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SHORT ANALYTICAL REVIEW

HIV-1 immunopathogenesis: How good interferon turns bad

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Abstract The hallmark of acquired immunodeficiency syndrome (AIDS) is the progressive loss of $CD4^+$ T cells that results from infection with human immunodeficiency virus type-1 (HIV-1). Despite 25 years of AIDS research, questions remain concerning the mechanisms responsible for HIV-induced $CD4^+$ T cell depletion. Here we briefly review the *in vitro* and *in vivo* literature concerning the protective role of interferon-alpha (IFN-α) in HIV/AIDS. We then develop a laboratory- and clinically supported model of $CD4^+$ T cell apoptosis in which either infectious or noninfectious HIV-1 induces the production of type I interferon by plasmacytoid dendritic cells (pDC). The interferon produced binds to its receptor on primary $CD4^+$ T cells resulting in membrane expression of the TNF-related apoptosis-inducing ligand (TRAIL) death molecule. The binding of infectious or noninfectious HIV-1 to CD4 on these T cells results in expression of the TRAIL death receptor 5 (DR5), leading to the selective death of HIV-exposed $CD4^+$ T cells.
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Introduction

Infection with human immunodeficiency virus type-1 (HIV-1) continues to develop as an expanding worldwide pandemic, resulting in the death of more than three million people annually. $CD4^+$ T cells are the cornerstone of adaptive immunity, and the critical loss of these T helper cells during progression to acquired immunodeficiency syndrome (AIDS) is the immunologic hallmark of HIV-1 immunopathogenesis, resulting in susceptibility to opportunistic infections. Recent reports have demonstrated a rapid and dramatic loss of $CD4^+$ T cells in lymphoid tissues (LT) during acute infection with both HIV-1 and [1,2] and SIV (simian immunodeficiency virus) [3,4]. Although partial repopulation with T helper cell is observed after the acute phase, a continuous gradual loss of $CD4^+$ T cell occurs throughout chronic disease, which is accelerated during AIDS [5]. Several mechanisms have been proposed to explain this depletion during chronic HIV-1 disease, ranging from direct cytopathic effects of HIV-1 infection on $CD4^+$ T cells [5] to HIV-induced immune activation of T helper cell death [6]. However, the frequency of infected circulating $CD4^+$ T cells is too low to account for the loss of $CD4^+$ T cells during the chronic phase [7]. Furthermore, because HIV-1 activates both $CD4^+$ and $CD8^+$ T cells [8], T cell activation does not account for the selective depletion of $CD4^+$ T cells. Therefore, novel hypotheses are needed to facilitate an understanding of HIV-induced immunopathogenesis. Here we summarize the findings of others concerning the role of type I interferon in HIV disease protection and pathogenesis, along with our laboratory-developed and patient-tested model that accounts for the selective depletion of HIV-infected and uninfected $CD4^+$ T cells. We showed

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that the noninfectious interaction between HIV-bound gp120 and cellular CD4 results in: (1) pDC production of IFN-α which induces STAT-1/2-regulated TRAIL expression on $CD4^+$ T cells and TRAIL expression/production by monocytes; and (2) expression of the TRAIL death receptor DR5 on $CD4^+$ T cells, leading to preferential apoptosis of T helper cells.

Interferon-α in HIV-1 disease and therapy

We are now approaching the 50th anniversary of the discovery of interferon and its antiviral activity [9]. During the intervening decades, several clinical trials were developed to test the efficacy of type I interferon (IFN-α/β) against different viral infections [10]. Much of the evidence that IFN-α would be effective in treating HIV-infected patients is based on *in vitro* studies [11,12]. The results of trials in other viral infections [10] and of the HIV-1 tissue culture experiments led to several clinical trials in which type I interferon was administered to HIV-infected patients. A modest therapeutic effect was reported in some but not all trials [13–16], leaving the issue of interferon therapy for HIV-1 disease unresolved. More recent phase I trials have been reported in which IFN-α2b was administered alone or in combination with didanosine [17], or with highly active antiretroviral therapy (HAART) [18] in patients with AID-associated Kaposi's sarcoma (KS). Some therapeutic efficacy was seen for KS in the 2002 report but no increase in survival was observed. The 2006 report established a safe dose regimen for IFN-α2b with HAART, but durable clearance of KSHV was not seen. The results of IFN-α trials for HIV-1 infection have not been encouraging when compared to the effects of type I interferon in treating non-HIV viral infections, and to the *in vitro* data showing HIV-1 inhibition. Clinical trials using IFN-α have been recently started again by the NIAID ACTG in the United States, and by the ANRS in France.

