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Review

Apoptosis in SIV infection

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Abstract

Pathogenic human immunodeficiency virus (HIV)/Simian immunodeficiency virus (SIV) infection is associated with increased T-cell apoptosis. In marked contrast to HIV infection in humans and SIV infection in macaques, the SIV infection of natural host species is typically nonpathogenic despite high levels of viral replication. In these nonpathogenic primate models, no observation of T-cell apoptosis was observed, suggesting that either SIV is less capable of directly inducing apoptosis in natural hosts (likely as a result of coevolution/coadaptation with the host) or, alternatively, that the indirect T-cell apoptosis plays the key role in determining the HIV-associated T-cell depletion and progression to acquired immune deficiency syndrome (AIDS). Understanding the molecular and cellular mechanisms responsible for the disease-free equilibrium in natural hosts for SIV infection, including those determining the absence of high levels of T-cell apoptosis, is likely to provide important clues regarding the mechanisms of AIDS pathogenesis in humans.
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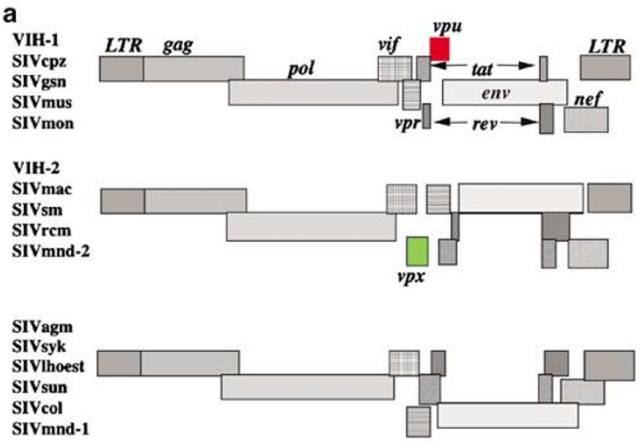
Abbreviations: HIV, human immunodeficiency virus; SIV, Simian immunodeficiency virus; SHIV, Simian-human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; NHPs, African non-human primates; SMs, sooty mangabeys; AGMs, African green monkeys; LNs, lymph nodes; FDC, follicular dendritic cells; HAART, highly active antiretroviral therapy; DISC, death-inducing signaling complex; zVAD-fmk, z-Val-Ala-Asp-fmk.

Non-human Primate (NHP) Models for HIV Infection and AIDS

The family of CD4+ T-lymphotropic primate lentiviruses is comprised of two human viruses (human immunodeficiency virus type 1 (HIV-1) and 2 (HIV-2)) and as many as 27 distinct simian immunodeficiency viruses (SIVs) found naturally in African non-human primates (NHPs)[1] (Figure 1a). The pathogenesis of HIV-1 infection is a complex, multifactorial process that depends on multiple, dynamic viral and host factors. The depletion of CD4+ T cells is a major determinant of pathogenicity in HIV-1 infection. In HIV-infected patients, CD4 T-cell depletion is associated with high viral turnover,[2] chronic generalized immune system activation,[3–5] and progressive loss of T-cell-mediated immunity.[6]

Several studies have found that HIV originally resulted from multiple episodes of zoonotic transmission to humans of CD4-tropic lentiviruses circulating in NHPs.[1] SIVs were shown to cluster in at least six major, approximately equidistant lineages.[7,8] HIV-1 and HIV-2 belong to two of these clusters and emerged most likely following transmissions of, respectively, SIVcpz from chimpanzees and SIVsm from sooty mangabeys (SMs).[9–13] The remaining clusters are formed by SIVs isolated from African green monkeys (AGMs), Syke's monkeys, l'hoest monkeys, and colobus monkeys.[7,14–21] AGMs (*Cercopithecus aethiops*), due to their numbers and wide geographical distribution in sub-Saharan Africa, represent the largest single reservoir of SIV (SIVagm), as upwards of 50% of wild monkeys are infected with the virus. The phylogeny of many SIVs resembles that of their host species, suggesting a coevolution.[11,14,22] In contrast to these, some viruses (SIVrcm, SIVagm.sab, SIVmnd-2, and SIVdrl) cluster in different lineages according to the genomic region analyzed.[23–26] These viruses most likely result from recombination events in monkeys dually infected by SIVs of two distinct lineages.

