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Review

Apoptosis of uninfected cells induced by HIV envelope glycoproteins

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Abstract

Apoptosis, or programmed cell death, is a key event in biologic homeostasis but is also involved in the pathogenesis of many human diseases including human immunodeficiency virus (HIV) infection. Although multiple mechanisms contribute to the gradual T cell decline that occurs in HIV-infected patients, programmed cell death of uninfected bystander T lymphocytes, including CD4+ and CD8+ T cells, is an important event leading to immunodeficiency. The HIV envelope glycoproteins (Env) play a crucial role in transducing this apoptotic signal after binding to its receptors, the CD4 molecule and a coreceptor, essentially CCR5 and CXCR4. Depending on Env presentation, the receptor involved and the complexity of target cell contact, apoptosis induction is related to death receptor and/or mitochondria-dependent pathways. This review summarizes current knowledge of Env-mediated cell death leading to T cell depletion and clinical complications and covers the sometimes conflicting studies that address the possible mechanisms of T cell death.

Introduction

HIV infection usually leads to progressive decline in functionality and number of CD4+ T lymphocytes, resulting in AIDS development [1]. Despite intensive studies, several crucial questions remain to be addressed about the mechanisms through which HIV infection induces T cell death and this subject is one of the most controversial issues in AIDS research.

First, T cell loss could be due to direct destruction by the virus. HIV infection results in high T cell activation and turnover, and accelerates both production and destruction of CD4+ T cells [1,2]. Using a mathematical model, Mohri and collaborators have demonstrated that T cell depletion observed in HIV-1 infection was due to an increased turnover of T lymphocytes rather than a decrease in cellular production [3], but the dynamics of T cells in HIV-infected patients remain controversial [4].

A strong immune response is a priori beneficial in controlling viral replication. However, independently of viral load, a chronic, heightened activation of the immune system may contribute in a direct manner to progressive CD4+ T cell depletion [4,5]. Two observations corroborate this hypothesis. First, sooty mangabeys, the natural host of simian immunodeficiency virus (SIV), which do not develop AIDS, support high levels of viral replication but fail to exhibit a clear increase in immune activation [6]. In contrast, SIV experimentally transferred to rhesus macaques induces a dramatic increase in immune

activation and rapid progression to AIDS and death. In the same way, HIV-1 and HIV-2-infected patients with similar degree of CD4+ T cell depletion show large differences in viral load [7]. CD4+ T cell loss during the chronic phase of HIV/SIV infection is thus more directly related to the overall immune response than the rate of virus replication. Immune activation could drive the progression of HIV disease by destabilizing or progressively changing the homeostatic states of resting T cell populations.

Second, T cell apoptosis has been proposed as early as 1991 as another mechanism responsible for T cell depletion in patients infected with HIV-1 [8,9] and an extensive body of literature since then has supported this hypothesis. In addition, there is a correlation between the extent of apoptosis and disease progression [10,11] and highly active antiretroviral therapy (HAART) is associated with a lower level of CD4+ T cell apoptosis in HIV-1-infected patients [12-14].

In HIV-infected persons, both infected and uninfected cells undergo accelerated apoptosis, in vitro and in vivo. Several mechanisms have been proposed to explain these results: (i) direct role of HIV-specific proteins, (ii) activation-induced cell death (AICD), (iii) direct infection of T lymphocytes, (iv) autologous cell-mediated killing of uninfected T cells and (v) dysregulation of cytokine/chemokine production [15]. However, HIV-1-induced apoptosis in bystander uninfected immune cells is likely the key to the depletion of T lymphocytes observed in HIV-1-infected patients since the degree of cell loss largely exceeds the number of infected cells. Furthermore, the vaste majority of T cells undergoing apoptosis in peripheral blood and lymph nodes of HIV patients are uninfected [16,17]. Using several animal models, such as rhesus macaques infected by SIV or highly pathogenic SIV/HIV chimeric viruses and human PBL-transplanted nonobese diabetic (NOD)-severe combined immunodeficient (SCID) mice, massive apoptosis was predominantly observed in uninfected CD4+ T cells present in lymph nodes, thymus or spleen [18-20].

