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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 DS 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 (pDCs). 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.

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 [2] 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 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

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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;14; 15;16], leaving the issue of interferon therapy for HIV-1 disease unresolved. More recent phase I trials have been reported in which IFN- α 2b was administered to 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- α 2b 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 is IFN- α 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 anti-retroviral 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 non-progressing 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;32;33;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.

To determine whether *in vivo* data that would support our *in vitro* findings could be obtained, the plasma of HIV-infected patients were tested for sTRAIL and their T cells for expression of mTRAIL, DR5 and apoptosis. Higher levels of sTRAIL were detected in plasma of HIV-1-infected patients than in healthy control individuals [53]. Furthermore, the amount of sTRAIL in plasma was directly proportional to the patients' viral load, and elevated sTRAIL in patients with low or undetectable viral load was not detected [53]. The presence of TRAIL alone is not sufficient to induce the death of CD4⁺ T cells, because TRAIL-induced apoptosis requires binding to one of its death receptors, DR4 or DR5. Apoptosis of CD4⁺ T cells was strictly associated with expression of DR5 in HIV-1-infected patients, but not in uninfected individuals. Analyses of CD4⁺ T cell death, TRAIL and DR5 expressions in a longitudinal study of HIV-1-infected patients receiving HAART indicated that the HAART-induced decline in plasma viral load was paralleled by a decrease in plasma TRAIL levels [54]. Furthermore, the HAART-induced increase in CD4 count was accompanied by a corresponding decrease in DR5 mRNA expression on CD4⁺ T cells [54]. Our finding that these levels of HAART-induced TRAIL and DR5 were reflected by the FDA-approved surrogate markers of viral load and CD4 count strongly suggests that TRAIL and DR5 are involved in HIV-1 disease progression. In addition, tonsils from HIV-1-infected patients with progressive disease expressed high levels of both TRAIL and DR5 mRNA, compared to tonsil tissue from patients with a nonprogressive disease [35]. Tonsil biopsies from uninfected donors did not express TRAIL or DR5 mRNA. Identification the same death ligand (TRAIL) and receptor (DR5) in both our *in vitro* and *in vivo* experiments lends credibility to our data of TRAIL/DR5-induced HIV-1 immunopathogenesis.

Effects of noninfectious HIV-1 in TRAIL/DR5-mediated T cell death

More than 99% of plasma HIV-1 particles has been estimated to be noninfectious [55;56], making it statistically more likely that CD4⁺ T cells interact with noninfectious HIV-1 particles than with their infectious counterparts. Furthermore, most of the cells undergoing apoptosis in the lymph nodes of HIV-1-infected patients are not productively infected [57]. Therefore, we studied the effects of HIV-1 that had been chemically inactivated with Aldrithiol-2 (AT-2) on T cell apoptosis. AT-2 treatment of HIV-1 destroys the viral RNA-nucleoprotein complex, rendering AT-2 HIV-1 noninfectious, while maintaining intact viral envelope functional and antigenic integrity [58]. The culture of PBMC from healthy blood donors with AT-2 HIV-1 for 10 days resulted in the apoptotic death of both CD4⁺ and CD8⁺ T cells although more CD4⁺ T cells died [38]. Both infectious HIV-1 and AT-2 HIV-1 induced TRAIL expression by monocytes and CD4⁺ T cells [32]. Furthermore, infectious and noninfectious HIV-1 were equally effective for inducing expression of DR5 on CD4⁺ T but not on CD8⁺ T cells, and for inducing selective apoptosis of CD4⁺ T cells [32]. These results, using noninfectious HIV-1, are important because they demonstrate that potentially all HIV-1 particles that express gp120 can induce HIV-1 immunopathogenesis by activating TRAIL, DR5 and CD4⁺ T cell apoptosis, whereas only a minor proportion of plasma virus can participate in productive infection. These findings provide a mechanism by which uninfected CD4⁺ T cells in HIV-1-infected patients can die without virological evidence of having been infected, and can also account for the observation that too few CD4⁺ T cells are infected for HIV-induced death to be due to an infectious cytopathic effect [7].