Natural hosts for SIV generally do not show any signs of acquired immune deficiency syndrome (AIDS) despite chronic sustained levels of viral replication.[27–32] Indeed, the development of AIDS has been observed in only one SM and in one mandrill, after a 18-year-incubation, exceeding the normal lifespan of wild primates.[33,34] Similar to humans and macaques, naturally or experimentally infected SMs, AGMs, and mandrills show viremia levels which are highly variable among the individual monkeys, but in many of them the plasmatic viral RNA levels are persistently as high or even higher than those known with progression in humans.[27–29,31,32,34,35] Studies of two subspecies (sabaeus and vervet) of naturally SIV-infected AGMs analyzed during the chronic phase shows signs of viral replication in the same tissues as during pathogenic infections, including gut and thymus.[29,35,36] Both T CD4+ lymphocytes and macrophages are infected.[29] In two naturally SIV-infected SMs, the number of virus replicating cells in lymph nodes (LNs) was similar to what has been observed in macaques and humans progressing to AIDS.[28] Lower numbers of viral DNA and RNA copy numbers were however observed in chronically infected AGMs as compared to pathogenic SIVmac and HIV infections.[31,37] Both SIVagm and SIVsm infection are



b

Hosts	Viruses	VL	AIDS	Apoptosis	
				CD4	CD8
Human	HIV-1	+	+	+	+
Chimpanzee	HIV-1	+/-	-	-	+/-
Macaque	SIVmac	+	+	+	+
Macaque	SIVΔnef	+/-	-	-	-
Macaque	SIVsm	+	+	?	?
Sooty mangabey	SIVsm	+	-	-	-
African green monkey	SIVagm	+	-	-	+/-
Mandrill	SIVmnd	+	-	?	?

Figure 1 Human and non-human primate (NHP) models. (**a**) The family of lymphotropic primate lentiviruses comprise large numbers of human (HIV) and simian immunodeficiency viruses (SIVs) found naturally in NHPs. They present three distinct genomic organization of which two are identical to HIV-1 and HIV-2. (**b**) The depletion of $CD4^+$ T cells is a major determinant of pathogenicity. Experimental primate models reveal a relationship between CD4 T-cell apoptosis and further progression towards AIDS

characterized by a low or absent viral trapping by follicular dendritic cells (FDC) in LN germinal centers. Importantly, accidental or experimental transmission of SIV from natural hosts, that is, SMs and AGMs, to Asian non-natural NHP host species, such as pigtailed and rhesus macaques, is followed by development of AIDS.[38,39] Similarly, SIVlhoest, which is genetically close to SIVmnd-1 and is also associated with asymptomatic infection in its natural host, appears to induce AIDS when inoculated in macaques.[40] Collectively, these studies demonstrate that the absence of major CD4 T-cell depletion and AIDS in natural hosts for SIV infection is not due to intrinsic lack of viral pathogenicity, but that host-specific factors play a crucial role in protection from disease progression. In addition, these studies provide evidence that the nonpathogenic nature of SIV infection in the natural host is likely to be not related to a more effective host control over viral replication. However, the exact molecular mechanisms underlying the lack of any AIDS-related illness in natural hosts for SIV infection are still unknown.

T-cell Apoptosis and AIDS

T-cell apoptosis (Figure 2) may be one of the mechanisms that is responsible for T-cell depletion during HIV and SIV infections. Several studies have found that abnormal levels of apoptosis occur both *in vitro*[41–51] and *in vivo*[52,53] in $CD4^+$ and $CD8^+$ T cells from HIV-1-infected persons. Importantly, the majority of T cells undergoing apoptosis in HIV-infected patients are not infected by the virus;[52,53] this observation led to the definition of 'bystander' apoptosis when referring to apoptosis that is not occurring as a direct cytopathic effect of HIV. Clinical studies have revealed that HIV-1 and HIV-2 differ in their natural course of infection. Thus, HIV-2 is characterized by higher CD4 counts, low level of viremia, and low transmission rate.[54] It has been reported that the low pathogenicity of HIV-2 is associated with a lower immune activation and a lesser degree of CD4 T-cell apoptosis.[55] Importantly, the magnitude of $CD4^+$ T-cell apoptosis observed in HIV-infected individuals correlates well with the stage of HIV disease.[56–61] In addition, changes in the levels of T-cell apoptosis after highly active antiretroviral therapy (HAART) predict the immunological response (i.e., increase in CD4 T-cell count), thus confirming the link between disease progression and apoptosis.[62–64] Taken together, these observations indicate that the increased susceptibility to apoptosis of T lymphocytes from HIV-infected individuals is a marker of HIV disease progression and support the hypothesis that the chronic immune system activation that

