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Disrupting T-cell Homeostasis: how HIV-1 Infection Causes Disease

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Abstract

In the absence of antiretroviral treatment, HIV-1 establishes a chronic infection that is marked by the progressive depletion of CD4+ T-cells. Of all the viral infections that afflict humans, only HIV-1 is known to cause such profound and inevitable CD4+ T-cell loss. Yet the mechanisms by which this depletion arises remain a matter of controversy. This review will address what is exceptional about HIV-1 infection that sets it apart from other viral infections. Recent attempts to understand HIV-1 pathogenesis have set aside the view that CD4+ T-cell depletion is effected solely by HIV-1-mediated killing in favor of a more complete explanation that also includes T-cell dynamics and, more specifically, chronic immune activation as a central factor in HIV-1 pathogenesis[1,2].
This review will address the contributions of the virus itself, T-cell activation, T-cell reconstitution, and target cell availability, in the shaping of these dynamics during the disease. The acute and chronic phases of HIV-1 disease will be addressed separately, as they manifest distinctive viral and T-cell dynamics and are the setting for different pathogenic mechanisms. New observations suggest that considerable damage is caused to the immune system during the acute phase of the infection, resulting in a substantial early lymphopenia of the memory CD4+ T-cell pool that may have a profound impact on the subsequent course of the infection. Other observations reveal a strategy in which HIV-1 induces immune activation to generate replaceable targets, activated CD4+ T-cells, which sustain its replication. Although the majority of these target cells are short-lived by physiological design, chronic activation can indirectly strain homeostasis of the naive and resting memory T-cell pools in a number of ways. In the context of virus-induced damage to the lymphoid tissues and cells that maintain these T-cell pools, and physiological limitations in peripheral CD4+ T-cell renewal, this homeostatic strain leads to the progressive depletion of the more vulnerable CD4+ T-cell pools.

Key words

HIV-1. T-cells. Activation. Lymphopenia.

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Acute HIV-1 infection

Initial exposure to HIV-1 is primarily through the gastrointestinal or reproductive mucosal tracts, and this results in local replication of the virus within CD4+ target cells of the mucosal tissue. Although CCR5 and CXCR4 are the major receptors used by HIV-1 *in vivo*, CCR5 is almost always the initial target coreceptor for naturally transmitted virus[3]. Studies of SIV infection in rhesus macaques show that, after intravenous, intrarectal, intravaginal or oral inoculation of SIV, the major cellular targets for the initial burst in viral replication are *lamina propria* CD4+ T-cells[4-8]. Dendritic cells (DCs) may act as local facilitators by binding and internalizing intact virions via DC-SIGN to enhance infection *in trans* of CD4+ T-cells[9,10]. Indeed, live-cell microscopy of *in vitro* interactions between DCs and CD4+ T-cells suggests that HIV-1 is concentrated in DCs at the site of cellular contact, while the HIV-1 receptors CD4, CXCR4 and CCR5 are recruited to the complementary surface on the T-cell[11]. Thus, HIV-1 may exploit the local physiological interactions between DCs and CD4+ T-cells to facilitate the spread of infection. Indeed, it is tempting to speculate that this mechanism may underlie the observations that HIV-1-specific CD4+ T-cells are preferentially infected, even at very early stages in the disease[12].

SIV is then rapidly disseminated, infecting CD4+ T-cells in local and distant lymphoid tissue including lymph node (LN), thymus, spleen and mucosal tracts[8]. There is also evidence from LN biopsies from acutely infected humans that T-cells are the major target for and source of HIV-1[8,13], resulting in the early establishment of a pool of latently-infected CD4+ T-cells[14]. Sequencing of HIV-1 isolates in the spleen suggests that propagation of infection depends on local cell interactions and on local target cell densities, such that an infected cell releases virus that efficiently infects only nearby targets[15]. These target cells are predominantly CCR5+ CD4+ T-cells, a memory T-cell subset which is infrequent in PB, LN and spleen, but which accounts for almost all CD4+ T-cells in other tissues, including the mucosal surfaces of the intestinal, respiratory and reproductive tracts[16]. Thus, during acute infection, the mucosal tissues offer an abundant supply of target cells through which the virus rapidly propagates and multiplies.

