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Persistent inflammation in HIV infection: Established concepts, new perspectives

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ABSTRACT

Immune activation is now considered a main driving force for the progressive immune failure in HIV infection. During the early phases of infection, a rapid depletion of gastrointestinal CD4+ T cells occurs that is followed by a deterioration of the gut epithelium and by the subsequent translocation of microbial products into the blood. Activation of innate immunity results in massive production of proinflammatory cytokines, which can trigger activation induced cell death phenomena among T lymphocytes. Moreover, persistent antigenic stimulation and inflammatory status causes immune exhaustion. The chronic immune activation also damages lymphoid tissue architecture, so contributing to the impairment of immune reconstitution.

Recently, new mechanisms were identified, so opening new perspective on the innate immune sensing in HIV-1 infection. Cell death is followed by the release of molecules containing "damage-associated molecular patterns", that trigger a potent innate immune response through the engagement of Toll-like receptors. Then, also different types of HIV-related nucleic acids can act as potent stimulators of innate immunity. All these events contribute to the loss of T cell homeostatic regulation and to the failure of adaptive immunity.

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1. Introductory remarks

In the last decade, in the area of HIV research a key concept has emerged, namely that the progression of the infection can be mediated, in a significant part, by a rapid depletion of gastrointestinal memory CD4+ T cells. Such depletion is followed by the deterioration of the gut epithelium and by an increased microbial translocation. The following release of bacterial products in the circulation provokes a persistent, systemic inflammation.

The increasing amount of data supporting this concept have profoundly changed the view of HIV infection, which is now also seen as an inflammatory disease. As a consequence, several non-AIDS related complications that patients experience despite a succesful antiviral treatment (*i.e.*, cardiovascular, neurocognitive, liver and kidney diseases, metabolic syndrome, osteoporosis, and non-HIV associated cancers, among others) can be considered a direct or indirect consequence of a chronic inflammatory status. Here we discuss some of the driving mechanisms that lead HIV+ patients to develop a state of chronic, persistent inflammation.

2. HIV infection damages gut *mucosae* by different mechanisms

2.1. Depletion of mucosal CD4+ cells

The first step in the process that leads to the chronic inflammation observed in HIV infection is the loss of CD4+ T cells resident in the gut, occurring during primary, acute infection. Most CD4+ T lymphocytes normally present in the gut mucosa are activated effector memory cells that express CCR5 molecule, which acts as an entry coreceptor for the virus. The expression of this receptor thus provides a further, large pool of target cells to the virus [1,2]. During acute HIV infection, CD4+ T lymphocytes in the gut mucosa are rapidly depleted, in part for the direct killing by the virus, and in part for bystander apoptosis [3,4].

Once these cells have been depleted, the CD4+ T cell pool present in the gut of HIV+ individuals is restored much more slowly than the peripheral blood one [5,6]. Patients' gut mucosa contains effector sites that are severely depleted of CD4+ T cells, despite the effective

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combination antiretroviral therapy (cART). This phenomenon is in marked contrast with the significant restoration of CD4+ T cells that can be observed either in peripheral blood and in immune inductive sites [7]. The reason of this discrepancy are not completely clear. It has been hypothesized that cART is not fully able to suppress HIV replication in the gut. Moreover, a lack of recruitment of CD4+ T cells homing to the gut has been reported [8].

The loss of Th17 CD4+ T cells that are normally present in the gut appears to be particularly relevant during HIV infection. Within gut CD4+ T cells, the Th17 cell subset is selectively preserved in the animals that are natural hosts of the simian immunodeficiency virus (SIV, the equivalent of HIV), like sooty mangabeys and African green monkeys, that control the infection and do not progress to AIDS [9]. In these animals, preserving Th17 lymphocytes could contribute to control bacterial flora, and blocks either microbial translocation and the subsequent systemic inflammation [10]. In humans, the depletion of Th17 cells in the gut mucosa after HIV infection could compromise the integrity of the gut mucosal barrier [11]. Indeed, it has been shown not only that HIV infection causes dramatic alterations in the functional capacity of mucosal Th17 cells, but also that these alterations occur even earlier than the reduction in Th17 number, and are less readily reversed after the initiation of effective ART [12].

2.2. Innate immunity and gut mucosa: A role for macrophages

A significant contribution to the loss of CD4+ T cells in the gut is given by macrophages that reside at the mucosal surface. A significant proportion of these cells are productively infected with HIV-1 [13]. Infected macrophages may transmit the virus to CD4+ T cells *via* cell-to-cell contact during HIV-antigen presentation [14]. Macrophages that infiltrate the intestinal mucosa may promote local inflammation and tissue injury, and their low phagocytic activity prevents the efficient elimination of luminal antigens that cross the damaged intestinal barrier [15]. Finally, since macrophages secrete cytokines that attract/recruit T lymphocytes to sites of infection, they can support establishment of viral infection by enlarging the number of primary target cells [16].