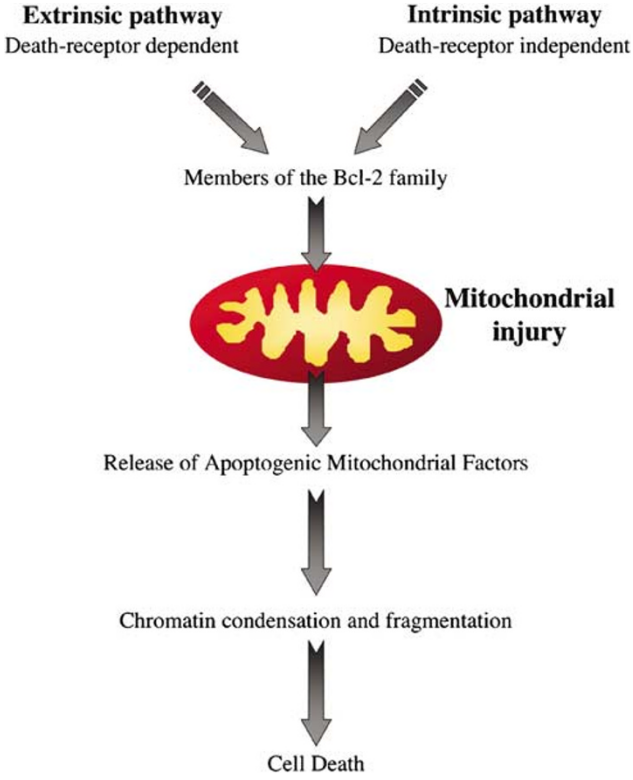


Figure 2 Overview of apoptosis pathway. Ligation of the death receptors ('extrinsic pathway') leads to the activation of the proapoptotic member of the Bcl-2 family, Bid, generating a truncated Bid (tBid). tBid tranlocates to the mitochondria where it acts with the proapoptotic Bax and Bak. The 'intrinsic pathway' is induced after apoptotic insults (for drugs, UV, growth factor deprival, etc.) leading to Bax and Bak activation and in turn induced mitochondrial membrane permeabilization ($\Delta\Psi_m$ loss). Mitochondria insult is manifested by the release of apoptogenic factors into the cytosol leading to chromatin condensation and fragmentation and cell death (for a review, see Petit *et al.*[190])

follows HIV infection could be one of the mechanism responsible for this cell death process.[27,30,52]

The primary acute phase of human (HIV) and simian (SIV) immunodeficiency virus infection is characterized by an early burst in viral replication, which results in an exponential increase in plasma viral load and the dissemination and seeding of the virus in all the peripheral lymphoid organs.[65–69] Following the induction of the host humoral and cellular immune response to the virus, a steady-state plasma viral load level is reached at the end of this primary phase, around 2–6 months after infection in macaques and in humans; the level of set-point viral replication predicts the progression towards disease, ranging from rapid development of AIDS to long-term slow progressive infection.[70–73] Recent findings support a dynamic model of pathogenesis in which the extent of apoptosis induced during the primary phase of SIV infection is predictive of the subsequent rapid or slow progression towards AIDS.[74] Furthermore, the extent of apoptosis in peripheral lymph nodes is greater in primates infected with a pathogenic SIV strain than in those infected with an attenuated, nef-deleted SIV.[75] Another study identified an early induction of apoptosis in thymic T-cell precursors (followed by a subsequent increase in cell cycling) in macaques infected with pathogenic SIV; this effect was lacking in the same macaque species infected with the nef-deleted SIV.[76] The fact that apoptosis in the thymus as well as in the LNs of macaques infected with pathogenic SIV occurs in both infected and uninfected T cells indicates again that mechanisms other than the direct cytopathic effect of HIV are involved in this disease process.[53,77]

Furthermore, studies performed in pathogenic and non-pathogenic primate models of HIV or SIV infection during the chronic asymptomatic phase have identified a correlation between the induction of enhanced *in vitro* T-cell apoptosis and the *in vivo* pathogenic nature of the retroviral infection[27,44,51,78–84] (Figure 1b). Thus, enhanced levels of apoptosis in $CD4^+$ T cells were observed in HIV-1-infected human individuals, rhesus macaques infected with a pathogenic strain of SIVmac, and chimpanzees infected with a pathogenic strain of SIVcpz leading to AIDS,[78,85] while enhanced CD8 T-cell apoptosis was observed in both pathogenic and nonpathogenic primate models. In contrast, no increased propensity of either CD4+ or CD8+ T-cell *in vitro* apoptosis and normal levels of T-cell apoptosis in the T-cell-dependent areas of the LN were observed in either naturally or experimentally SIV-infected SMs.[27] Altogether, these reports suggest that the capacity to induce apoptosis during primary SIV infection is a feature that does not depend solely on the genetic makeup of the virus itself, but is related to specific features of the host–virus interaction; these features will then play a key role in determining the potential for a given virus to induce AIDS in a specific host species.

