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Death of effector memory T cells characterizes AIDS

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1. ABSTRACT

The adaptive effector $CD4^+$ T helper-mediated immune response is highly heterogeneous, based on the development of distinct subsets that are characterized by the expression of different profiles of cell surface markers. Functional impairment of T cells is characteristic of many chronic mouse and human viral infections. Excessive induction of apoptosis in infected and uninfected $CD4^+$ T cells has been proposed as one of the pathogenic mechanisms that may impair the immune response and cause the development of acquired immune deficiency syndrome (AIDS). Thus, the death of effector/memory $CD4^+$ T cells during both the acute and chronic phase represents one the main characteristic of such viral infection that predicts disease outcome. Improving our understanding of the molecular mechanisms leading to the death of memory $CD4^+$ T cells should enable us to improve vaccination protocols and treatments, by combining them with antiretroviral drugs and molecules designed to decrease apoptotic phenomena.

2. INTRODUCTION

Programmed cell death and its main phenotype, apoptosis, is a cell suicide program essential for development and for adult tissue homeostasis of all metazoan animals (1). The stereotypical death throes of a cell undergoing apoptosis include DNA fragmentation, nuclear condensation, cell shrinkage, blebbing, and phosphatidylserine externalization (2-4), all features that promote the physiologically silent removal of the cell by its phagocytic neighbors.

Mitochondria are implicated in the two major apoptotic pathways currently accepted as the model (s) for cell death. The death receptor-mediated pathway (« extrinsic pathway ») involves mitochondria mainly as an amplification loop, whereas cellular deprival and stress-mediated apoptosis is regulated predominantly at the mitochondrial level (« intrinsic pathway »). In both pathways, the involvement of the mitochondria is manifested by the release of cytochrome c. The release of

apoptogenic factors from the mitochondria is regulated by the members of the Bcl-2 family (5-8). Members of the Bcl-2 family proteins can be subdivided into three distinct groups: (i) anti-apoptotic members such as Bcl-2 and Bcl-XL with sequence homology at BH1 (Bcl-2 homology region), BH2, BH3, and BH4 domains; (ii) pro-apoptotic molecules, such as Bax and Bak, with sequence homology at BH1, BH2 and BH3; and (iii) pro-apoptotic proteins that share homology only at the BH3 domain, such as Bid, Bik, Noxa, and Bim (5).

Defaults (inhibition or exacerbation) in programmed cell death are involved in several pathologies like neurodegenerative diseases, cancers or AIDS (9-11).

3. THE LEVEL OF APOPTOSIS PREDICTS FURTHER PROGRESSION TO AIDS

The depletion of $CD4^+$ T cells is a major determinant of pathogenicity in human immunodeficiency virus type 1 (HIV-1) infection. $CD4^+$ T cell depletion is associated with high viral turnover (12), and is preceded by the progressive loss of T-cell-mediated immunity (13). T cell apoptosis may be one of the mechanisms that is responsible for T cell depletion during HIV infection. Several studies have found that abnormal levels of apoptosis occur both *in vitro* (9, 14-20) and *in vivo* (21, 22) in $CD4^+$ and $CD8^+$ T cells from HIV-1-infected persons. Excessive induction of apoptosis in infected and uninfected T cells (22) has been proposed as one of the pathogenic mechanisms that may impair the immune response and cause the development of immune deficiency. The magnitude of apoptosis observed in HIV-infected individuals correlates well with the stage of HIV disease (23-28) and changes in apoptosis during antiretroviral therapy confirm the link between disease progression and apoptosis (29). Finally, it has been shown excessive apoptosis in patients treated with drugs in which despite having undetectable plasma viral loads they display persistent low $CD4^+$ T cell counts. This result suggests that apoptosis may represent a mechanism responsible for the low level of reconstitution in these patients (30).

Several studies have found that HIV originally resulted from viruses circulating in African non human primates (NHP) So far, thirty distinct African NHP species have been shown to carry SIV (31). Interestingly, these natural hosts for SIV do not show any signs of AIDS (32-36). The lack of induction of AIDS in the natural hosts contrasts with their capacity to support SIV replication. Importantly, transmission of SIV from natural hosts, *ie* sooty mangabeys (SMs) or African green monkeys (AGMs, *C. aethiops*), to Asian NHP, such as pigtailed macaques, induces AIDS. This demonstrates that the lack of induction of AIDS is not due to viral attenuation, but that host specific responses play a crucial role in protection.

Studies performed in pathogenic and non-pathogenic primate models of HIV or simian (SIV) immunodeficiency virus infection have identified during the chronic phase a correlation between the induction of enhanced *in vitro* T cell apoptosis and the *in vivo* pathogenic nature of the retroviral infection (16, 19, 33, 37-39). Thus, enhanced levels of apoptosis in CD4+ T cells were observed in the models leading to AIDS: HIV-1-infected human individuals, Rhesus Macaques (RMs) infected with a pathogenic strain of SIVmac, and chimpanzees infected with a pathogenic strain of SIVcpz (37, 40). In contrary, no apoptosis was observed in AGMs or SMs (19, 33).

