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Review

Biochemical mechanisms of HIV induced T cell apoptosis

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Abbreviations: TNF, tumor necrosis factor; PBL, peripheral blood lymphocytes; FAK, focal adhesion kinase; HIV, human immunodeficiency virus

Introduction

Acute HIV infection is often accompanied by a flu-like illness and is associated with a high-titer viremia. This viremia is quickly controlled by the immune response, mediated predominantly by cytotoxic $CD8^+$ T lymphocytes (CTL), and, to some extent, by anti-HIV antibodies.[1,2] In most individuals, plasma viral load is maintained at low levels for years and the individual remains asymptomatic. However, during this 'clinical latency', plasma viral RNA is detectable and viral turnover is brisk, with large numbers of viruses produced and destroyed each day.[3] For reasons that are not yet clear, a break in this control leads to a significant decline in the number of $CD4^+$ T cells, and a rapid increase in viral load. It is after this break in immune control that the clinical symptoms of AIDS appear.[4]

Over the past several years, tremendous progress has been made in our understanding of the biology of HIV infection and the mechanisms of HIV replication and its control. However, the biochemical mechanism(s) of HIV-induced T cell death, including death of uninfected $CD4^+$ and $CD8^+$ T cells, are not well defined. Here, we discuss the role of viral and cellular proteins in HIV-infected and -uninfected T cell death. We also discuss mechanisms by which HIV may actually protect infected T cells from apoptosis. Current therapy to enhance immune system function and to decrease bystander T cell death (thereby, increasing $CD4^+$ T cell number) in HIV infected individuals will also be discussed.

Apoptosis of HIV infected T cells

In HIV infected individuals, viral load is a good predictor of disease progression: the higher the viral load, the faster the disease progression.[5,6] Some studies have also shown a correlation between the extent of apoptosis and disease progression,[7,8] suggesting that, *in vivo*, HIV kills the $CD4^+$ T cell that it infects. These observations argue that the virus is responsible for the depletion of $CD4^+$ T cells. Not addressed by these studies, however, are the mechanisms by which HIV depletes its host of $CD4^+$ T cells. In this section of the review, we will focus on mechanisms of T cell killing by HIV, although recent data suggest that failure of T cell regeneration also plays an important role in $CD4^+$ T cell loss in HIV disease.[9,10] In later sections of this review, we will discuss an alternate thesis, based on data suggesting that HIV and SIV have evolved mechanisms of blocking or delaying the cellular suicide program. Tables 1–3 summarize much of the published data on cell death in HIV disease. Interestingly, several HIV gene products have been reported to both induce and inhibit apoptosis, a recurring theme in the apoptosis literature.

One major pathway of T cell apoptosis is mediated through the tumor necrosis factor (TNF) family of receptors. The Fas receptor, in particular, has been extensively studied in recent years. Ligation of Fas by Fas ligand (FasL), present on the same or on a neighboring cell, can induce apoptosis.[11–13] Data are controversial regarding involvement of Fas in HIV-induced T cell death (reviewed in[14,15]).

Peripheral blood lymphocytes (PBL) from HIV^+ individuals have higher Fas expression,[16] and the proportion of Fas-expressing T cells increases with disease progression.[17] $CD4^+$ and $CD8^+$ T cells from HIV infected individuals are more susceptible to death induced by Fas ligation.[16,18] *In vitro* studies from our lab show that HIV infected T cells become more susceptible to Fas induced apoptosis.[19] In this study, we showed that the increase in sensitivity of HIV infected cells to Fas killing mapped to the HIV gene product, Vpu. Another viral protein, Tat, has been shown to sensitize T cells to TCR- and CD4-induced apoptosis by upregulation of FasL expression,[20] and to increase the sensitivity to Fas mediated apoptosis by upregulation of caspase-8.[21] Furthermore, Nef has been shown to increase surface expression of both Fas and FasL, and Nef's ability to interact with cellular kinases is required for this increased expression and for apoptosis.[22]

Viruses are notorious for interfering in 'internal matters' of the host cell in ways which may be beneficial to the virus, but which may ultimately induce cell death. Tat, one of the early HIV gene products, has been shown to induce reactive oxygen intermediates, caspase activation, and activation of NF-κB, AP-1, and JNK, in a $p56^{lck}$ dependent manner.[23] These data suggest that binding of HIV to CD4 activates $p56^{lck}$ and other downstream signaling events, which prepares the cell for HIV production (for example, by NF-κB activation), but which also induces apoptosis (for example, by caspase activation).