Extrinsic and Intrinsic Programmed Cell Death Pathways and AIDS

Activation-induced cell death

The increased level of T-cell apoptosis observed in HIV-infected human individuals is associated with enhanced expression of the CD95/Fas receptor and its ligand (CD95L) (Figure 3a), and increased sensitivity of T cells to apoptosis mediated by CD95/Fas ligation using either agonistic CD95 monoclonal antibodies or recombinant CD95L.[48–50,86–94] Other members of the TNF-receptor ligand family (TRAIL, TNF-α) have also been implicated in the increased T-cell apoptosis seen in HIV-1-infected individuals.[95–100] Similarly, T cells from macaques infected with a pathogenic strain (SIVmac251) are more prone to undergo apoptosis following ligation of CD95/Fas than the other death receptors.[101] Moreover, in HIV-infected individuals and SIV-infected macaques, increased CD95/Fas sensitivity of CD8+ T cells did not correlate with plasma viral load.[102]

Ligation of CD95/Fas by its counterpart CD95L induces the aggregation of several proteins from the death-inducing signaling complex (DISC) leading to the activation of the initiator caspase-8.[103] Once activated, caspase-8 can trigger activation of downstream effector caspases (i.e., caspases 3, 6, and 7), which can be modulated by the caspase inhibitor zVAD-fmk (z-Val-Ala-Asp-fmk). However, an alternative pathway, independent to the caspase-8, involving the kinase RIP and inducing a necrotic type of cell death that is not prevented by zVAD-fmk has also been reported.[104] In macaque as well as in humans, zVAD-fmk prevents CD95-mediated T-cell death, indicating that a RIP-dependent pathway of T-cell death is not a prominent factor under these circumstances.[49,101] Interestingly, the enhancement in CD95-mediated T-cell death in rhesus macaques is not associated with either an upregulation of caspase-3 and caspase-8 or a decrease of FLIP-L and FLIP-S. Similarly, Badley *et al*.[105] found that death of T cells from HIV-infected individuals was not associated with a change in the amount of FLIP. T-cell activation occurring in the course of immune responses has been shown to increase sensitivity to CD95-induced apoptosis. Antiretroviral therapy is followed by a significant decrease in CD95-induced, activation-induced, and spontaneous apoptosis in *ex vivo* cultured peripheral blood lymphocytes[60,96] which correlates with decreased immune activation.[105] Thus, effective viral suppression decreases immune activation and apoptosis, thereby contributing to immune reconstitution.

Death by neglect

Activated lymphocytes can undergo death by neglect after antigen and inflammatory cytokine stimulations and those dying cells are cleared at the end of an immune response. Cell death as a result of neglect occurs after the loss of mitochondrial homeostasis.[106] Spontaneous apoptosis during infection is associated with a loss of mitochondrial transmembrane potential ($\Delta\Psi_m$), suggesting that changes in mitochondrial permeability could be a central event in the regulation of T-cell death in HIV-infected individuals[107] (Figure 3b). Recently, we found that spontaneous T-cell death of pathogenic SIVmac251-infected macaques was not prevented by zVAD-fmk.[101] Thus, although caspase activation was occurring in the course of spontaneous apoptosis, it was dispensable for cell killing. Bim is required for efficient death-by-neglect, as Bim−/− mice have lymphoid hyperplasia and lymphocytes display partial resistance to death-by-neglect.[108,109] The cell death observed in multiple tissues of Bcl-2−/− mice also