When considering the impact of acute HIV-1 infection, it is important to bear in mind that the GI tract may be the largest lymphoid organ in the body, accounting for at least half of the total body T-cell load[17]. Thus, a large proportion of CD4+ T-cells in the body reside in the mucosal tissues, express CCR5, and are prime targets for R5-tropic HIV-1 infection and replication. This abundance of mucosal substrates for viral replication accounts for a profound impact of the virus on the immune system early after infection. In macaques infected intravenously or mucosally with SIV, there is a precipitous loss of intestinal CD4+ T-cells, such that their numbers are almost entirely depleted by three weeks after infection[18]. Rapid loss of intestinal CD4+ T-cells also occurs in early HIV-1 infection of humans, and this loss is maintained at later stages of the disease[19-21]. Thus, acute R5-tropic virus infection results in a precipitous, massive, but somewhat concealed, depletion of pre-existent CD4+ memory T-cells. Indeed, PB CD4+ T-cell counts likely *underestimate* the total body depletion of CD4+ T-cells that begins during acute infection. The almost complete elimination of mucosal CCR5+ CD4+ T-cells within 2-3 weeks of infection is consistent with excess cell death, due to direct or indirect viral cytopathicity[22,23] and CD8+ T-cell-mediated destruction of infected CD4+ T-cells[24].

To understand how the events of acute HIV-1 infection set the stage for the homeostatic mayhem of the chronic phase, we must first examine how T-cell homeostasis is maintained in a normal immune system. Figure 1 illustrates the main principles of T-cell homeostasis: (a) more CD4+ than CD8+ naive T-cells exit the thymus; (b) turnover within the naive T-cell pools is minimal; (c) naive T-cells may be activated to enter the memory T-cell pools where they may remain activated or return to a resting memory state; (d) the expansion of the activated CD8+ T-cell pool is much greater than that of the activated CD4+ T-cell pool; (e) the vast majority of activated T-cells die, far more so for activated CD4+ T-cells than activated CD8+ T-cells; (f) many more activated CD8+ T-cells re-enter the resting memory T-cell pool than activated CD4+ T-cells, thus the memory CD4+ T-cell pool is more dependent upon input from the naive CD4+ T-cell pool. In a healthy individual, these homeostatic processes maintain adequate CD4+ and CD8+ T-cell numbers over the course of a lifetime. However, with age, naive T-cells decrease with respect to memory T-cells, and CD4+ T-cells with respect to CD8+ T-cells[25]. Indeed, it has been proposed that chronic HIV-1 infection may be akin to accelerated immune senescence[26].

In contrast to the picture outlined in figure 1, as the infection enters its chronic phase the memory CD4+ T-cell pool is already profoundly depleted. It is at this point that the generalized immune activation associated with chronic infection results in the proliferative generation of new CCR5+ CD4+ memory T-cells, which provide new targets for viral replication. Even if the progress of the disease were completely halted at this stage, physiological limitations on CD4+ T-cell renewal exacerbate that struggle to reconstitute this depleted memory CD4+ T-cell pool. For example, after chemotherapy and hematopoietic stem-cell transplantation, whereas reconstitution of CD8+ T-cell numbers is rapid, recovery of CD4+ T-cell numbers is limited, delayed[27-29], and is constrained by the age-dependent decline in thymopoiesis. Successful CD4+ T-cell reconstitution after chemotherapy, or under HAART in HIV-1 infection, is determined to a large degree by thymic output[30-35]. However, HIV-1 infection is not controlled after the acute infection; it now enters a chronic phase where ongoing viral replication impairs thymic output, dis-