Table 1 HIV gene products implicated in the control of cell death. Means by which HIV may cause apoptosis or necrosis in highly infected cells

HIV gene product	Alteration of cellular function	Reference
Vpr	Cell cycle arrest in G2	33,106
	Cell cycle arrest in G1	37
	Caspase activation	38
	Dissipation of the mitochondrial transmembrane potential	24
Vpu	Increased susceptibility to Fas-induced death	19
Tat	Increased activity of cyclin A-dependent kinases	88
	Increased Fas and Fas-L expression	20,66
	Increased caspase-8 activity	21
	Decreased Bcl-2 activity	28
Nef	Upregulation of Fas and FasL	22
Env (gp120 /gp160)	Increased fas expression	107
	Induction of CD4-Lck interaction	108
	Increased membrane permeability	109
	Syncytia formation	110
	Formation of intracellular CD4-gp160 complexes	111
	Activation of AP-1	112
	Activation of Lck and Raf-1	113
HIV protease	Cleavage of Bcl-2	29,30
Unintegrated viral DNA	Induction of cytolysis	reviewed in [114]
Many	Targeting for cytotoxic T lymphocyte-mediated killing	115
Many	Targeting for lymphokine-activated killers	116
Many	Targeting for antibody-dependent cellular cytotoxicity	116
Many	Targeting for complement-mediated lysis	117
Unknown	Induction of necrosis	118
Unknown	Activation of ICE-like proteases	119
Unknown	Increased expression of Fas-L on macrophages	120

Table 2 HIV gene products implicated in the control of cell death. Means by which HIV may induce death in uninfected bystander cells

HIV gene product	Alteration of cellular function	Reference
Tat	Increased Fas-L expression	20,66
Env (gp120 /gp160)	Induction of 'mitotic catastrophe'	106,110
	Increased Fas expression	107
	Induction of cytolysis	45,46,121
	Induction of apoptosis of preactivated cells	122
	Priming for activation-induced apoptosis	123,124
	Increased membrane permeability	109
	Activation of AP-1	112
	Activation of Lck and Raf-1	113
	Activation of caspase-3 and caspase-6 and induced cleavage of Focal adhesion kinase	47,50
	Decreased Bcl-2 expression	56
	Decreased JAK3 expression and activation	58
Vpr	Cell cycle arrest in G2	33
Many	Cytokine-induced cell death or cytokine withdrawal	reviewed in [114]
Many	Exhaustive activation	125
Unknown	Telomere shortening in $CD8^+$ T cells	126,127
Unknown	Activation of ICE-like proteases	119
Unknown	Increased susceptibility to Fas-induced cell death	16,18,128
Unknown	Increased expression of Fas-L on macrophages	120

Table 3 HIV gene products implicated in the control of cell death. Means by which HIV may prevent or delay apoptosis in infected cells

HIV gene product	Alteration of cellular function	Reference
Tat	Inhibition of apoptosis	129–131
	Inhibition of antigen-induced proliferation	132
	Decreased MHC class I expression	133
	Increased Bcl-2 expression	134
	Decreased p53 expression	88
Nef	Increased endocytosis of CD4	76
	Inhibition of Lck activation	81,83,135
	Downregulation of TCRζ	83,84
	Increased FasL expression	85
	Binding of p53, Hck, pp44 MAPK/ERK1	83,136
	Decreased expression of IL-2Rα chain	83,135
	Inhibition of proliferation in response to IL-2	83
	Decreased MHC class I surface expression	86,133
Vpu	Degradation of CD4	77,78
Vpr	Inhibition of activation of pp34cdc2-cyclin B	34,35, 137,138
	Increased Bcl-2 and decreased Bax	90
	Decreased NKκ-B activity	139
Env (gp120 /gp160)	Inhibition of surface expression of CD4 by binding to CD4 in the ER	77
Capsid	Binding to cyclophilins A and B	140