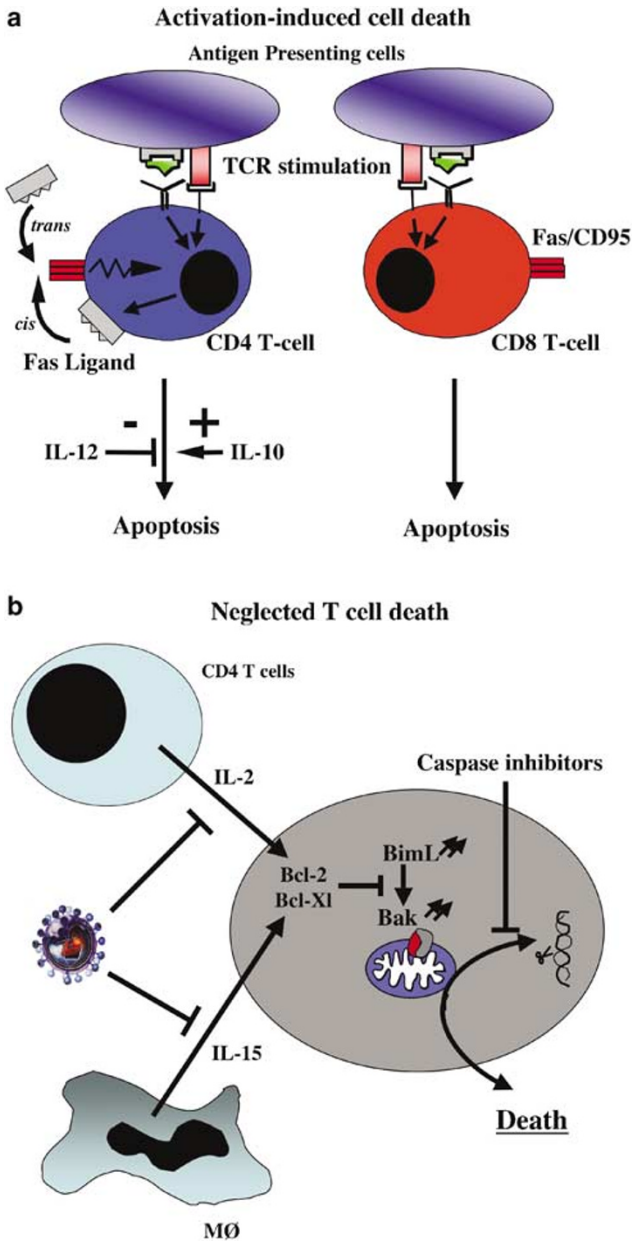


Figure 3 Indirect mechanisms that mediate programmed cell death or apoptosis during SIV infection. (**a**) Activation-induced cell death: Restimulation of activated T cells induces death at least in part through a CD95/Fas pathway in $CD4^+$ T cells. Cytokines exert either a positive (IL-12) or negative (IL-10) effect on CD4 T-cell apoptosis. (**b**) Neglected cell death: Members of the Bcl-2 family regulate cell death. Upregulation of Bim and Bak-mediated mitochondrial membrane potential lossleads to the release of apoptogenic factors from the mitochondria into the cytosol. In this form of cell death, caspase inhibitor (zVAD-fmk) prevented apoptotic phenotype (chromatin condensation and fragmentation) but did not prevent subsequent cell death. Cytokines, in contrast, prevented both the apoptotic phenotype and the cell death by preserving mitochondrial membrane potential

requires Bim activity, because Bim deficiency can rescue some aspects of Bcl-2-deficiency.[110] The role of Bax and Bak in the regulation of death-by-neglect and loss of mitochondrial homeostasis has also been demonstrated in mice deficient in these genes.[111] Despite their potent ability to promote cell death, individual Bax and Bak knockout mice show remarkably little changes in the immune phenotype. Bax-deficient mice have mild lymphoid hyperplasia and Bak-deficient mice have no discernable phenotype.[112] In contrast, combined deficiency of both Bax and Bak results in the appearance of multiple phenotypes, in the immune system as well as in other organs.[113]

In chronic SIVmac251-infected macaques, T-cell apoptosis was not associated with an increase in Bax expression. Our findings do not, however, exclude the possibility that SIV infection favors the translocation of Bax from the cytosol to the mitochondria. This phenomenon has been reported in other cell types in response to growth factor deprivation.[114,115] In fact, a clear increase in the levels of two other proapoptotic proteins, Bak and BimL, was observed. The increased levels of these proteins in SIV-infected monkeys suggest that the upregulation of Bak and Bim may be involved in the loss of ψ_m loss and spontaneous T-cell death. However, the mechanisms involved in the changes of Bim and Bak expressions upon SIV infection remain unknown.

Preventive effect of cytokines

Consistent with the idea that costimulatory signals expressed by accessory cells play a key role in the control of T-cell survival and T-cell death during HIV infection, we and others have found that cytokines exert a preventive effect on T-cell death of HIV-infected individuals.[46,48,49,102,116–122] Thus, the addition of antibodies to IL-10 or the addition of IL-12 have a preventive effect on abnormal programmed cell death induction in response to *in vitro* stimulation in HIV-infected persons.[46,48] Moreover, we found that IL-12, which upregulates TH1 functions and prevents TCR-mediated CD4 T-cell apoptosis, also prevents Fas-mediated apoptosis of CD4 + T cells from HIV-infected persons.[48] In contrast, IL-10 prevents Fas-mediated apoptosis of CD8 + T cells from HIV-infected persons while having no preventive effect on CD4 T-cell death.[49] IL-2, a cytokine secreted by activated T cells and involved in cell-mediated immunity, had a preventive effect on Fas-mediated death of both CD4 + and CD8 + T cells. IL-15 can also inhibit T-cell apoptosis and enhances the function of HIV-specific CD8 + T cells. Similarly, IL-2 and IL-15 reduced the death rate of CD4 + and CD8 + T cells from SIVmac251-infected macaques following spontaneous apoptosis and induction by Fas ligation, while IL-10 only prevents CD8 T-cell death.[101] Therefore, the relative contribution other than overwhelming, direct-virus-mediated destruction might also be operative for the role of lymphoid microenvironment (IL-15, IL-12, and IL-10 are produced by macrophages). Thus, the destruction of such support, concomitant with the loss of CD4 + T cells, could impaire T-cell immune response.