Role of IFN- α in TRAIL/DR5-mediated apoptosis and immunopathogenesis

As noted above, IFN- α is produced mainly by pDC [24], and has broad anti-viral activity [10]. The evidence that IFN- α offers therapeutic benefit against HIV-1 infection has been largely provided by *in vitro* studies involving inhibition of HIV-1 replication [11;12], and therapeutic trials using type I interferon have yielded mixed results [13;14;15;16]. Murine viral infection induced IFN- α/β production and activated STAT-1 and STAT-2 signaling molecules, resulting in p53 expression, and apoptosis of virus-infected cells [59], suggesting this as a protective mechanism for destroying virus-infected cells [60]. Therefore, we tested whether HIV-1-induced TRAIL, DR5 and apoptosis in CD4⁺ T cells was dependent on type I interferon. HIV-1-induced TRAIL expression was IFN- α dependent and was mediated by STAT-1 and STAT-2. TRAIL expression and apoptosis of HIV-1-exposed CD4⁺ T cells were blocked by antibodies against IFN- α/β [32]. pDC cultured with either infectious or noninfectious HIV-1 produced IFN- α , as previously reported [31]. This pDC-generated IFN- α was responsible for TRAIL expression on primary CD4⁺ T cells [32]. HIV-1 also induced expression of interferon regulatory factor 7 (IRF-7) and the MyD88 adapter molecule by pDCs *in vitro* and *in vivo* [35]. Importantly, we recently reported that tonsils of patients with progressive HIV-1 disease expressed increased mRNA for IFN- α , TRAIL and DR5 compared to tonsils of patients with non-progressive disease [35]. The T cell-rich areas of tonsils from acutely-infected and progressing patients showed elevated levels IFN- α , in contrast to the tonsils of long-term non-progressors and uninfected controls which did not show IFN- α [35]. These immunohistopathologic findings suggest that IFN- α produced by pDC in LT induces expression of sTRAIL and mTRAIL, which binds to HIV-induced DR5 expressed on CD4⁺ T cells, resulting in their apoptosis.

How good interferon turns bad

Our model of HIV-1-induced CD4⁺ T cell death using noninfectious HIV-1 is similar to that proposed for type I interferon-dependent apoptotic death of virus-infected cells [59;60]. Thus, by comparing the effects induced by infectious HIV-1 with those induced by noninfectious

AT-2 HIV-1, we demonstrated that the same type I interferon-regulated mechanism that induces the death of HIV-1-infected CD4⁺ T cells also kills uninfected CD4⁺ T cells that bind HIV-1 without becoming productively infected [54]. From this perspective, the IFN- α -dependent, HIV-mediated death of CD4⁺ T cells described above would be protective when it destroys CD4⁺ T cells that have become infected by infectious HIV-1: “good interferon”. However, when pDC and CD4⁺ T cells bind noninfectious HIV-1, uninfected pDC will produce IFN- α and CD4⁺ T cells will express TRAIL and DR5, resulting in the immunopathogenic apoptosis of uninfected T helper cells by the same mechanism: “bad interferon”. Because the frequency of circulating noninfectious HIV-1 particles exceeds that of infectious HIV-1 by a factor of 10²-10⁴ [56], the binding of noninfectious HIV-1 to CD4 on both pDC and CD4⁺ T cells would be expected to occur much more frequently than the binding of infectious virus to these important anti-viral cells. Therefore, the apoptosis of HIV-exposed but uninfected CD4⁺ T cells would outpace the apoptosis of productively infected CD4⁺ T cells. This predominant death of uninfected CD4⁺ T cells would provide a distinct advantage for the virus, by destroying T helper cells that are specific for opportunistic pathogens, as well as those that recognize HIV-1 antigens. This effect on CD4⁺ T cells might be unique to HIV-1 because this virus uses the CD4 molecule as its primary receptor. We also demonstrated that only the binding of viral gp120 to cellular CD4 is required to induce IFN- α , even when we use the AT-2-inactivated virus to trigger this death-inducing event [32;54]. The binding of HIV-1 to pDC was recently shown to induce IFN- α by a 2-step mechanism. The first step involves endocytosis of HIV-1, which is followed by toll-like receptor-mediated stimulation of pDC by viral RNA [61].