One of the accessory proteins of HIV-1, Vpr, has been shown to induce T cell apoptosis. Synthetic Vpr added to intact T cells causes a rapid dissipation of the mitochondrial transmembrane potential, as well as the release of cytochrome *c* and cellular apoptosis.[24] These data support evidence of Macho *et al*. showing that T cells from HIV^+ individuals have dysfunctional mitochondria, reduced mitochondrial transmembrane potential, and increased generation of superoxide anion.[25] The dissipation of the mitochondrial transmembrane potential and the apoptosis induced by Vpr can be inhibited by the cellular anti-apoptotic protein, Bcl-2.[24] But HIV has also been shown to down-regulate Bcl-2 by a number of different mechanisms. Levels of Bcl-2 are significantly lower in PBL from HIV infected individuals with high levels of viral replication.[26] Spontaneous apoptosis of $CD4^+$ and $CD8^+$ T cells from HIV infected individuals correlates with downregulation of Bcl-2 and is partially prevented by anti-retroviral therapy or by IL-2.[27] The HIV-1 transcriptional regulatory protein, Tat, has been shown to decrease Bcl-2 expression.[28] HIV protease has been shown to cleave Bcl-2 and this is correlated with induction of apoptosis.[29,30] Another mechanism of HIV induced downregulation of Bcl-2 may be via inhibition of the JAK3 (Janus Family kinase)/STAT5 (Signal Transducers and Activators of Transcription) activation pathway, which is necessary for growth factor-dependent T cell proliferation and survival.[31] Interestingly, our data show that the HIV-1 clonal isolate, NL4-3, inhibits the JAK3/STAT5 activation pathway (Selliah and Finkel, manuscript submitted). The JAK3/STAT5 signaling pathway has been shown to upregulate anti-apoptotic proteins, such as Bcl-2 and Bcl-xL.[31,32] These data suggest that HIV mediated inhibition of

anti-apoptotic mechanisms in host cells may further enhance spontaneous apoptosis or the apoptosis induced by Vpr or other viral proteins.

Another function of Vpr is cell cycle arrest. Relevant to our subsequent discussion of HIV-induced death of bystander cells, Vpr induces cell cycle arrest in both infected and uninfected cells.[33] Vpr arrests cells in the G2 phase of the cell cycle by inhibiting activation of $p34^{cdc2}$-cyclin B.[34,35] The activity of $p34^{cdc2}$-cyclin B is critical for entry into mitosis and requires removal of the phosphate residues on $p34^{cdc2}$ that inhibit kinase function.[35] In Vpr expressing cells, phosphatase cdc25C, which removes phosphate from $p34^{cdc2}$, is in an inactive form, suggesting that the target for Vpr is either cdc25C or an upstream regulator of cdc25C. Recently, Hrimech *et al*. reported that Vpr mediates G2 arrest by forming a complex with protein phosphatase 2A (PP2A), an upstream regulator of cdc25, and enhances the nuclear import of PP2A.[36] In the nucleus, Vpr-PP2A complex binds and dephosphorylates cdc25, rendering it inactive.

G2 arrest by Vpr has been characterized as beneficial to HIV, resulting in production of more virions, although the cellular response to this arrest is suicide.[34,35] Interestingly, Nishizawa *et al*. reported recently that a carboxy-terminal truncation of Vpr induces apoptosis via G1 arrest of the cell cycle.[37] Another study showed that apoptosis induced by Vpr requires caspase activation.[38] These data show that Vpr may regulate cellular function, including the cell cycle, and induce apoptosis via multiple and complex pathways. Our recent data suggest that another HIV-1 accessory protein, Vif, contributes to the aberrant cell cycle regulation and apoptosis in HIV infected T cells (Casella *et al*., manuscript submitted). Collectively, these data argue that HIV interferes with cellular functions for the benefit of replication and production of more virus, but that the cellular response to this interference is activation of apoptotic signaling pathways (Figure 1).

