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When being a bystander is not so innocent

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Abstract

A new mechanism to explain massive depletion of CD4⁺ T cells in HIV-1 infection despite the low frequency of productively infected cells involves innate immune sensing of HIV 1 by abortively infected “bystander” CD4⁺ T cells. The result is death of the bystander cells through an inflammatory process known as pyroptosis. These findings may provide long sought explanations for both CD4⁺ T cell depletion and HIV-associated inflammation. See Article on page X.

Subject terms

Immunology; Infectious Diseases

In the first paper describing AIDS, Gottlieb et al. observed that patients had very few CD4⁺ T lymphocytes in the blood¹. Depletion of this critical T cell subset is central pathophysiologic feature of the disease but mechanisms responsible for CD4 depletion have remained unclear. HIV-1 replicates in activated CD4⁺ T cells and kills them quickly, within 1–2 days^{2,3}. Direct killing of productively infected cells is important during acute infection, when viremia is very high and massive depletion of CD4⁺ T cells occurs in the gastrointestinal track⁴. However, in untreated individuals, most of the CD4 loss occurs in the prolonged asymptomatic phase between acute infection and the development of AIDS. During this period, the frequency of infected CD4⁺ T cells is low, suggesting that the infection may somehow promote death of non-infected CD4⁺ T cells. Levels of immune activation are high in untreated HIV-1 infection, perhaps reflecting the translocation of microbial products across a compromised gastrointestinal barrier⁵, and it is commonly assumed that immune activation is responsible for CD4 cell loss. Perhaps the best evidence comes from studies of simian immunodeficiency virus (SIV) infection in natural hosts in which there is high virus replication, but little immune activation or CD4 depletion⁶. Nevertheless, the mechanistic link between immune activation and CD4 depletion has remained unclear.

On page X of this issue, Doitsh and colleagues elucidate a new mechanism for CD4 depletion⁷. Using human lymphoid aggregate tissue (HLAC) of fresh tonsil or spleen, they demonstrate that more than 95% of quiescent CD4⁺ T cells die by caspase-1 mediated pyroptosis. Pyroptosis is a cell death mechanism distinct from apoptosis and necroptosis⁸. While apoptosis depends on caspase-3 activation, pyroptosis is triggered by inflammasome-activated caspase-1. Inflammasomes are multi-protein cytosolic complexes that integrate pathogen-triggered signaling cascades then recruit and activate inflammatory caspases.

Pyroptosis results in lysis and release of cytosolic contents into the extracellular space and is highly inflammatory. Doitsh and colleagues previously demonstrated that abortive infection of quiescent CD4⁺ T cells in which incomplete reverse transcripts accumulate results in selective depletion of these cells⁹. This process depends on virus binding to CD4 and an HIV-1 co-receptor, entry, and early steps of reverse transcription, but not later events in the life cycle. Using proteomic and biochemical approaches and gene knockdown in primary CD4⁺ T cells, Monroe and colleagues recently identified interferon-gamma-inducible protein 16 (IFI16) as the host DNA sensor required for CD4⁺ T cell death due to abortive HIV-1 infection.¹⁰ Interestingly, this form of cell death is not seen following infection of peripheral blood CD4⁺ T cells.

In this issue, Doitsh and colleagues show that productively infected CD4⁺ T cells, which represent the minority of dying cells, undergo death via caspase-3 mediated apoptosis while the majority of T cell death results from pyroptosis in quiescent CD4⁺ T cells that are nonpermissive for productive HIV-1 infection (Figure 1). Treatment with an HIV-1 entry inhibitor, a non-nucleoside reverse transcriptase inhibitor, or with a pan-caspase inhibitor prevented activation of both caspases. Inhibition of caspase-3 or caspase-6 (important in apoptosis) or receptor interacting protein (RIP) kinases (important in necroptosis) did not prevent most of the CD cell loss. The cytosolic enzyme lactate dehydrogenase (LDH) was released into the supernatant following HIV-1 infection pyroptosis and its associated release of intracellular contents. Caspase-1 was detected in resting CD4⁺ T cells in the paracortical zone that surrounds the zone of activated CD4⁺ T and B cells in HIV-1- infected lymph node tissue, providing in vivo evidence for this mechanism. Caspase-1 was not detected in the zone of activated CD4⁺ T cells or in uninfected tissue.

Independent confirmation that abortive HIV-1 infection of CD4⁺ T cells leads to caspase-1 activation was obtained by detection of an active subunit of caspase-1 in the lysates of HIV-1-infected cultures. Treatment with viral or caspase-1 inhibitors, but not caspase-3 inhibitors, prevented caspase-1 activation. Caspase 1 activation results in secretion of the highly inflammatory antiviral cytokines interleukin-1 β (IL-1 β) and IL-18^{11, 12}. IL-1 β and IL-18 contribute to inflammatory conditions including atherosclerosis and metabolic syndromes^{11–14}. Doitsh and colleagues show in this paper that IL-1 β release after infection with HIV-1 is primarily by coreceptor CCR5-expressing CD4⁺ T cells and requires caspase-1 activation..

Lastly, Doitsh and colleagues show that pyroptosis induced by HIV-1 could be prevented with VX-765, a safe and well tolerated caspase-1 inhibitor tested previously in chronic epilepsy and psoriasis.. VX-765 inhibited caspase-1 cleavage, IL-1 β secretion, and CD4⁺ T cell death in HIV-1- infected HLAC. This study raises the possibility of reducing immune activation and inflammation in response to chronic viral infections through caspase-1 inhibition. This research suggests two new approaches to improve HIV-1 therapy: use of antiretroviral agents that act early in the life cycle to block abortive infection and use of agents that inhibit caspase-1. Combination therapy with multiple classes of antiretroviral drugs is the standard of care and results in very effective suppression of HIV-1 replication. Suppression of caspase-1 activation may not be necessary if combination therapy prevents abortive infection as well. Although IL-18 is not measured by Doitsh and colleagues, it is

generally produced with IL-1 β following inflammasome activation and elevated levels are associated with inflammatory conditions, including cardiovascular disease, seen more commonly in HIV-1 infected individuals.^{13–15} Serum IL-18 levels, known to be high in HIV-1 infection, are reduced by antiretroviral therapy^{14,15}. Thus, it remains to be seen whether caspase-1 inhibitors will add to antiretroviral therapy in the treatment of HIV-1 infection. Either way, the implication of pyroptosis in lymphoid tissue CD4⁺ T cell depletion is a novel explanation for this 30 year old mystery in HIV-1 pathogenesis.

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Figure 1. Following HIV-1 infection, most lymphoid CD4⁺ T cell death is mediated by caspase-1 activation and pyroptosis in abortively infected quiescent CD4⁺ T cells

A. Productively infected CD4⁺ T cells represent the minority of dying CD4⁺ T cells and undergo death via caspase-3 mediated apoptosis. **B.** The majority of CD4⁺ T cell death results from caspase-1 mediated pyroptosis in quiescent CD4⁺ T cells. Abortive infection of quiescent CD4⁺ T cells, in which incomplete HIV-1 transcripts accumulate and are sensed by the host DNA sensor IFI16, results in caspase-1 cleavage and activation with 1) selective depletion of CD4⁺ T cells via pyroptosis and 2) release of the highly inflammatory cytokine IL-1 β . HIV-1-induced CD4⁺ T cell death via pyroptosis was blocked by a caspase-1 inhibitor and antiretroviral agents that act on early stages of the HIV-1 life cycle.