Cell cycle dysregulation

Peripheral blood lymphocytes isolated from HIV-infected patients show complex perturbation of cell cycle control, consisting mainly of (i) increased intracellular levels of cyclin B1 with consequent inappropriate activation of the p34 cdc2 kinase, and (ii) abnormal nucleolar structure, as shown by

staining for the argyrophilic Nucleolar Organizing Regions (AgNOR) and the subcellular localization of nucleolin in confocal microscopy.[122–127] Importantly, the HIV-associated cell cycle dysregulation is exacerbated by *in vitro* treatment with mitogens and appears to be correlated with induction of T-cell apoptosis;[122,123,126] however, these cell cycle perturbations and apoptosis are reduced after exogenous administration of IL-2 *in vitro*.[122] In mitogen-activated lymphocytes from HIV-infected patients, the inappropriate activation of the cyclin B1/p34 cdc2 kinase complex is temporally associated with increased threonine phosphorylation, augmented fragmentation, and prominent extranuclear and cell surface localization of nucleolin.[127] It is of note that increased lymphocyte apoptosis is observed at the time of cell surface localization of nucleolin. Interestingly, a recent comparative study of cell cycle dysregulation in two models of pathogenic (i.e. rhesus macaques) and nonpathogenic (i.e., SMs) SIV infection has shown that a variety of cell cycle perturbations is observed in apoptosis-sensitive T cells derived from the peripheral blood and lymph nodes of macaques infected with SIV and progressing to AIDS, while normal cell cycle regulation is observed in apoptosis-resistant T cells from naturally SIV-infected SMs that do not progress to AIDS.[128] Taken together, these findings suggest that during pathogenic HIV and SIV infections (but not during nonpathogenic SIV infection of natural hosts), the presence of cell cycle dysregulation is involved in determining the abnormal susceptibility to apoptosis of T lymphocytes.[124]

The Interaction between the Envelope Glycoprotein and CD4/coreceptors is a Crucial Factor in the Pathogenesis of AIDS

HIV-1 infection can cause apoptosis via a variety of mechanisms, some of which rely directly on the intricate interaction between the virus and the host cells, and some of which act indirectly through activation of the host's inflammatory reaction and immune system activation. Despite intensive investigations, several important questions remain about the mechanisms through which HIV infection directly induces CD4 T-cell apoptosis. Although direct *in vitro* cytopathic effect of HIV and SIV strains is a well-established phenomenon, it is unclear what is the relevance of this direct cytopathic effect in the context of *in vivo* viral replication. Indeed, a very intriguing feature of nonpathogenic SIV infections, such as those in SMs, AGMs, and mandrills, is that CD4 T-cell depletion and AIDS do not arise despite *in vitro* cytopathicity and levels of viremia that can be as high or higher than those observed in the HIV-infected humans and SIV-infected macaques.[27–32] Thus, virus–host cell-specific interactions have been proposed as significant contributors to the development of aberrant signaling events and progressive immunodeficiency.[53]