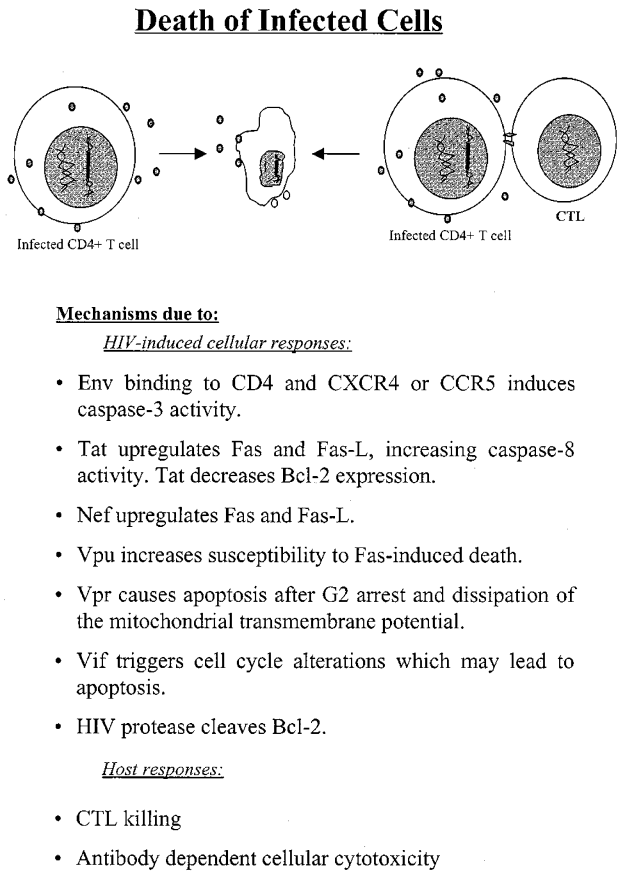

Figure 1

Apoptosis of uninfected T cells: bystander cell death

Despite the high viral burden and turnover throughout the course of HIV infection, only a small fraction (<0.1%) of $CD4^+$ T cells are productively infected.[39] Notably, the number of apoptotic $CD4^+$ T cells from the peripheral blood of HIV-infected individuals is greater than the number of infected cells, suggesting that uninfected cells die by apoptosis.[40] Apoptosis is seen in PBL of HIV infected individuals in both the $CD4^+$ and $CD8^+$ T cell subsets.[7,8,40,41] A study of a large cohort of HIV-infected individuals at various stages of disease showed that the degree of apoptosis was significantly higher in $CD4^+$, $CD8^+$, and B cells, compared to uninfected individuals, and was correlated with disease progression.[7] This study showed a low level of apoptosis in long-term non-progressors and a high level of apoptosis in rapid progressors. In the lymph nodes, the major site of viral replication,[4,39] we have shown that apoptosis is increased in the lymph nodes of HIV-infected children, adults and SIV-infected macaques, when compared to lymph nodes from uninfected controls.[42,43] Intriguingly, productively infected cells were only rarely apoptotic and apoptotic cells were only rarely productively infected.[43] These data have been corroborated by Haase and coworkers in subsequent *in situ* analyses of apoptosis and infection[44] (and personal communication). In addition, numbers of apoptotic cells in lymphoid tissue exceeded the numbers of productively infected cells, suggesting the occurrence of bystander cell death.[40]

The best-studied mechanism of bystander cell death in HIV infection is mediated by the binding of envelope glycoprotein (Env) to its cellular receptors (CD4 and a chemokine coreceptor), prior to viral fusion and entry. Apoptosis occurs in the absence of viral replication when infected and uninfected cells are cultured together.[45,46] These data suggest that viral proteins interact with uninfected cells and induce an apoptotic signal. The binding of HIV-1 Env to CD4 and CXCR4 (the chemokine receptor utilized by T cell line-tropic HIV) or CCR5 (the chemokine receptor utilized by macrophage-tropic HIV) has been shown to induce apoptosis in primary T lymphocytes.[47] Env exerts an inhibitory effect when cells are in the G0/G1 phase of the cell cycle.[48] Thus, naïve T cells (CD45RA cells) may be the most affected by Env mediated negative signaling. Interestingly, binding of HIV virions to CD45RA cells decreased mitogenic responses and induced activation-induced cell death (AICD), while memory T cells

(CD45RO cells) were less affected.[49] Furthermore, cell cycle arrest at the G1/S restriction point was seen only in CD45RA cells following binding of HIV virions.