Several HIV-1 proteins, such as HIV envelope glycoproteins (Env), Tat, Vpr, Nef, Vpu and the protease can induce T cell apoptosis. No one has a full grasp of the real importance of this process in vivo, but cumulative data demonstrate a major role of Env in cell death of uninfected lymphocytes [21-24].

These two global mechanisms leading to T cell loss in HIV disease are not mutually exclusive. Over the past several years, many data were obtained on signaling induced after Env binding to its receptors leading to T cell apoptosis. The purpose of this review is thus to summarize recent information on apoptotic pathways shown to be activated by Env in uninfected cells and to highlight the pathological consequences of this cell death. Novel avenues for clinical managements of AIDS based on this research are also discussed.

HIV envelope glycoproteins as inducers of apoptosis

The mature HIV-1 envelope glycoproteins are composed of gp120, the exterior envelope glycoprotein, and gp41, the transmembrane glycoprotein assembled as trimer by non covalent interactions. Obviously, the viral envelope can be considered as an extracellular ligand. Consequently, binding of HIV-1 Env gp120/gp41 to its receptors constitutes the primary interface between viruses and T cells and this event is likely able to modulate T cell signaling.

In most cases, to enter a target cell, HIV-1 must bind two molecules on the surface of target cells. gp120 first interacts with CD4, which triggers conformational changes leading to increased exposure of the gp120 V3 loop that is then able to bind to several coreceptors that determine the tropism of the virus for particular cell types [25]. CCR5 and CXCR4 are the main HIV coreceptors [26-28] but several other members of the chemokine receptor family, such as CCR1, CCR2b, CCR3, CCR4, CCR8, CX3CR1, BOB/GPR15, Bonzo/CXCR6, GPR1, US28 and APJ can also be used as coreceptors for viral entry [29-34]. These events trigger the formation of a coiled-coil structure in the gp41 ectodomain that places the hydrophobic aminoterminal region of gp41 in close proximity to the cellular membrane, thereby inducing cell fusion [35].

Transmissible, macrophage-tropic HIV-1 strains, named R5, use CCR5 as a coreceptor. As the disease progresses, in many individuals, viruses emerge that have T-tropic characteristics. These strains are able to use CXCR4 alone or in combination with other coreceptors. The correlation between the clinical outcome and extended viral tropism is still a subject of debate. Indeed, in most cases, disease progression does not seem to correlate directly with the emergence of variants that can use multiple coreceptors [36] but viral adaptation has also been described to follow in vivo HIV-1 disease progression [37]. Evolution of coreceptor use is a continuous process that may lead to change in the way coreceptors are used, with the potential of altering signaling at that receptor and sensitivity to inhibition by chemokines, neutralizing antibodies or drugs that target coreceptor binding. HIV-1 Env interaction with each of these receptors (CD4 and a coreceptor) can thus dictate the molecular mechanisms transducing apoptosis in uninfected T cells.

Depending on Env presentation and on the complexity of target cell contact, the mechanisms leading to cell death

