In HIV infection, a profound CD4+ T-cell depletion occurs in the gut very early in primary infection to a greater extent than in blood [1]. This depletion occurs both in humans and in nonhuman primate models, with a predominant depletion of memory CCR5 CD4+ T cells [2] and of the T-helper type 17 (Th17) subset among CD4+ T cells [3]. Chronic immune activation is another hallmark of HIV infection, and the levels of activated T lymphocytes correlate with the progression of the disease in untreated HIV type 1 (HIV)–infected patients [4]. In 2006, Brenchley et al reported that microbial translocation was abnormally high during HIV infection and that the level of lipopolysaccharide (LPS), a component of the wall of gram-negative rods, in blood was positively correlated with the immune activation of T cells [5]. This suggested that alterations of intestinal epithelium integrity contribute to the chronic activation state present in HIV-infected individuals. Antiretroviral therapy (ART) is not able to completely normalize the levels of immune activation and the CD4+ T-cell counts in patients with chronic HIV infection [6]. Developing new therapeutic strategies to supplement ART and allow so-called efficient CD4+ T-cell restoration is, therefore, an important goal. However, what defines efficient CD4+ T-cell restoration remains unclear. Does it rely on absolute numbers or T-cell subset distribution? Is T-cell lymphopenia deleterious predominantly in mucosal sites or in peripheral blood?

The study reported by Kovacs et al [7] in this issue of The Journal of Infectious Diseases provides interesting insights in the context of ICL. ICL is a rare syndrome characterized by CD4+ T-cell lymphopenia and opportunistic infections in the absence of HIV infection or any other known immunodeficiency or therapy associated with lymphopenia. Interestingly, ICL recapitulates several features of HIV infection, such as increased CD4+ T-cell activation, lower proportion of naive CD4+ T cells, impaired T-cell receptor signaling, decreased interleukin 7 and interleukin 12 responsiveness, and accelerated T-cell senescence [8–11]. A defect in chemokine receptor expression [12] was also described in ICL, suggesting decreased chemotactic responses and disruption of CD4+ homing. Indeed, discrepancies in lymphopenia between lymphoid organs and/or effector sites such as the gut have been described. In mouse models of aging, peripheral CD4+ lymphopenia is associated with a significant decrease of CD4+ T cells in lymphoid organs, contrasting with the preservation and accumulation of CD4+ T cells in the gut [13]. Peripheral blood lymphopenia could be the result of a redistribution of CD4+ T cells, rather than generalized CD4+ T-cell decay.

In this report, Kovacs et al [7] described the extent of CD4+ T-cell lymphopenia developing in the colonic mucosa of patients with ICL. Focusing on the gut mucosa is, indeed, a crucial point since gut-associated mucosa has been considered a major site of CD4+ T-cell accumulation. The authors provide evidence of T-cell depletion in the colonic mucosa of the patients with this rare syndrome. Their results are supported by a large number of patients studied, despite the rarity of the syndrome. Compared with healthy controls, they found depletion of CD4+ and CD8+ T cells in patients with ICL. This decrease of T cells in the gut did not seem to be related to a homing defect, as the expression of the integrin β7 was not different, compared with healthy controls. However, the proportions of T-cell...
subsets and those of naive, central memory, and effector memory CD4+ T-cell subsets were preserved in the colon (contrasting with blood). The authors looked for functional alterations of the CD4+ T-cell subsets, especially the Th1 and Th17 subsets. They found that the proportion of mucosal CD4+ T cells producing IL-17 was higher in patients with ICL, compared with healthy controls, suggesting that the Th17 subset is preserved in patients with ICL and seems to be functional. Treg proportions were not different between patients with ICL and healthy controls, but the functionality of the Treg subset was not tested. As the Th17 subset is strongly involved in the homeostasis of the mucosal barrier, the authors looked for evidence of mucosal damage. However, they did not find evidence of alterations of the gut epithelium: fatty acid–binding protein and LPS levels were not significantly increased, compared with controls. Levels of the inflammatory cytokines interleukin 6 and tumor necrosis factor α were also not increased.

Interestingly, an enrichment of macrophages and polymorphonuclear cells was shown, which could be the explanation of the increase of soluble CD14 (sCD14) levels. Although this study provides meaningful information, the role of other non–T-cell partners present in the gut (eg, macrophages, innate lymphoid cells, and γδ T cells) remains to be investigated in ICL (and in HIV infection). A recruitment of γδ T cells, in combination with Th17 cells, could also provide protection against pathogens in some of these patients.

These results showed that, in ICL, there is a quantitative depletion of CD4+ T cells in the gut but that the Th17 CD4+ cell subset seems to be preserved. This observation strengthens the notion that CD4+ T-cell lymphopenia per se does not directly induce gut pathophysiology, an observation that is reminiscent of previous reports in nonpathogenic simian immunodeficiency virus (SIV)–infected macaque models [14, 15]. In ICL, CD4+ T-cell depletion is not sufficient to induce a strong proinflammatory state, suggesting that the depletion of the Th17 subset is probably much more deleterious and may constitute a key event at the origin of chronic inflammation. Alternately, it is tempting to speculate that, more than the number, it is the functional equilibrium between Th1, Th17, and Tregs that ensures efficient mucosal homeostasis.

These results provide novel information about the pathogenesis of ICL and, perhaps indirectly, are relevant to HIV infection, as well. In ICL, the Kovacs et al study raises questions regarding the mechanisms responsible for chronic immune activation associated with CD4+ T-cell lymphopenia. Alterations of the gut mucosa do not appear to be strongly involved. It would be interesting to determine the nature of CD4+ T-cell lymphopenia developing in other lymphoid or nonlymphoid sites. In the context of HIV infection, these observations emphasize the crucial need to preserve or restore the Th17 cell subset. Preserving the Th17 subset may reduce microbial translocation and, as a consequence, the chronic inflammation involved in CD4+ T-cell dysfunction.

Interestingly, several recent reports support such a strategy. ART initiated very early in primary infection seems to preserve mucosal Th17 function and reverses HIV-related immune activation [16]. In a model of SIV-infected macaques, interleukin 21 preserved Th17 cells, leading to reduced levels of intestinal T-cell proliferation, microbial translocation, and systemic activation/inflammation in chronically infected animals [17]. Microbiota in HIV-infected patients are disturbed [18]. Strategies aiming at the restoration of normal microbiota in the gut of HIV-infected patients are promising and should be pursued [19].

Note

Potential conflict of interest. Both authors: No reported conflicts.

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References