Binding of Env to CD4 and to a coreceptor activated caspase-3 and caspase-6, and induced cleavage of focal adhesion kinase (FAK).[47,50] Cleavage of FAK by caspase-3 and caspase-6 leads to the disassembly of focal adhesion complexes and programmed cell death.[51,52] It appears that while CXCR4 induced apoptosis is dependent upon caspase-3 activation, it is insensitive to pertussis toxin and does not involve the activation of the p38MAPK or JNK.[50] Activation of caspase-3 and caspase-6 was induced by HIV-1 macrophage tropic Env in PBL from a CCR5Δ32 donor (which have a non-functional coreceptor, due to a CCR5 deletion), suggesting that CD4 receptor engagement is sufficient to provide the stimulus for apoptosis.[47] Caspases have been implicated in HIV-mediated apoptosis[53] and patients with progressive HIV disease demonstrate increased caspase-3 activity.[54] Caspase-3 has been shown to mediate cleavage of Bcl-2 and promotes apoptosis.[55] Interestingly, it has been reported that CD4 ligation decreases Bcl-2 expression and induces apoptosis.[56] Bcl-2 downregulation was observed in cultured $CD4^+$ T cells, $CD8^+$ T cells and B cells from HIV^+ individuals.[57] Thus, multiple signaling pathways appear to contribute to the apoptosis induced by ligation of the CD4 receptor.

Recently, we have shown that increases in JAK3 expression and JAK3 activation induced by antigen receptor ligation are inhibited by prior CD4 ligation by HIV gp120 or anti-CD4 mAb.[58] The JAK3/STAT5 signaling pathway has been shown to play a major role in the development, proliferation, and survival of T cells[59–61] (and reviewed in[62,63]). *In vivo* evidence for inhibition of the JAK-STAT pathway in HIV disease comes from data of Pericle *et al*.[64] The authors observed a selective reduction of STAT5B expression in HIV infected PBMC and reduced expression of STAT1α, STAT5A and STAT5B in T cells from HIV seropositive individuals. These data argue that T cell dysfunction and apoptosis in HIV disease may be due, in part, to aberrant regulation of the JAK3/STAT5 signaling pathway.

HIV-1 Tat protein has been shown to induce cell death by apoptosis in a T cell line and in cultured peripheral blood mononuclear cells from uninfected controls.[65] This Tat-induced apoptosis was inhibitable by growth factors and was associated with enhanced activation of cyclin-dependent kinases. Tat is secreted from infected cells[66] and may upregulate FasL on uninfected cells.[20] These cells could then either kill themselves by binding Fas expressed on the same cell or kill another cell that has upregulated Fas. In addition, McCloskey *et al*. reported that addition of exogenous Tat induced apoptosis in Jurkat cells.[67] Finally, it has been suggested that Tat binds to cell surface molecules, possibly to CD26 and the integrin, $\alpha_5\beta_1$, both of which transduce apoptotic signals.[68–70]

One mechanism of $CD8^+$ T cell death in HIV disease, as reported by Herbein *et al*., is dependent upon macrophages.[71] These authors showed that ligation of CXCR4 increased membrane bound TNF on macrophages and TNFRII on $CD8^+$ T cells. The interaction between TNF and TNFRII induced death of the $CD8^+$ T cells. As discussed above, secreted Tat could also induce apoptosis of $CD8^+$ T cells. Thus, as described previously for $CD4^+$ T cells, there are multiple mechanisms of $CD8^+$ T cell death in HIV disease (Figure 2).

Inhibition of apoptosis by HIV

HIV may kill the $CD4^+$ T cell that it infects *in vivo* (as discussed above). However, emerging data suggest that HIV and SIV have evolved mechanisms of blocking or delaying the cellular suicide program. As has been described for many other viral infections,[72] it may be beneficial for HIV to inhibit cellular apoptosis, at least until high levels of progeny virus are produced. As discussed below, several HIV-1 gene products have been shown to have anti-apoptotic activity, at least *in vitro*, and expression of known anti-apoptotic genes (i.e. E1B 19K or a caspase inhibitor, N-benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone [z-VAD-fmk]) in HIV-1 infected cell lines increases virus production.[73,74] In fact, recent studies demonstrating the persistence of latent or low level HIV-1 infection *in vivo*, in the face of intense anti-retroviral therapy,[75] argue that not all infected cells die.