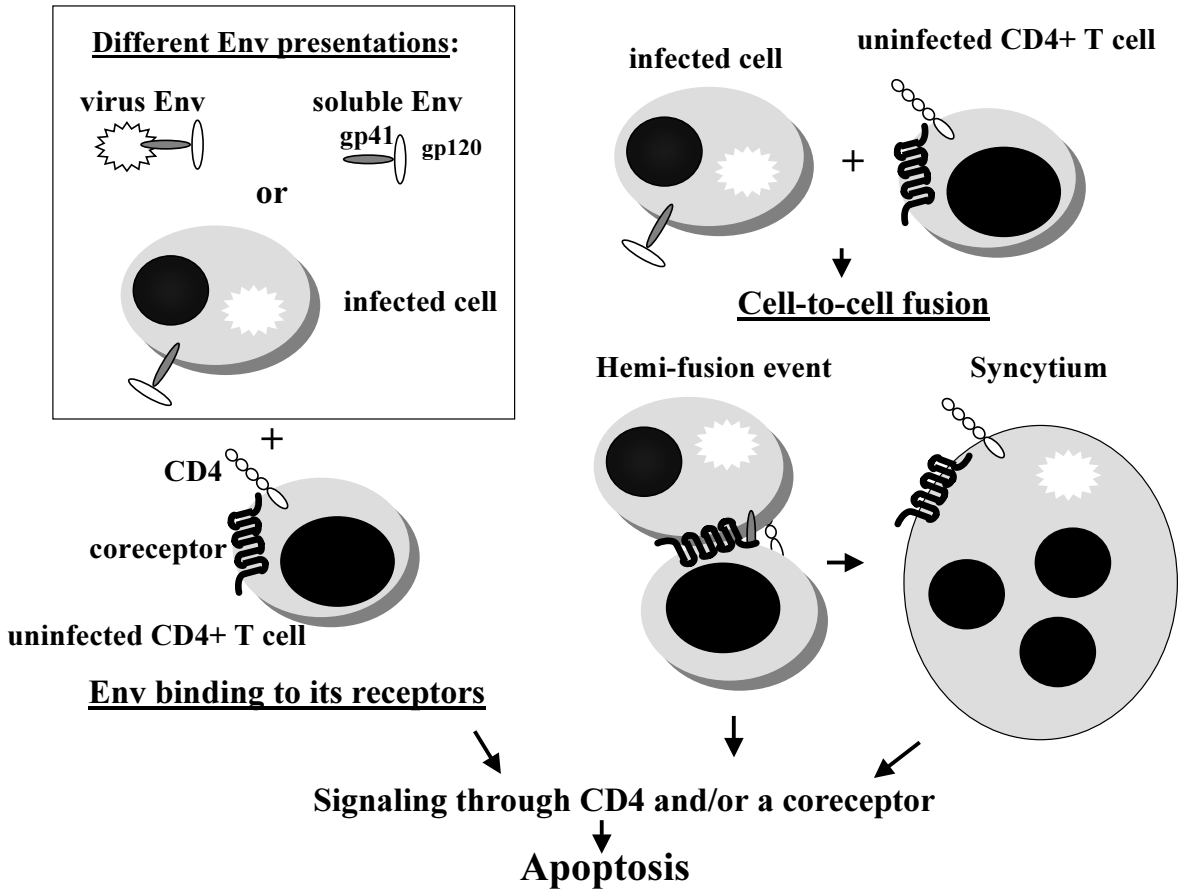

Figure 1
Schematic diagram of Env-induced CD4+ T cell apoptosis

may also be different. Indeed, soluble Env, secreted from infected cells, Env expressed on virions or at the cell surface of infected cells, are able to induce apoptosis of uninfected T cells. Soluble Env resulting from shedding of the surfaces of viral particles or infected cells can be considered as a ligand of CD4 and coreceptor molecules and acts as a signaling molecule through these receptors. Noninfectious virions provide a powerful tool to dissect mechanisms activated through HIV particles without viral replication. Finally, infected cells expressing Env at their surface can interact with uninfected T cells presenting CD4 and coreceptor molecules and can elicit several events, (i) an apoptotic signaling through one of these receptors, (ii) an hemifusion event leading to target cell death or (iii) syncytium formation (Fig. 1).

It is worth noting that apoptosis is seen in both CD4+ and CD8+ lymphocytes from peripheral blood [10,11,38,39] and correlates with disease progression.

Furthermore, Env of HIV-2 (gp105/gp36) generally binds to the same receptors as HIV-1, even if several primary HIV-2 strains can infect CCR5+ or CXCR4+ cell lines without the requirement of CD4 interaction in vitro [40]. However, T cell decline and clinical progression to AIDS occur at a slower rate [41,42]. HIV-2 Env has much more

marked inhibitory properties on TCR-mediated lymphoproliferative responses that HIV-1 Env does, without over-inducing apoptosis, explaining the model of "attenuated disease" [43].