The primary acute phase of HIV and SIV infections is characterized by an early burst in viral replication, an exponential rise in plasma viral load, the dissemination and seeding of the virus in all the peripheral lymphoid organs (41-45). The steady state plasma viral load levels that are reached at the end of this primary phase around 2 months after infection predict the progression towards disease, ranging from rapid development of AIDS to long term slow progressive infection (46-49). Several observations indicate that the early induction of an effective immune response against the virus plays a role in determining levels of viral load at the end of the primary phase (i.e., set-point) Importantly, the early stages of non-pathogenic SIV infection of AGMs and SMs are also characterized by a peak of virus replication in peripheral blood accompanied by rapid dissemination of the virus and depletion of $CD4^+$ T-cells from the MALT (50, 51).

T cells from peripheral blood of SIV-infected macaques were more prone to die during primary infection (52). Moreover, cell death in tissues was higher in animals infected with pathogenic SIV than in those infected with the attenuated strain SIVΔ*nef* (53, 54). We also found that the extent of T cell death in LNs during primary infection predicts disease progression (55) and increase of apoptosis was also seen in lamina propria (56). Interestingly, SIVmac infection is milder in Chinese RMs as compared to Indian RMs. It has been initially proposed that this may have resulted in the selection of viral variants that are adapted for more efficient replication and/or increased pathogenicity for these animals (57). Thus, the SIVmac strains were propagated either *in vivo* or *in vitro* in cells derived from Indian monkeys (57, 58). We showed by using a SIVmac251 propagated on cells of Chinese origin that the levels of apoptosis correlated with the extent of viral replication and the rate of disease progression to AIDS (59). Thus, the extent of apoptosis was higher in RMs of Indian genetic background when compared to those of Chinese origin. This demonstrated that increased pathogenicity is due to host factors. In stark contrast, no changes in the levels of lymphocyte apoptosis were observed during primary infection in the non-pathogenic model of SIVagm-sab infection of AGMs despite similarly high viral replication (59-61).

4. EFFECTOR MEMORY T CELL SUBPOPULATION EXPRESSING CCR5 IS THE MAIN POPULATION PRONE TO DIE BY APOPTOSIS

During antigenic stimulation, T cell differentiation takes place according to the following sequence: naive T cells ($CD45RA^+$ $CD62L^+$) forming a

population of "central" (central-memory T cells, TCM) or early memory T cells that lose the CD45RA molecule. Further stimulation of central-memory T cells leads to proliferation of intermediate memory cells that have lost CCR7 followed by the production of "effector" (effector memory T cells, TEM) which lack CD62L expression. These effector-memory T cells may re-express the CD45RA molecule, in response to antigen stimulation, becoming "terminal differentiated" effector T cells (TDT). We have previously shown that the response to recall-antigens (for example, BCG) is lost at an early stage following SIV-infection (55, 62, 63). In humans, it has been shown that CD4+ T cell differentiation was abortive and HIV-specific $CD4^+$ T cells died during the asymptomatic phase (64) and that early highly active antiretroviral therapy (HAART) preserved $CD4^+$ T cell immune response (65, 66). We recently demonstrated that effector memory $CD4^+$ T cells (TEM) were more prone to apoptosis during primary infection (62), explaining, at least in part, how HIV and SIV infections impair the immune response very early. Interestingly, variable rates of T cell death were observed amongst the individual animals, despite the fact that they received the same batch of virus and the same dose via the same route. These results suggest the existence of individual host factors that predispose to AIDS.

Among host factors, it has been shown that chemokine receptors may contribute to AIDS. The risk of progressing to AIDS in SIV-infected Indian RMs is associated with a rapid and sustained depletion of circulating and mucosal $CD4^+CCR5^+$ memory T-cells (67-71). This observation represents a somewhat striking difference with HIV infection, as several studies reported that, in HIV-infected individuals, the proportion of $CD4^+$ T-cells expressing CCR5 greatly increases following HIV infection (72, 73) and that this increase in $CD4^+CCR5^+$ T-cells is a marker of disease progression associated with apoptosis (74-76). Collectively, these findings raise the concern that, beyond a series of obvious similarities, the SIVmac-infected RM model does not reproduce correctly the pathogenic events occurring during HIV infection, particularly with respect to the dynamics of the $CD4^+CCR5^+$ T-cell subset. To this end, it should be noted that the two main driving forces behind the dynamics of $CD4^+CCR5^+$ T-cells during SIV infection are viral replication (that tends to reduce the number of these cells) (67-69) and the immune activation that promotes the expression of CCR5 (and thus increases the number of $CCR5^+$ T-cells) (77, 78). As such, the differences in $CD4^+CCR5^+$ T-cell dynamics observed between humans and RMs of Indian origin may reflect a different contribution of the two above-described mechanisms by which a retroviral infection affects this cellular subset. In this context, we demonstrated that the dynamics of $CD4^+CCR5^+$ T-cells in SIV-infected Chinese RMs are more similar to those in HIV-infected humans (63). Thus, we have proposed that SIV infection of Chinese RMs may be an extremely useful and particularly relevant model to study AIDS pathogenesis and vaccines.