A first line of defense for HIV against cellular apoptosis would be to reduce the levels of surface CD4, to prevent infection by new viruses ('super-infection interference'), and to inhibit binding and negative signaling by soluble or cellular gp120. At least three HIV-encoded proteins, Nef, Env, and Vpu, contribute to the down-regulation of CD4. Nef, a protein predominantly expressed early in infection, reduces the level of CD4 on the surface by inducing endocytosis.[76] Env binds CD4 in the endoplasmic reticulum

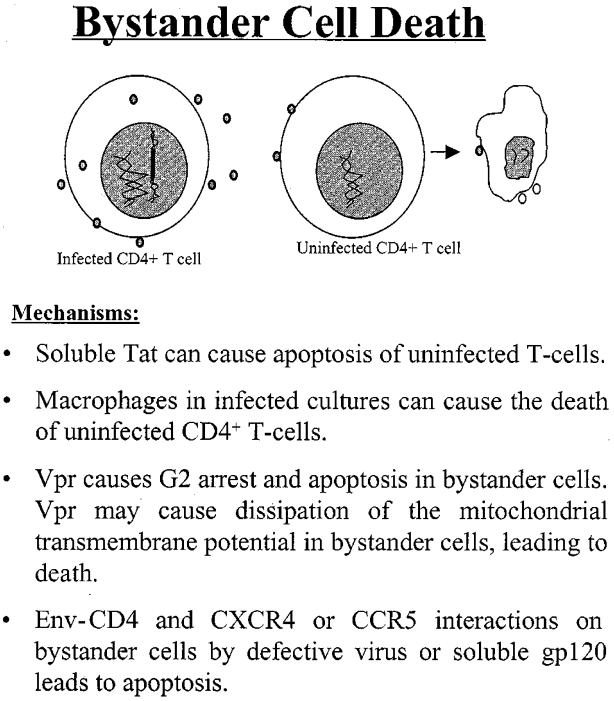

Figure 2

and thereby inhibits expression.[77] Vpu, a protein expressed late in the viral life cycle, facilitates the degradation of CD4 by binding to a cellular factor, h-βTrCP, and targets CD4 for ubiquitin-mediated proteolysis.[78,79]

Nef has been shown to inhibit T cell activation pathways by interaction with cellular signal transduction proteins [reviewed in [80]]. Nef binds to p56^{lck} and inhibits its kinase activity.[81] In addition, recent data show that Nef binds to TCR ξ-chain, resulting in downmodulation from the cell surface.[82] Both p56^{lck} and TCR ξ-chain are required for downstream events of T cell signal transduction. Thus, the interaction of Nef with p56^{lck} and TCR ξ-chain may prevent AICD of HIV infected cells.[83,84] In related studies, Xu *et al.* have shown that Nef binds to TCR ξ-chain and increases FasL expression.[85] The authors suggest that Nef binds to TCR, initiating signaling and upregulation of FasL, without the requirement for antigen engagement. Nef has also been shown to reduce MHC class I on the surface by inducing endocytosis.[86] Downregulation of MHC class I and upregulation of FasL by HIV-1 and SIV Nef may protect infected cells from CTL mediated lysis.[86,87]

Nef has also been reported to bind to p53[83] and Tat decreases transcription of p53.[88] Downregulation of p53 and inactivation of p53 regulatory functions may promote cell cycle progression, inhibit apoptosis, and produce cell transformation. Recently, Clark *et al.* reported that HIV infected T cells bypass the G1/S checkpoint by inhibiting p21^{Waf1}, a known cyclin dependent kinase inhibitor.[89] This inhibition is mediated by the binding of p53 by Tat, and sequestration of its transactivation activity. The authors postulate that this loss of the G1/S checkpoint provides a selective advantage for HIV by allowing virus associated transcription and production of virions, processes which require T cell cycling.