Env-mediated apoptosis of bystander CD4+ T cells

Apoptosis of single cells

Signaling through CD4

The CD4 molecule is a transmembrane glycoprotein which is essential for the helper functions of mammalian T cells since it acts as a receptor for major histocompatibility complex (MHC) class II. In lymphocytes, apoptosis is an important physiological mechanism that regulates the capacity of immune responses to maintain tolerance to self-antigens. Two apoptotic pathways have been described as operative in T lymphocytes: activation-induced and spontaneous or passive cell death. AICD occurs as a result of repeated antigenic stimulation and is mediated by the interaction of the cell death receptor Fas and its ligand (Fas-L), expressed either on the same cells or on neighbouring activated T cells. The role of this Fas/FasL apoptotic pathway in HIV disease has been previously reviewed by D. Kaplan and S. Sieg [44]. The proportion of Fas-expressing T cells in patients increases with disease progression, and peripheral blood CD4+ T lymphocytes from HIV-infected individuals undergo apoptosis in response to stimulation through Fas antigen at a much higher frequency than from uninfected controls [45-53]. In the same way, high levels of Fas-susceptibility found in peripheral CD4+ T cells before HAART are significantly reduced after treatment, coinciding with a decrease in viral load and an increase in peripheral CD4+ T lymphocytes counts.

Cross-ligation of CD4 molecules prior to T cell receptor (TCR) stimulation triggers an up-regulation of Fas on purified T cells and expression of FasL upon antigen-, mitogen- and CD3 stimulation, rendering the T cells susceptible to Fas-mediated apoptosis [54]. It is quite likely that CD4+ uninfected T cells from HIV-infected patients are continuously undergoing CD4 cross-linking through interaction with virions or via Env expressed at the surface of infected cells. This phenomenon occurs essentially in lymphoid tissue which is a major reservoir of viral infection in HIV disease and a primary site of antigen presentation and lymphocyte activation. Indeed, apoptosis is predominantly seen in uninfected bystander cells present in HIV-1 infected individual lymph nodes [17]. When these CD4-cross-linked uninfected T cells encounter antigen-presenting cells in the local environment, they receive stimulatory signals through the TCR, leading to increased apoptosis [54,55]. This supports the concept that circulating T lymphocytes from HIV-infected patients are in an enhanced state of immune activation, which, in fact, may translate into the observed increased levels of ex vivo spontaneous T cell apoptosis, activation-induced T cell apoptosis and T cell susceptibility to Fas-dependent apoptosis [13,52,56-59].

Another mechanism for depletion of bystander T cells, observed in the lymph nodes of AIDS patients, was suggested when it was discovered that about one-half of the resting CD4+ lymphocytes that were pre-exposed to HIV (but not infected) were induced into apoptosis following signaling through receptors necessary for homing to lymph nodes [60].

However, the possible involvement of the Fas/FasL pathway in activation-induced cell death of T lymphocytes from HIV-1-infected persons has not produced a clear consensus [61-64]. These discrepancies may reflect different stages of disease, level of peripheral blood T cell activation or mode of T cell stimulation (e.g., superantigen or anti-CD3-induced T cell apoptosis).

In addition, tumor necrosis factor (TNF) [58,65,66] and TRAIL (DR4 and DR5) receptors [67,68] may also be involved in deregulated apoptosis during HIV-1 infection.

Besides the fact that CD4 is engaged in T cell activation, direct cross-linking of CD4/HIV gp120 complexes by antibodies can initiate T cell apoptosis using in vitro cellular experiments from transgenic mice expressing human CD4 at the surface of lymphocytes [69,70].

Identification, in 1996, of G-protein-coupled receptors as HIV coreceptors, has brought a higher level of complexity in signals that can be triggered after HIV-1 Env binding to its target cell. Thus, consequences of Env binding to T cells are multiple, engaging at the same time CD4 and a coreceptor molecule.

Signaling through the coreceptors

The coreceptors are chemokine receptors that belong to the large family of 7-transmembrane domain receptors coupled to heterotrimeric G_i proteins. The misappropriation of chemokine receptor function by HIV Env has important consequences on cell homeostasis. Compared to the natural chemokines, X4 and R5 HIV Env have overlapping but distinct binding sites on chemokine receptors [71,72]. They are thus able, after interaction with their respective receptors, to transduce some functional responses such as proliferation, differentiation, chemotaxis and proinflammatory cytokine secretion [73,74] in addition to apoptosis. However, several studies indicate that cell signaling is not needed for HIV-1 Env fusion with the plasma membrane of the target cell [75-78].