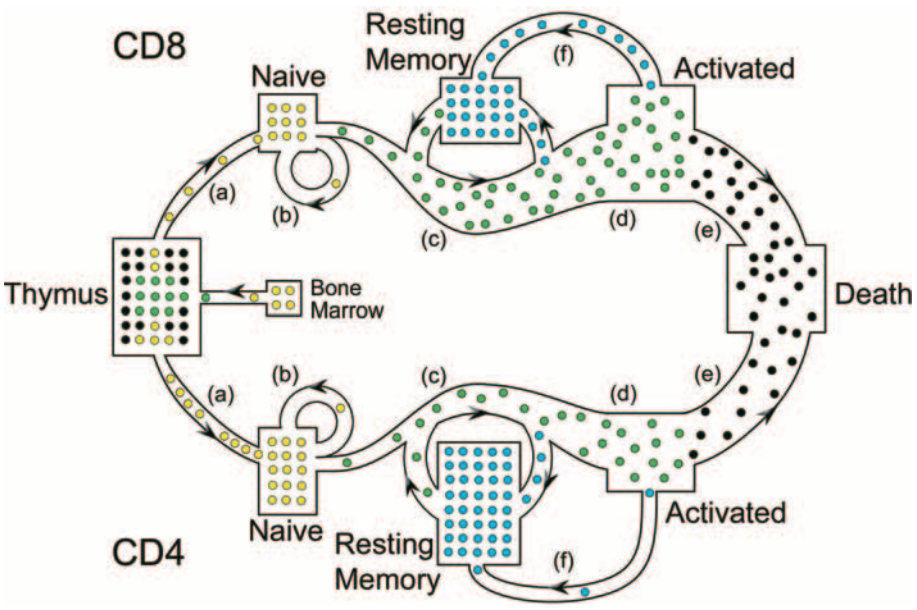

Figure 1. *A scheme of T-cell dynamics in a healthy individual. Resting cells along the bone marrow to naive T-cell axis are shown in yellow. Activated T-cells are shown in green. Resting memory T-cells are shown in blue. Dying cells are shown in black. The arrows depict movement of cells between the pools. The sizes of the boxes depicting the pools and the number of cells represent the relative magnitude of those cellular pools, but are not to scale.*

rupts lymph node architecture, and induces CD4+ T-cell activation. This puts an additional homeostatic strain on an already damaged CD4+ T-cell pool.

Chronic HIV-1 infection

Both viral and T-cell dynamics change as the infection enters its chronic phase. Although plasma viral loads are lower, and PB CD4+ T-cell counts partially recover compared to those in the acute phase, chronic HIV-1 infection is characterized by a high level of activation of both CD4+ and CD8+ T-cells. Indeed, the degree of chronic activation may be a better predictor of disease progression than the plasma viral load[36,37].

The many studies of T-cell turnover in chronic HIV-1 and SIV infection have resulted in many, often contradictory, hypotheses of T-cell dynamics. These studies have analyzed T-cell telomere lengths, maturation phenotypes, Ki67 expression as a marker of cell proliferation, *in vivo* incorporation and loss of BrdU, and *in vivo* labeling with stable deuterium isotope. The interpretations tend to disagree on which subsets are affected, whether naive or memory, CD4+ or CD8+, and to what degree they are affected. However, the basic conclusion is that all such analyses describe a state of "high turnover" affecting both CD4+ and CD8+ T-cells, with memory T-cells being affected far more than naive ones[38-46]. "High turnover" simply refers to a higher amount of proliferation and death with the T-cell pools.

Is it the virus that causes massive CD4+ T-cell death, with increased activation being the homeostatic response; or does the virus cause massive T-cell activation, with death being the natural immunological consequence? To answer this question we should consider some observations: (1) it is unlikely that the virus directly causes massive death of CD4+ T-cells in chronic infection, because the degree of their productive infection appears to be very low in both PB and LN, with estimates ranging from about 0.01-1%[12,47]; (2) the cells that *are* infected are likely to die anyway as they are usually activated[48]; (3) CD8+ T-cell death occurs at the same rate as that of CD4+ T-cells in kinetic models, yet their numbers are not significantly depleted until late in the course of infection; (4) when viral replication is suppressed, T-cell death rates do not immediately change, implying that HIV-1 does not directly affect the death of recently-divided cells[43]. Thus, the high rates of T-cell death in chronic infection seem to be the consequence, rather than the cause, of HIV-1 infection-associated T-cell activation[1]. This highlights the critical point that the predominant mechanism for CD4+ cell death during chronic infection seems to differ from that during acute SIV infection.