Other *in vivo* reports indicated that elevated IFN-stimulated gene expression was associated with disease progression in HIV-infected patients following cessation of HAART (R A Lempicki et al., unpublished observations), as well as in SIV-infected cynomolgus macaques [19]. Type I interferon produced in lymphoid tissue (LT) of macaques infected with SIV did not inhibit viral replication [20]. Additional studies reported that IFN-α induced immune impairment, which was blocked by anti-IFN-α antibodies [21], and that immunization of AIDS patients against IFN-α reduced HIV-1 disease progression [22]. These latter reports raised the possibility that not only IFN-α is not efficacious in HIV-infected patients, but may actually contribute to HIV-1 disease. Because IFN-α was detected in the plasma of HIV-1-infected patients during both early and late-stages of HIV-1 disease, this cytokine could contribute to pathogenesis [23]. In conclusion, a dichotomy exists between the findings of *in vivo* studies and *in vitro* experiments concerning the protective effects of IFN-α.

Plasmacytoid dendritic cells in HIV-1 disease

Plasmacytoid dendritic cells (pDC), which constitute 0.5–0.8% of blood leukocytes, were identified as the major source of type I interferon [24]. These rare, specialized cells found in blood and LT produce up to 1000-fold more IFN-α than other leukocytes following activation by viruses [25]. Evidence favoring the hypothesis that IFN-α protects HIV-infected patients from HIV-1 disease progression and opportunistic infections is based partly on earlier clinical studies demonstrating reduced IFN-α production in patients' PBMC [26], which was reversed by antiretroviral therapy [27]. Because the frequency of circulating pDC was also reported to be decreased in HIV-infected patients with progressing disease compared to the frequencies in nonprogressing patients and healthy controls, pDC and the IFN-α they produce were considered to provide protection against HIV-1 disease progression [28,29]. Furthermore, circulating pDC from HIV-infected patients appeared to be deficient because they produced less IFN-α than pDC from uninfected donors [30]. However, we and others recently found that maturing pDC express the CCR7 and CXCR3 cell migration markers, indicating that these pDC migrate to LT [31–34]. In addition, recent reports indicate that HIV-induced pathogenesis occurs mainly in LT [1,4,35]. The above finding have led us to an alternate interpretation that pDC migrate to LT in progressing HIV-infected patients, where the IFN-α they produce contributes to pathogenesis in these lymphoid sites by TRAIL-mediated apoptosis of HIV-exposed but uninfected $CD4^+$ T cells [35]. Thus, the controversy over whether or not IFN-α is beneficial to HIV-infected patients extends to pDC and the migration and localization patterns of these major producers of IFN-α.

TRAIL/DR5-mediated death of $CD4^+$ T cells in HIV-1 immunopathogenesis

HIV- and SIV-induced apoptosis is currently considered to contribute to the loss of both infected and uninfected $CD4^+$ T cells during HIV-1 disease progression. The Fas/FasL apoptotic pathway has been extensively studied, and was suggested to contribute to the loss of $CD4^+$ T cells in progression to AIDS [36,37]. However, other reports indicated that $CD4^+$ T cell apoptosis was not due to a Fas/FasL mechanism [38,39], suggesting that multiple death molecules are involved. Other TNF superfamily death molecules have been studied including TRAIL, which was shown to induce apoptosis of anti-CD3-activated T cells [40], virus-infected cells [41] and tumor cells [42,43]. TRAIL has two death receptors (DR) that induce apoptosis (DR4 and DR5) [44]. Several reports suggested that TRAIL contributes to T cell death, resulting from HIV-1 infection [45,46], and both $CD4^+$ and $CD8^+$ T cells from HIV-1-infected patients exhibited increased susceptibility to TRAIL-mediated death [47,48]. TRAIL induced apoptosis of uninfected $CD4^+$ T cells in HIV-1-infected hu-PBL-NOD-SCID mice [49]. Monocytes exposed to HIV-1 Tat produced TRAIL, resulting in apoptosis of uninfected $CD4^+$ T cells [50]. Expression of TRAIL by monocytes and DR5 by neurons found in brain tissue of HIV-1-infected patients, may contribute to AIDS dementia [51,52]. We reported that monocytes produce soluble TRAIL (sTRAIL) and membrane TRAIL (mTRAIL) following short-term culture with HIV-1 [53]. HIV-1 also induced expression of mTRAIL and DR5 on $CD4^+$ but not $CD8^+$ T cells, which induced selective apoptosis of $CD4^+$ T cells [54]. These *in vitro* results raise the possibility that the TRAIL/DR5 mechanism is involved in $CD4^+$ T cell depletion during progression to AIDS.