2.3. Alteration of the integrity of the mucosal barrier and translocation of bacteria from the lumen

The loss of function of the epithelial barrier during HIV-1 infection is a consequence of direct and indirect mechanisms that lead to the production of inflammatory cytokines. Activated mucosal T cells release cytokines, and exposure of HIV at the mucosal surface leads to direct response of the mucosal epithelium [17]. This latter response is rapid, independent of viral infection, and likely plays a key role in initiating the mucosal damage [18].

The human gastrointestinal (GI) tract is colonized with approximately 10^{14} bacteria that form the normal flora, which live in symbiosis with the host and can enhance immune function [19], but are under strict immunological control. A serious consequence of the depletion of mucosal CD4+ T cells during acute infection is the loss of immune protection of the intestinal mucosa, whose alterations allow the translocation of microbial products into the *lamina propria* of the GI tract and, eventually, into systemic circulation.

Microbial translocation during HIV infection was first described in 2006, when it was demonstrated that bioactive microbial products, including lipopolysaccharide (LPS) and bacterial DNA, were significantly elevated in plasma from HIV+ infected individuals [20]. The levels of LPS in these individuals directly correlated with activation of both the adaptive and innate arms of the immune system [20]. High levels of plasma LPS and bacterial DNA then persist throughout all the course of the infection [21]. The dysfunction of the intestinal barrier contributes to the systemic immune activation during chronic phase of HIV infection [22], and the degree of microbial translocation is linked to the severity of HIV-1 progression [23,24]. Several studies have also indicated that microbial translocation is associated with massive immune activation, and that the production of sCD14 and pro-inflammatory cytokines represents an important driver of the pathogenesis of the disease, being partially responsible for CD4+ T-cell depletion and HIV-related co-morbidities [25].

Thus, paradoxically, the immune activation can be considered a main driving force for the progressive immune failure leading to immunodeficiency [26,27]. Despite successful virological control obtained by cART, some patients (defined "immunological non responders") are not able not restore their cellular immunity and the pool of CD4+ T lymphocytes. A possible role for microbial translocation in their persistent CD4+ T-cell depletion has been suggested [28].

3. Stimulation of the innate immunity and formation of a proinflammatory milieu

3.1. A role for proinflammatory cytokines

HIV infection is characterized by an increased production of proinflammatory cytokines, that can be observed from the very first phases of infection, and persists throughout its natural course. Even in the presence of an effective suppression of viral replication, significant higher levels of proinflammatory cytokines such as IL-6 can be observed in patients' plasma. During a viral acute infection, the first detectable marker of an innate immune response is an increase in the levels of some acute-phase proteins, such as serum amyloid A; a further wave of acute-phase protein production coincides with a cytokine response and a rapid increase in plasma viraemia [29]. The production of acute-phase proteins can be triggered by pro-inflammatory cytokines [such as interleukin-1 (IL-1)] and by extrinsic factors such as LPS. The levels of cytokines and chemokines in the plasma increases as viral load becomes higher.

Levels of IL-15, type I interferons (IFNs) and CXC-chemokine ligand 10 (CXCL10) increase rapidly but transiently; IL-18, TNF-α, IFN-γ and IL-22 also increase rapidly but are sustained at high levels, whereas the increase in IL-10 is slightly delayed. Some of these cytokines have antiviral activity; for example, type I IFNs inhibit HIV replication in severe combined immunodeficient mice reconstituted with human lymphocytes. Also, type I IFNs, IL-15 and IL-18 enhance innate and adaptive immune responses. However, the intense cytokine response during acute HIV infection may also promote viral replication and mediate immunopathology (reviewed in [29]). The cellular sources of the acute-phase cytokines and chemokines during early HIV infection have not been definitively identified, but probably include, among others, infected CD4+ CCR5+ T cells, activated DCs, monocytes, macrophages, NK cells, NKT cells and, subsequently, HIV-specific T cells. (Fig. 1)

3.2. Loss of peripheral CD4+ T cells

The chronic phase of HIV infection is characterized by an immune activation with a massive production of proinflammatory cytokines [30,31], which in turn is responsible for clonal deletion [32] and gradual loss of peripheral CD4+ T cells over time [33,34]. During HIV-induced immune activation the dynamics of CD4+ and CD8+ T cells are altered in many ways. Although both subsets show evidence of increased proliferation and preferential loss of the naïve subset, CD4+ T cells are depleted, and CD8+ T cells expanded [35].

Distinct pathways differentially influence proliferation of CD4+ and CD8+ T cells in patients with HIV-1 infection. Proliferation of CD4+ T cells is driven by a combination of the homeostatic response

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