As discussed above, Vpr has been shown, in some systems, to induce T cell apoptosis. In contrast, low level constitutive expression of Vpr has been shown to *inhibit* apoptosis by up-regulation of Bcl-2 and down modulation of Bax.[90] While non-physiologic or ectopic expression of Vpr may explain these contradictory findings, it is possible that early in infection, low levels of Vpr protect cells from apoptosis, allowing the cells to increase virus production (Figure 3).

Our own work has shown that T cells productively infected with HIV-1 IIIB undergo less apoptosis than control uninfected T cells.[91] This relative paucity of apoptosis is characteristic of IIIB infection, since a large number of cells infected with the viral clone, HIV-1 NL4-3, are apoptotic. Mapping studies of IIIB and NL4-3 have not revealed the gene product(s) responsible for this marked difference in the death of infected cells, and the mechanism of inhibition of apoptosis by IIIB is not known. Of interest, Bottarel *et al.* reported that Env from IIIB does not induce CD4 lateral association with Fas, while Env from the apoptosis-inducing strains 451 and MN induces this association.[92] In related studies, we have shown that productive infection with HIV-1 NL4-3, but not IIIB, inhibits JAK3/STAT5 activation, a signaling pathway required for normal T cell function and survival (Selliah and Finkel, manuscript submitted). We hypothesize that activation of the JAK3/STAT5 pathway protects IIIB infected cells from

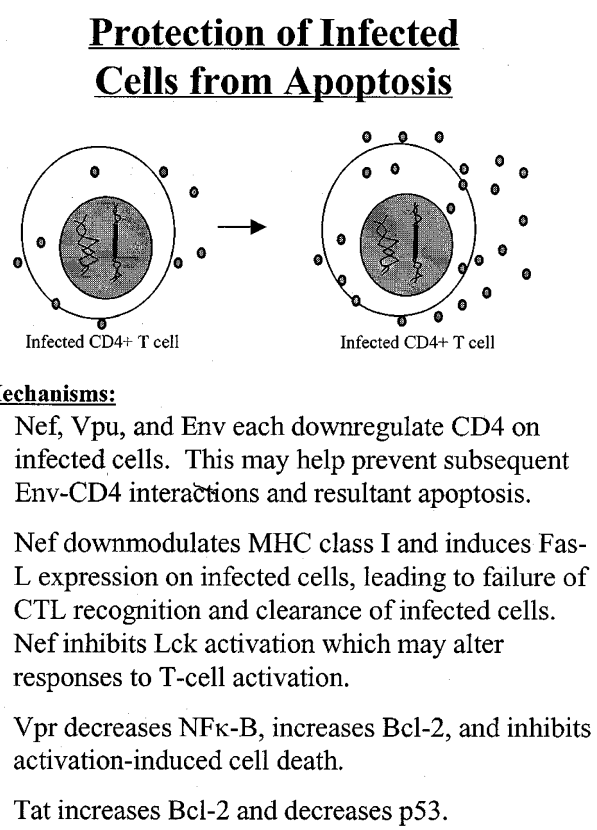

Figure 3

apoptosis, possibly via activation of the anti-apoptotic targets of JAK3, PI3 kinase and Akt.[93]

Finally, and of most relevance to *in vivo* infection, we have analyzed apoptosis and HIV-1 RNA in lymph nodes from HIV infected individuals. Lymphoid tissue is a major reservoir of viral infection in HIV disease and a primary site of antigen presentation and lymphocyte activation. Surprisingly, apoptosis is seen predominantly in uninfected bystander cells and not in productively infected cells,[43] suggesting that infected cells are relatively protected from apoptosis *in vivo*. While our *in vitro* work comparing IIIB and NL4-3 did not analyze primary viral isolates, it is intriguing to speculate that these isolates behave like IIIB and inhibit apoptosis in infected cells. Furthermore, we speculate that, as in other viral infections, 'attenuated' HIV is a virus that kills its host cell, having lost or mutated putative anti-apoptotic genes. Viral or cellular targets that inhibit apoptosis, thereby promoting the survival and persistence of HIV-infected cells, may be attractive targets for future therapeutics.