However, the concept that chronic immune activation might explain the high CD4+ and CD8+ T-cell death rates does not immediately explain why CD4+ T-cells are depleted. Yet, evidence is accumulating that chronic activation can indeed cause T-cell depletion. Perhaps most striking are the observations that SIV-infected sooty mangabeys – natural hosts of this virus– develop high viral loads but neither profound CD4+ T-cell depletion nor progressive disease, and that there is no

generalized increase in T-cell activation[49]. Consistent with this concept is the finding of decreased levels of immune activation in individuals whose viremia is not controlled by HAART, but who maintain increasing CD4+ T-cell counts[50]. As we have discussed above, the proliferative responses to antigen and regenerative capacities of the CD4+ and CD8+ memory T-cell pools differ markedly by physiological design, and this should result in differential susceptibility of the two subsets to the detrimental effects of chronic immune activation. The rounds of memory T-cell expansion and death would place a greater strain on maintenance of the resting CD4+ memory T-cell pool because of its inherently greater dependency on input from the naive T-cell pool.

Chronic immune activation is also likely to be the cause of the observed pathological changes in lymph-node architecture in HIV-1 infected individuals[51-54]. Animal models have shown that the CD4+ T-cell compartment is more dependent on lymph nodes for its maintenance and homeostatic function than the CD8+ T-cell compartment[55]. Indeed, there is a strong inverse correlation between lymph-node fibrosis and both the size of the LN CD4 T-cell population and the change in peripheral CD4 T-cell count with anti-HIV-1 therapy[56]. While considering the effects of HIV-1-induced generalized activation, we should not overlook the fact that HIV-1 has a particular fondness for infecting CD4+ T-cells, is cytopathic, and renders infected cells targets for HIV-1-specific CD8+ T-cells. Those cells which contribute to the maintenance of the resting memory CD4+ T-cell pool – the small proportion of activated naive and memory CD4+ T-cells which survive to enter or re-enter the resting memory CD4+ T-cell compartment– are also subject to HIV-1-mediated killing. In particular, studies show that naive T-cells which have been activated are exquisitely sensitive to HIV-1 infection[12]. This would further attenuate maintenance of the vulnerable resting memory CD4+ T-cell pool.

If we take a step further back on the supply routes that maintain the T-cell pools, we find that a burden now exists on the thymus to support the increased demand on the naive T-cell compartment. However, both age-associated attenuation and HIV-1-mediated thymic inhibition[57-68] render it increasingly difficult for the thymus to keep up with the constant drain on the peripheral naive T-cell pool caused by persistent homeostatic and antigen/inflammation-driven flow of naive T-cells into the memory T-cell pools. Furthermore, evidence clearly suggests that, while the hematopoietic progenitor populations of the bone marrow are unaffected in HIV-1 infection, the stromal auxiliary cells are persistently infected and dysfunctional[69], and this would likely impair the marrow's hematopoietic function.

The scheme shown in figure 2 summarizes T-cell dynamics during the chronic phase of HIV-1 infection that we have discussed above. It should be contrasted with figure 1 to appreciate how the pathogenic effects mediated by HIV combine to dramatically affect T-cell homeostasis, and particularly maintenance of the memory CD4+ T-cell pool. The key points are: (a) the resting memory CD4+ T-cell pool is already decreased in size after the acute phase; (b) both the CD4+ and CD8+ T-cell pools become chronically activated; (c) the expansion of the activated CD8+ T-cell pool is much greater than that of