Since expression of FasL has been shown to be type I interferon dependent [62], it is possible that a similar Fas/FasL-mediated mechanism contributes to the death of uninfected CD4⁺ T cells. In fact, a recent study demonstrated that IFN- α plays a dual role in human TCR-activated CD4⁺ T cells proliferation and Fas-mediated apoptosis [63]. Furthermore, we recently found that the mRNA levels of both TRAIL and its DR5 death receptor and FasL and its Fas death receptor are elevated in the tonsils of HIV-1 progressor patients compared to the tonsils of HIV-1 nonprogressors and uninfected controls [35]. These parallel findings compared in the same patients and controls, suggest that both the TRAIL/DR5 and Fas/FasL apoptotic mechanisms contribute to HIV-1 immunopathogenesis.

Therapeutic implications

Based on the above findings, reducing HIV-induced IFN- α and TRAIL production might be an effective therapeutic strategy for patients progressing to AIDS [64]. However, because IFN- α also has broad beneficial anti-viral effects, the use of anti-IFN antibodies could exacerbate the existing immunodeficiency in antibody-treated patients. We reported that the binding of HIV-1 to CD4 was essential for HIV-induced IFN- α production by pDCs, and also for TRAIL and DR5 expression by CD4⁺ T cells [32]. Furthermore, HIV-coreceptor binding did not appear to be essential for inducing these apoptotic events [54]. Therefore, we suggest that molecules that block the initial gp120-CD4 interaction would be effective apoptosis inhibitors. Such blocking molecules would inhibit the binding of viral gp120 to cellular CD4, irrespective of whether the viral particles were or were not infectious. The net effect would be to reduce HIV-1 infection and HIV-1 pathogenesis by decreasing TRAIL/DR5-mediated apoptosis of CD4⁺ T cells, and also IFN- α production by HIV-activated pDC. The injection of PRO 542, a tetrameric derivative of sCD4-IgG was reported to reduce the viral load of HIV-1-infected patients [65]. However, small water-soluble CD4-like molecules might be more efficient, because they could be administered orally. A 27-amino acid CD4 mimic (CD4 M33) has been recently shown to block HIV-1 infection of primary CD4⁺ T cells [66]. It is our opinion that this relatively new AIDS therapeutic strategy offers the unique advantages of simultaneously inhibiting HIV-1 infection and blocking the HIV-1-induced immunopathogenesis described here.

Conclusions and model

The loss of CD4⁺ T cells during HIV-1 disease progression has been attributed to direct and/or indirect effects [67]. Our findings implicate the involvement of both direct and indirect mechanisms. The indirect effect is the production of soluble TRAIL (sTRAIL) by monocytes or expression of membrane TRAIL (mTRAIL) on monocytes, dendritic cells or CD4⁺ T cells, and requires IFN- α production by pDC (Fig. 1, Progressors). The binding of HIV-1 to CD4⁺ T cells does not induce TRAIL expression directly, but requires IFN- α produced by pDC and possibly other DC. Furthermore, pDC can be activated to produce IFN- α not only by HIV-1 binding to CD4, but also by other viruses (not shown in model). Therefore, the production of IFN- α leading to TRAIL expression by CD4⁺ T cells is not an HIV-1-specific event. In contrast, the direct effect on CD4⁺ target T cells is the expression of DR5, which is strictly dependent on the binding of HIV-1 to CD4⁺ [54]. Apoptosis of CD4⁺ T cells depends on expression of both DR5 by these target cells (direct effect), and on production of sTRAIL by monocytes and/or expression of mTRAIL by monocytes, dendritic cells or CD4⁺ T cells (indirect effect). Therefore, both direct and indirect effects are required in our model. The rate-limiting step in this death process is DR5 expression by CD4⁺ T cells. This step is HIV-1-specific, in contrast to TRAIL expression and production. In patients who are not progressing (Fig. 1. Nonprogressor), HIV-1 did not induce detectable IFN- α in the T cell-rich areas of patients' tonsils [35]. We do not know whether the absence of IFN- α was due to the failure of pDC to produce type I interferon, whether the pDC did not migrate to the LT, or was due to some other mechanism such as low plasma viral load. We also showed that DR5 mRNA was increased in the tonsils of progressors but not in tonsils of nonprogressors [35]. In conclusion, since we induced TRAIL, DR5 and apoptosis using noninfectious HIV-1, our model provides a mechanism that can explain the selective death of HIV-uninfected CD4⁺ T cells [57], which involves non-infectious virus-induced IFN- α production by pDC.