The main difference between HIV-1 R5 and X4 strains resides in the Env protein sequence, which leads to CCR5 or CXCR4 coreceptor usage, respectively, independently from their common interaction with CD4. CXCR4 and CCR5 stimulation by the corresponding HIV-1 Envs induce several common signaling pathways such as phosphorylation of the tyrosine kinase Pyk2 [79], increased intracellular Ca^{2+} [73,80] and c-Jun N-terminal kinase (JNK) activation [81,82] but differ in their ability to activate the extracellular signal-regulated kinase (ERK) pathway [83]. In the same way, HIV-1 R5 and X4 strains induce differential mechanisms in mediating uninfected T cell death, which could explain the physiopathology of HIV-1 infection.

There is now evidence that Env, either in a soluble or membrane-bound form, mediates death of uninfected bystander CD4+ T cells [17,22,66,84,85]. Death of uninfected T cells has been shown to occur in lymphoid tissue from HIV-infected patients when contacted by an HIV-infected cell [17]. Soluble gp120 produced within the infected lymphoid tissue could also directly kill or sensitize T cell to subsequent death. Indeed, gp120 at 120–960 ng/mL may exist in lymph nodes of HIV-infected individuals [86-88] and 500 ng/mL of soluble gp120 is sufficient to mediate significant T cell death [89].

CXCR4

CXCR4 is a receptor for the chemokine stromal cell-derived factor-1 (SDF-1) [28,90] and is widely expressed in various hematopoietic cells. SDF-1/CXCR4 regulates pre-B-cell proliferation, myeolopoiesis, cerebellar development and cardiogenesis [91-93]. Furthermore, upregulation of CXCR4 that occurs in T cells from lymphoid tissue in HIV-infected patients may favor X4 Env/CXCR4 interactions.

The first experiments indicating that Env-induced death program could be independent of CD4 signaling, and thus coreceptor dependent, were done with human T cell lines in which the cytoplasmic part of CD4 was missing. Indeed, infectious X4 isolates of HIV-1 induce apoptosis of different T cell lines lacking the CD4 cytoplasmic domain and thus unable to transduce a signal through CD4 [94,95]. In parallel, L. Moutouh and collaborators demonstrated that $p56^{lck}$ signaling is dispensable for HIV-1-mediated apoptosis [63]. Similarly, the capability of SDF-1 and CXCR4 antagonists to block Env-induced cell death underlines the role of CXCR4 in this death signaling [61,96,97].

As early as 1998, a consensus has emerged that CXCR4 triggers a death signal in CD4+ T cells after interaction with Env, independently of G-protein signaling [61,98-102]. Using a human embryonic kidney 293(HEK.293) cell line stably cotransfected with CXCR4 and a mutated form of CD4 lacking its cytoplasmic domain, T cell lines and primary umbilical cord blood CD4+ T lymphocytes, we demonstrated that the apoptotic signaling induced in these target cells after contact with cells expressing X4 Env is specifically triggered by CXCR4, dependent of the mitochondrial intrinsic pathway but does not involve activation of the stress- and apoptosis-related mitogen-activated protein kinases (MAPKs) p38 and JNK [96,98,103]. Notably, binding of HIV-1 Env to CXCR4 induces mitochondrial transmembrane depolarization, cytochrome c release from the mitochondria to the cytosol and activation of the caspases-9 and -3. Furthermore, Env-induced apoptosis through CXCR4 is Fas independent [61,64,100,101,103,104]. However, there is some controversy as to the conformation of gp120 needed to induce cell death. In a majority of cellular models, Env has to be expressed on cells to trigger T cell apoptosis but recombinant gp120 alone or cross-linked with anti-gp120 antibodies was also shown to trigger CD4+ T cell death [61,105].

Direct implication of caspases in Env-mediated cell death of CXCR4+ cells is still a subject of debate. Berndt and collaborators described no involvement of known caspases in cross-linked recombinant gp120- and anti-CXCR4-induced apoptosis of human peripheral blood lymphocytes [61] and Vlahakis and collaborators reported that CXCR4-dependent cell death is caspase independent on the basis of caspases inhibitors [89]. However, caspase-3 is cleaved in primary T lymphocytes [103,105] and endothelial cells [106,107] following binding of HIV-1 Env.