The envelope glycoprotein complex (Env) appears to be one of the dominant apoptosis-inducing molecules encoded by the HIV-1 genome (Figure 4). The gp120 is present on the surface of infected T cells, on viral particles, or as a soluble protein[129,130] and can bind to and crosslink CD4. The interaction of the gp 120 with the CD4 molecule can prime CD4+ and CD8+ T cells for apoptosis,[95,131–135] and can promote cell-to-cell fusion leading to syncytia formation that can undergo apoptosis. This apoptosis is characterized by the translocation of Bax from the cytosol to mitochondria leading to the mitochondrial membrane permeabilization with loss of the $\Delta\Psi_m$), release of apoptogenic intermembrane proteins, in particular apoptosis-inducing factor and cytochrome *c*, caspase activation, and nuclear chromatin condensation.[136] *In vitro* studies have also identified a positive correlation between CD4 T-cell depletion and infection by syncytium inducing HIV-1[137,138] or SIV variants.[75,139–141] In addition, multinucleated giant cells, a pathological hallmark of AIDS encephalopathy are also found during SIV-encephalitis[142,143] and these cells revealed DNA fragmentation.[144] The HIV envelope protein has also been reported to cause apoptosis by binding to a chemokine coreceptor.[145–148] Several studies have indicated that macrophages are capable to trigger apoptosis of uninfected bystander $CD4^+$ and $CD8^+$ T cells.[149] Apoptosis involve the interaction between several death receptors (Fas, TNF-R, TRAIL-R) and their counterparts, their death ligands.[96,100,102,150–153] As tissue macrophages from HIV-infected individuals have been shown to harbor the virus and have the potential to act as reservoirs of virions, the role of macrophages in inducing T-cell death *in vivo* merit to be further explored in particular regarding pathogenic and nonpathogenic primate models of AIDS. Recently, it has been also observed that incubation of resting $CD4^+$ T cells from healthy donors with HIV, even in the presence of an inhibitor of the viral replication, is sufficient to prime $CD4^+$ T cells for apoptosis.[154,155] Therefore, as most of the HIV particles produced are noninfectious, the simple fixation and/or penetration of viruses, without integration, may be sufficient to prime T cells for apoptosis in quiescent cells.

Several studies have suggested a link between coreceptors usage and disease progression in HIV-infected individuals. The role of CCR5 in transmission has been highlighted by the protective effect of a 32-bp deletion in CCR5 (CCR5Δ32) that results in a truncated molecule that is not expressed at the cell surface.[156–158] Individuals homozygous for CCR5Δ32 are resistant to HIV-1 infection, whereas the disease progresses slowly in individuals who are heterozygous for this mutation.[159–161] Other studies have shown that the proportion of T cells expressing CCR5 differs greatly between individuals and increases chronically in HIV-infected individuals during disease progression,[162,163] and others have shown that the cell surface density of CCR5 correlates positively with disease progression.[164,165] It has been also reported that T-cell depletion in peripheral blood during primary infection was related to T cells expressing CCR5.[166–168] However, this latter observation remains controversial.[169]

Since HIV-1 does not replicate efficiently in non-human primate species, chimeric simian-human immunodeficiency viruses (SHIVs) have been created that can infect NHPs. SHIVs contain HIV-1-derived segments encoding the viral envelope glycoproteins and the Tat, Rev, and Vpu regulatory proteins in an SIV background.[170] A SHIV containing the envelope glycoproteins of a primary HIV-1 isolate, 89.6, replicated efficiently in rhesus monkeys but did not deplete $CD4^+$ T lymphocytes or induce disease in these animals.[171]