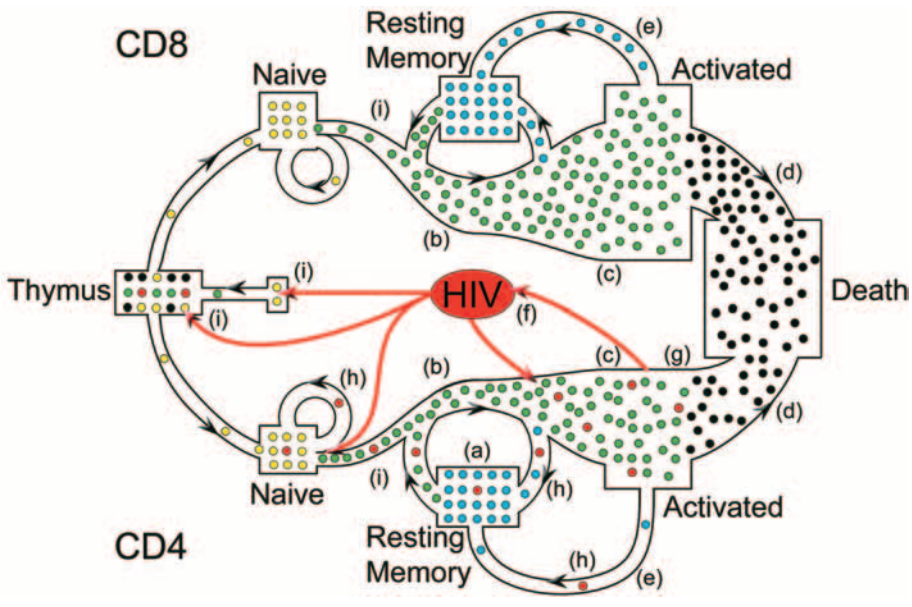

Figure 2. *A scheme of T-cell dynamics in an individual in the chronic phase of HIV-1 infection. The colors of the cells are as in figure 1. HIV-1-infected T-cells are shown in red. The red arrows depict both direct and indirect negative effects of HIV-1 on T-cell production and/or survival, including destruction of lymphoid organ architecture.*

the activated CD4+ T-cell pool; (d) increased T-cell activation results in increased T-cell death of both the CD4+ and CD8+ T-cell pools; (e) the majority of activated T-cells die, and fewer activated CD4+ T-cells re-enter the resting memory T-cell pool than activated CD8+ T-cells; (f) the main source of virus is the activated CD4+ T-cell pool; (g) the majority of infected activated CD4+ T-cells are physiologically destined to die, simply due to their activation; (h) a fraction of the already small proportion of infected CD4+ T-cells which are destined to enter the resting memory CD4+ T-cell pool can be infected and will fail to contribute to that pool; (i) there are pathological changes in bone marrow, thymus and lymph node architecture, resulting in a decrease in thymic output and poor lymph node homeostatic function.

Other chronic viral infections in humans do not cause AIDS[70-73]. Even chronic parasitic infections can cause high-level T-cell activation, inversion of CD4+/CD8+ T-cell ratios and reduction of naive T-cell numbers in PB, but they do not cause profound CD4+ T-cell loss, unless there is co-infection with HIV-1[74,75]. HIV-1 infection differs from other chronic infections in that HIV-1 infection itself induces immune activation – the very "engine driving viral replication"[1]. HIV-1 is a virus that generates its own targets. Even when viral loads are low during chronic infection, cell-to-cell transmission of virus may occur through local bursts of immune activation provoked by antigenic and inflammatory stimuli[15,76,77]. Indeed, one such stimulus may be the HIV-1-specific T-cell response itself[12]. As most of the viral targets –activated CD4+ T cells– are, by nature, short-lived, their subsequent death does not immediately affect, in the chronic phase, the crucial cellular resources of the immune system, namely, the naive and resting memory T-cell pools. However, chronic immune activation may slowly but progressively drain these pools while the supply routes and anatomical niches which maintain the T-cell compartments are destroyed. In the midst of this homeostatic upheaval, the virus itself targets those T-cells attempting to sustain the resting memory CD4+ T-cell pool. All of these events affect CD4+ T-cells more than CD8+ T-cells, both due to physiological differences between the two subsets and to the CD4+ T cell lymphopenia established in acute infection, hence their preferential loss. This is how HIV-1 infection triggers the self-perpetuating series of events under which the immune system eventually collapses.

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