The manner in which Env is presented, the cell population analyzed and the nature of the receptor directly involved in this cell death could be responsible for the discrepancies between these reports. However, multiple experiments, using different cell lines, human primary T cells and human lymphoid cultures ex vivo [108] support the view that Env interaction with CXCR4 on bystander CD4+ T cells triggers apoptosis. These results are consistent with observations made from AIDS patients and explain the high CD4+ T cell depletion that occurs after X4 isolate emergence.

CCR5

Only about 15 to 30% of the CD4+ T lymphocytes express detectable levels of CCR5 on the cell surface in contrast to CXCR4 which is expressed on nearly all of these T cells [109,110]. This explains, at least in part, that X4 strains exert a profound cytopathic effect on a much wider range of target cells via their particular capacity to induce bystander apoptosis. However, even if bystander apoptosis is an important characteristic of X4 HIV-1 strains,

mediated by binding of X4 Env to CXCR4 on CD4+ T lymphocytes, R5 Env binding to CCR5 expressed on uninfected resting primary T cells and human vascular endothelial cells has also been shown to trigger apoptosis [111,112]. Stimulation of CCR5 by R5 Env or anti-CCR5 antibody leads to FasL up-regulation, inducing caspase-8 activation in resting primary CD4+ T cells [111]. Yao and collaborators also demonstrated that R5 and X4 Env expressed on simian HIV virus-like particles induce apoptosis through their respective coreceptors expressed on human osteosarcoma (HOS) cells [113]. However, apoptosis of bystander CD4+ T cells observed in human lymphoid tissues ex vivo after infection with R5 viruses was shown to be only a minor mechanism [108].

Apoptosis after cell-to-cell fusion

HIV-1 Env (gp120/gp41) expressed at the surface of infected cells drives cell-to-cell fusion with adjacent uninfected CD4+ T cells [21,22,114,115], which results in formation of multinucleated syncytia [114,116]. Hemifusion events as well as syncytium formation have been shown to trigger cell apoptosis and thus to participate to the global loss of CD4+ T cells during AIDS.

Role of gp41-mediated hemifusion-like events

Destruction of primary CD4+ T cells can occur by cell-cell interaction in HIV-1 infection in vitro [117]. Furthermore, agents interfering with cell-to-cell fusion, such as the peptide T20 which abolishes a correct gp41 folding after gp120 binding to its receptor molecules and insertion of the gp41 fusion peptide into cell membrane [118], prevent cell death and T cell depletion [117]. Blanco and collaborators recently demonstrated that Env-induced cell death of single CD4+ T cells requires both gp120 and gp41 functions [119].

These data indicate that besides the role of gp120, gp41 could actively participate in the molecular events leading to Env-induced cell death.

Apoptosis of syncytia

Syncytia are not stable over an extended time-period [114,116] and are not detectable in infected individuals except in brain [120] and tonsils [121] but can amplify the global apoptotic signaling [122].

Syncytium formation leads to apoptosis mediated by the intrinsic mitochondrial pathway [123] and involves a precise sequence of events: (i) activation of the mammalian target of rapamycin mTOR, (ii) mammalian target of rapamycin (mTOR)-mediated phosphorylation of p53 on serine 15, (iii) p53-dependent upregulation of Bax expression, (iv) Bax-mediated permeabilization of mitochondrial membranes with reduction of the mitochondrial transmembrane potential and release of proapoptotic mitochondrial proteins such as apoptosis-inducing factor AIF and cytochrome c and (v) activation of caspase-3 and nuclear chromatin condensation [124,125].

Env-mediated apoptosis of CD8+ T lymphocytes

HIV infection is characterized by a persistent immune activation and a concomitant decline in both CD4+ and CD8+ naïve lymphocytes in the early stages of the disease [126]. In the later stages, both CD4+ and CD8+ memory T cells decline at similar rates. Notably, apoptosis is seen in peripheral blood CD4+ and CD8+ T lymphocytes of HIV-infected patients [10,11,38,39] as well as in CD4+ and CD8+ T cells present in lymph nodes of HIV-infected persons [127]. The degree of apoptosis observed in these cells is significantly higher in infected patients than in uninfected individuals [11] and CD8+ as well as CD4+ peripheral blood T cells from HIV-infected persons are susceptible to Fas- and activation-induced apoptosis [58]. Furthermore, this cell death correlates with disease progression and severity [49,52]. These data suggest that survival and differentiation of HIV-specific CD8+ T cells may be compromised by Fas apoptosis induced by FasL-expressing HIV-infected cells [128]. In addition to direct CD8+ T cell death mediated by the death receptor Fas, CD4 cross-linking by Env interaction in uninfected CD4+ lymphocytes prior to TCR stimulation leads to the generation of FasL-expressing CD4+ T cells that can trigger CD8+ T cell apoptosis [54].