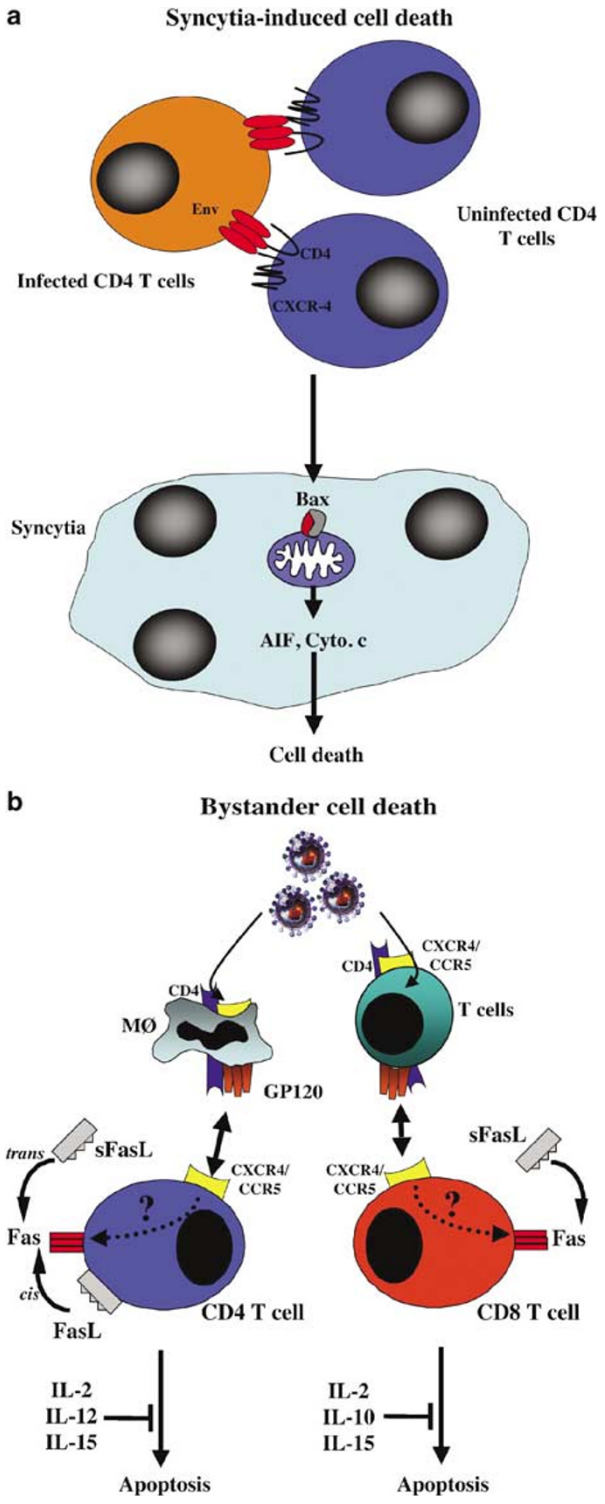


Figure 4 Coreceptor engagment-mediated T-cell apoptosis. (**a**) Syncytia induced cell death: Cell-to-cell fusion leads to syncytia formation that induces Bax upregulation and translocation to the mitochondria and subsequent release of apoptogenic factors and cell death. (**b**) Bystander cell death: The envelope glycoprotein interacts with the CD4 receptor at the cell membrane and subsequently with the coreceptor (CXCR4/CCR5). This interaction induces signal transduction leading to CD95/Fas sensitization. Fas ligand (FasL/CD95L), *in cis* or *in trans*, induces cell death. Environmental factors like cytokines prevent CD95-ligation-mediated cell death

Serial transfer of blood from SHIV-89.6-infected monkeys to naive monkeys generated a virus, SHIV-89.6P, that exhibited only modest increases in replication in infected monkeys compared with SHIV-89.6.[171] However, SHIV-89.6P caused rapid loss of $CD4^+$ T lymphocytes and, subsequently, AIDS-like illness in inoculated monkeys. The risk of developing AIDS-related disease in monkeys infected with SHIV-89.6P variants is strongly influenced by the degree of decline in $CD4^+$ T lymphocytes during the acute phase of infection.[172,173] Interestingly, infection of macaques with a pathogenic CCR5-specific enveloped virus ($SHIV_{SF162P}$) compared with infection with a pathogenic CXCR4-specific enveloped virus ($SHIV_{SF33A.2}$) demonstrated that despite comparable levels of viral replication, animals have distinct pathogenic outcomes. R5-tropic SHIV causes a dramatic loss of $CD4^+$ intestinal T cells and a gradual depletion in peripheral $CD4^+$ T cells, while infection with X4-tropic SHIV causes a profound loss in peripheral T cells that was not paralleled in the intestine.[174] Altogether, these reports suggest that the capacity to induce T-cell depletion in monkeys is a feature that depends at least in part on the genetic makeup of the envelope protein (X4 *versus* R5).

The fact that in natural host species, such as SMs and AGMs, SIV infection is nonpathogenic despite high viral loads and CCR5 usage raises an apparent paradox. Indeed, HIV-1, HIV-2, and both pathogenic and nonpathogenic SIVs use CCR5 in association with the CD4 molecule.[175–177] Moreover, $CD4^+$ T cells expressing CCR5 decreases at the peak of viral replication in both pathogenic and nonpathogenic SIV-infected monkeys.[166,178–180] Altogether, these observations may indicate that depletion of $CCR5^+CD4^+$ T cells is an important event but likely is not the only factor involved in AIDS pathogenesis. These observations also raise questions about the role of alternative chemokine receptors in the immunopathogenesis of AIDS. HIV uses CXCR4 as an alternative coreceptor, whereas SIVs use several chemokine orphan receptors such as BOB/GPR15 and Bonzo/STRL33/CXCR6 for efficient infection and replication *in vitro*.[181–183] Several lines of evidence indicated that *in vitro* BOB/GPR15 is an important SIV coreceptor[184–186] exhibiting greater activity than CCR5.[184] Several reports have found that nonpathogenic SIV strains such as SIVagm, SIVsun, SIVlhoest, and SIVrcm use Bonzo/STRL33/CXCR6 *in vitro* but less BOB/GPR15.[187–189] In contrast, pathogenic SIV strains (SIVmne, SIVmac) have been reported to use *in vitro* both CCR5 and BOB/GPR15 but not Bonzo/STLR33/CXCR6.[184–186] However, the *in vivo* role of BOB/GPR15 and Bonzo/STRL33/CXCR6 upon SIV infection is unknown and merit to be further explored.

Thus, studies in NHPs represent key approaches in deciphering the mechanisms leading to CD4 T-cell apoptosis which in turn favors further progression to AIDS.

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