Does current therapy inhibit T cell apoptosis in HIV disease?

In the early stages of HIV disease, CD4$^+$ and CD8$^+$ naïve T cells decline, while CD8$^+$ memory T cells expand.[94] At least one study suggests that naïve T cells are more susceptible to HIV induced bystander cell death.[49] In the later stages of HIV

disease, both CD4+ and CD8+ memory T cells decline at similar rates. Within weeks after administration of highly active anti-retroviral therapy (HAART; combination therapy, in general including at least one protease inhibitor and two other anti-retroviral agents), CD4+ and CD8+ memory T cell populations increase, although significant increases in naïve cells have not been seen.[94,95] Alteration of the CD4+ T cell repertoire is not immediately corrected by anti-retroviral and/or immune-based (IL-2) therapy,[96] although several studies have shown that administration of IL-2 boosts CD4+ T cell number and function, when used in conjunction with anti-retroviral therapy.[96–99] These studies showed that late expansion of naïve CD4+ T cells was more pronounced with IL-2 plus HAART than with HAART alone. Furthermore, a recent study showed that while HAART plus IL-2 did not decrease spontaneous apoptosis or AICD, there was a delayed and significant increase in CD4+ naïve T cells.[99] Since IL-2 did not decrease apoptosis, it has been suggested that the increase in naïve T cells may be due to restoration of thymic function or to increased cellular proliferation.[99] However, only PBL were analyzed in this study, leaving open the possibility that a decrease in apoptosis in lymphoid tissue led to the increase in naïve T cell numbers. In fact, Pandolfi *et al*. reported that intermittent low dose IL-2 with HAART decreased spontaneous apoptosis and increased the number of CD4+ T cells.[100] Other studies have shown that anti-retroviral drugs given with IL-2 significantly elevated CD45RO and CD45RA cell numbers and decreased plasma viral load.[97,101] In addition, CD45RA cells recovered the ability to produce IL-2, IL-4 and IFN-gamma *in vitro*, suggesting that treated individuals might have an improved immune response.[97] Collectively, these studies show that the combined use of anti-retroviral drugs and IL-2 may be effective in decreasing viral load, increasing CD4+ T cell numbers, and improving immune system function.

Kovacs *et al*. reported that intermittent courses of IL-2 (with one anti-retroviral drug) increased CD4 numbers by 50% in HIV patients with CD4 counts higher than 200 per mm^3, but found only minor improvement in patients with low CD4 counts.[102] IL-2 therapy in patients with low CD4 counts was associated with increased viral replication, but few immunologic improvements.[102] These data suggest that the use of IL-2 with anti-retroviral drugs may activate resting T cells that harbor replication-competent HIV. A recent report showed that three patients treated with continuous HAART and intermittent IL-2 had significantly fewer resting CD4+ T cells harboring replication-competent HIV RNA.[103] IL-2 therapy with anti-retroviral drugs not only activates the immune system and, possibly, HIV from latently infected cells, but also, interestingly, decreases the plasma viral load in some patients.[104] These studies are encouraging, although more patients and long term monitoring are required before definitive conclusions can be drawn.

IL-2 prevents apoptosis of CD4+ T cells from HIV seropositive individuals *in vitro*, and this is correlated with increased Bcl-2 expression.[57] Interestingly, IL-15, another γ_c (the common γ chain on IL-2, IL-4, IL-7, IL-9 and IL-15 cytokine receptors) related cytokine, decreased spontaneous apoptosis of T cells from HIV infected individuals.[105] This inhibition of apoptosis was associated with upregulation of Bcl-2 expression. As discussed above, γ_c related cytokines may prevent spontaneous apoptosis by activation of the JAK3/STAT5 pathway and by upregulation of survival proteins, such as Bcl-2 and Bcl-$_{xL}$. Thus, signaling through γ_c may protect bystander cells from Env mediated apoptosis and facilitate reconstitution of the T cell immune system. We hypothesize that γ_c cytokines, related to but less toxic than IL-2, or selective activation of JAK3, may provide valuable therapeutic tools. In combination with aggressive anti-retroviral therapy, therapies that boost the immune system could significantly delay progression of HIV disease.

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