In addition to Fas sensitivity, CD8+ T lymphocytes from HIV-infected patients are susceptible to proapoptotic signaling through both tumor necrosis factor receptor TNFRI and TNFRII, and this is associated with expression of caspase-8 and -3 and lack of physiological protection by Bcl-2 [67]. IL-15 induces both Bcl-2 and Bcl-xL expression in HIV-specific and total CD8+ T cells, and this phenomenon is correlated with apoptosis inhibition and increased cell survival. Thus, reduced Bcl-2 and Bcl-xL expression found in HIV-specific CD8+ T cells may play an important role in the increased sensitivity to apoptosis [129]. Furthermore, Vlahakis and collaborators demonstrated that CXCR4 activation by X4 Env induces a caspase-independent death of uninfected CD8+ T lymphocytes [89]. One mechanism by which CD8+ T cells undergo apoptosis in HIV disease is dependent upon macrophages [130]. The data indicate that ligation of CXCR4 increased membrane bound TNF on macrophages and TNFRII on CD8+ T cells, and that interaction between TNF and TNFRII triggers CD8+ lymphocyte apoptosis. HIV-1 X4 Env expressed at the surface of conformationally authentic noninfectious virions is also able to trigger apoptosis of CD8+ T lymphocytes [131]. Inhibition of CD4+ and CD8+ T cell apoptosis was observed in HIV patients undergoing potent antiretroviral therapy. Recently, Grelli and collaborators demonstrated that inhibition of apoptotic CD8+ T

cells rather than CD4+ T cells are correlated with CD4+ T cell increase during therapy [132], underlying the role of CD8+ T cell apoptosis in disease progression.

CD8+ T cells are known to be essential in controlling HIV infection. Apoptosis of either HIV-specific or total CD8+ T lymphocytes can thus contribute to impair the global immune response against HIV. In addition to HAART, IL-15 could be used as an immunorestorative agent to boost immunity against HIV and to inhibit HIV-induced apoptosis of T cells in HIV patients [133-135].

Complications of HIV infection due to Env-induced apoptosis

Besides pathological complications due to opportunistic pathogens, several disorders are direct consequences of HIV infection. Here are described complications that involve Env-mediated apoptosis. Indeed, different in vivo cell types are able to express a coreceptor and/or CD4 and are thus susceptible to Env-mediated apoptosis.

HIV-1-mediated neurotoxicity

HIV-1 Env has been proposed as the major etiologic agent for neuronal damage, mediating both direct and indirect effects on the central nervous system (CNS). Indeed, gp120 has been revealed in the central nervous system of AIDS patients [136] and in the brain of patients with HIV encephalitis and dementia [137]. There is also evidence that gp120 can cross the blood-brain barrier [138]. Furthermore, chemokine receptors have been identified in macrophages/microglia, astrocytes and neurones [139].

HIV-1-associated dementia (HAD) is a common complication of the viral infection late stages affecting nearly 20% and 50% of infected adults and children respectively. In addition to indirect neuronal injury triggered by neurotoxic molecules released from HIV-infected or -activated macrophages and microglia [140-144], HIV Env directly triggers apoptosis of both primary rodent and human neurons [81,145-150] and astrocytes [151-153] and is probably a cause of CNS injury in AIDS [81,154-158] even if neuronal cells are not productively infected by HIV-1. A direct role of HIV-1 coreceptors is also possible since association between HIV-1 gp120 and CCR5 or CXCR4 expressed in human neurons is CD4 independent [102,159,160].

Two major features now emerge from AIDS neurotoxicity studies. First, chemokine receptors are involved in apoptosis of neuronal cells, and second, HIV-1 Env is the major determinant of the HIV-dependent neurodegenerative mechanisms [150,154,161]. Understanding the precise role of CXCR4 and other chemokine receptors in HIV-1 neuropathogenesis will help to advance the development of new therapeutic strategies for the prevention and treatment of neurologic disorders associated with HIV-1 infection.