A unique aspect of this model is that the noninfectious HIV-1-induced death utilizes the same type I interferon-regulated death mechanism that has been proposed for the elimination of cells that are infected with different viruses [60]. If correct, this model predicts that the same molecular signaling events that initiate the IFN- α -dependent apoptotic death resulting from productive infection of CD4⁺ T cells will also be activated by noninfectious interactions that result in the apoptotic death of uninfected CD4⁺ T cells. These noninfectious, apoptosis-inducing, interactions between viral gp120 and cellular CD4 would not be detected by viral DNA or RNA assays as having occurred, and would be classified as "bystander killing". As noted above, circulating HIV-1 particles that are not productively infectious are far more numerous than productively infectious virus [55;56] and are included in viral load measurements. Therefore, noninfectious interactions between viral gp-120 and cellular CD4 that result in CD4⁺ T cell apoptosis will far exceed those that result in productive infectious events, and immunopathogenesis defined as IFN- α -dependent apoptotic death of HIV-uninfected CD4⁺ T cells will occur more frequently than clearance by productively-infected CD4⁺ T cells by the same mechanism (Fig. 2). In this model the immunopathogenic aspects of IFN- α would outweigh its beneficial effects in patients with detectable viral burden in LT. It remains to be determined whether type I interferon-dependent death of virus-exposed, but uninfected cells is unique to HIV-1 and its CD4⁺ T cell target, or whether this model can be extended to other viruses.

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Figure 1.

Progressor. Model showing that either infectious or noninfectious HIV-1 binds to CD4 on pDC, resulting in their activation, type I interferon (IFN- α) production and migration from blood to lymphoid tissue. IFN- α binds to its receptor on CD4⁺ T cells, resulting in STAT-1/2-regulated expression of membrane TRAIL. The binding of HIV-1 to CD4 on CD4⁺ T cells is required for expression of the TRAIL death receptor 5 (DR5). Membrane TRAIL expressed by CD4⁺ T cells, or soluble TRAIL produced by monocytes (not shown) binds to DR5, resulting in CD4⁺ T cell apoptosis.

Figure 1, Nonprogressor. Model showing that the pDC of nonprogressing patients who have low or undetectable plasma viral loads, do not produce IFN- α that is required for TRAIL expression on CD4⁺ T cells. The lack of viral particles may account for the fact that DR5 is not expressed on CD4⁺ T cells, which do not undergo apoptosis.

Figure 2.

Comparison of protective and immunopathologic effects of IFN- α on HIV-1 infection. The protective effects include IFN- α -mediated inhibition of HIV-1 replication and formation of infectious viral particles, and the IFN- α -induced apoptosis of infected CD4⁺ T cells, resulting in the destruction of the source of new virus production. The immunopathogenic effect involves IFN- α -induced apoptosis of HIV-exposed but uninfected CD4⁺ T cells by the same mechanism that destroys HIV-infected CD4⁺ T cells. These uninfected, HIV-exposed, dying T helper cells include HIV-specific, as well CD4⁺ T helper cells that are specific for many pathogens. The protective/immunopathogenic balance is statistically tipped in favor of immunopathogenesis, due to the fact that noninfectious HIV-1 particles has been estimated to outnumber infectious particles by a factor of 10^2 - 10^4 .

Definitions: pDC, plasma dendritic cells. CD123 and BDCA2 are pDC markers; CCR7: migration marker of pDC.