Other complications of HIV-1 infection

HIV-associated cardiomyopathy

Annual incidence of HIV-associated cardiomyopathy is estimated to be 15.9 cases per 1,000 asymptomatic Italian HIV-1-positive patients [162] and leads to a high cardiovascular morbidity and mortality in young and middle-aged adults. Infected hearts show a strong expression of gp120 without productive infection of cardiomyocytes. Twu and collaborators demonstrated in vitro that gp120 induces cardiomyocyte apoptosis by a mitochondrion-controlled pathway and in vivo that death receptor ligands from macrophages are a major cause of apoptosis and that the apoptotic signaling may occur through chemokine receptors [163].

HIV-associated nephropathy

HIV-associated nephropathy (HIVAN) is accompanied by tubular cell proliferation, apoptosis and microcystic dilatation. Through murine and human studies, it is now clear that HIVAN is caused by a direct effect of HIV-1 infection of renal cells and that the virus actively replicates in renal cells [164,165]. In particular, gp120 induces apoptosis of tubular epithelial cell through p38-MAPK phosphorylation [166]. Furthermore, dysfunction and/or damage of mesangial cells that are susceptible to HIV/SIV strains using GPR1 as coreceptor is thought to be involved in the development of HIV-associated HIVAN [34]. Its remains to investigate whether the interaction of these cells with specific HIV-1 strains through GPR1 plays a significant role in the development of HIVAN.

HIV-mediated hepatocyte death

Liver dysfunction causes significant morbidity among HIV-infected individuals. End-stage liver disease is the most frequent cause of death among HIV-infected hospitalized patients [167]. Although the cause of liver injury in HIV-infected individuals is multifactorial, Vlahakis and collaborators established that HIV-1 X4 Env and the entire virion induce apoptosis of human hepatocytes via CXCR4 [168].

Conclusion

Apoptosis of uninfected CD4+ T lymphocytes is closely linked to activation of the immune system and change in coreceptor usage. One hypothesis might be that, at the first stages of the disease, Env binds to the CD4 and CCR5 molecules, triggering chronic and continuous activation of the immune system that induces a Fas-dependent CD4+ T cell apoptosis upon mobilization of the T cell receptor and antigen. During the progression toward AIDS, X4 strains emerge and their higher pathogenicity may derive from the fact that CXCR4 is able to activate

either directly or indirectly a Fas-independent apoptotic signaling pathway, accelerating the immune destruction observed at late stages of AIDS. Furthermore, CXCR4 is widely expressed on immune cells, still increasing the cytopathogenicity of X4 strains. Treatment of HIV-infected patients with protease inhibitors leads to a decrease in CD4+ T cell apoptosis, inducing an increase in CD4+ T cell number and a decrease in viral loads, resulting in clinical improvement. Therapies that block or decrease bystander death could thus have significant clinical benefit. Several interleukins, IL-2, IL-7 and IL-15 could also be used for therapeutic intervention. IL-15, in particular, because of its anti-apoptotic properties and its role in enhancing survival and function of CD8+ T cells, can be an immunorestorative agent in HIV treatment. Finally, as X4 strains are the most pathogenic ones, inducing massive apoptosis of bystander T cells, CXCR4 antagonists would improve clinical AIDS chemotherapy in suppressing Env binding to CXCR4 and X4 HIV-1 entry into target cells. In the same way, Env-binding agents such as plant lectins and glycopeptide antibiotics seem also worthy of further preclinical development. Novel approaches focusing on apoptosis of bystander T cells are required to maintain the homeostatic states of the immune cell populations.

List of abbreviations

AICD, activation-induced cell death; AIF, apoptosis-inducing factor; CNS, central nervous system; Env, HIV envelope glycoproteins; ERK, extracellular signal-regulated kinase; HAART, highly active antiretroviral therapy; HAD, HIV-associated dementia; HEK, human embryonic kidney; HIVAN, HIV-associated nephropathy; HOS, human osteosarcoma; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; SDF-1, stromal cell-derived factor-1; TCR, T cell receptor; TNF, tumor necrosis factor; mTOR, mammalian target of rapamycin.

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