5. PRODUCTIVE HIV-1 INFECTION MEDIATES CD4 T CELL DEATH

Excessive induction of apoptosis in infected and uninfected T cells (22) has been proposed as one of the pathogenic mechanisms that may impair the immune response and cause the development of immune deficiency. Thus, despite intensive investigations, several important questions remain about the mechanisms through which HIV infection induces $CD4^+$ T cell death. Classical apoptosis with its hallmarks (cell shrinkage, strong chromatin condensation, OMM rupture and caspase activation) has long been viewed as the major cell death mechanism affecting the cells of HIV-1-infected $CD4^+$ T cell cultures (79). However, several studies with productively HIV-1-infected primary $CD4^+$ T cell cultures described a programmed death pathway insensitive to the peptide z-VAD-fmk (a broad-spectrum caspase inhibitor) and to reagents that specifically inhibit the death receptors of the TNF-R superfamily (80, 81). This suggests that a caspase-independent death pathway, also operating in infected cells, could substitute for the caspase-dependent one. In a number of cell death models, lysosomal destabilization and ensuing efflux of cathepsins play an early and important role in the destruction of the cells (82, 83). Cathepsin-B, which is an essential mediator of TNF-α-induced cell death in murine embryonic fibroblasts, depends on caspase-9-induced lysosomal membrane permeabilization (84). On the contrary, Cathepsin-D, which is primarily involved in oxidative stress and staurosporine (STS)-induced apoptosis in human fibroblasts, acts upstream from cytochrome c release and caspase activation (85). Released Cat-D has been shown important by promoting Bax activation and insertion into the OMM (86). Thus, we demonstrated that lysosomes are rapidly permeabilized in $CD4^+$ T lymphocytes productively infected with HIV-1, resulting in the release of cathepsins into the cytosol, and that the permeabilization of lysosomes precedes that of mitochondria (87). During early commitment to apoptosis, released Cathepsin-D acts upstream from Bax conformational change and subsequent Bax insertion into the OMM. Inhibition of Cathepsin-D activity confers a transient survival advantage upon infected cells, indicating that Cathepsin-D behaves as an early trigger of apoptosis.

Among the factors encoded by HIV-1, the Nef protein is essential for AIDS pathogenesis, promoting high-level viral replication (88). Nef has multiple effects, including the downregulation of cell surface proteins such as CD4, MHC class I, CD28 (reviewed in (89)) and chemokine receptors (90). Studies with cell lines stably expressing *nef* have shown that Nef also enhances the apoptotic responses to a number of cell death agonists (91). In mice, *nef* transgene expression alone induces the development of a severe AIDS-like disease, whereas *vpu*, *vpr* or *tat* transgene expression are dispensable for the emergence of this disease phenotype (92). Interestingly, the transfection of activated $CD4^+$ T lymphocytes with a Nef expression vector rapidly induced the permeabilization of lysosomes and the release of Cat-D (87). Thus, Nef HIV-1 protein in activated $CD4^+$ T lymphocytes is sufficient to

trigger lysosomal membrane permeabilization and its effects.

6. EXPOSURE TO HIV VIRAL PARTICLES PRIMES MEMORY CD4 T CELLS FOR APOPTOSIS

The increased level of T cell apoptosis observed in HIV-infected human individuals is associated with enhanced expression of the CD95 receptor and its ligand (CD95L), and increased sensitivity of T cells to apoptosis mediated by CD95 ligation using either agonistic CD95 monoclonal antibodies (mAb) or recombinant CD95L (19, 93-105). 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 (106-110). 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 (111).

CD95/CD95L interactions play a significant role in peripheral T cell homeostasis. Several reports have reported that CD95L is significantly expressed by macrophages independently of posttranslational mechanisms following HIV infection (27, 107, 112, 113). Thus, macrophages can provide a source for CD95L, following HIV infection and can thus participate in $CD4^+$ T cell depletion in HIV-infected individuals. Moreover, we also demonstrated the presence of CD95L within vesicles derived from apoptotic cells capable to induce the death of uninfected $CD4^+$ T cells (114). Thus, cell death induced *in vivo* during HIV-1 infection may by itself provide an amplification loop in AIDS pathogenesis.

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 (115). In macaque as well as in humans, zVAD-fmk prevents CD95-mediated T cell death. Interestingly, the enhancement in CD95-mediated T cell death in rhesus macaques is not associated with either an up-regulation of caspase-3 and caspase-8 or a decrease of FLIP-L and FLIP-S (111). Similarly, Badley *et al.* (116) found that death of T cells of 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, and may be involved. Antiretroviral therapy show a significant decrease in CD95-induced, activation-induced, and spontaneous apoptosis in *ex vivo* cultured PBLs which correlates with decreased immune activation (29). Thus, effective viral suppression decreases apoptosis, which in turn may contribute to immune reconstitution.

The envelope glycoprotein complex (Env) appears to be one of the dominant apoptosis-inducing molecules encoded by the HIV-1 genome. The gp120 is present on the surface of infected cells, on viral particles, or as a soluble protein and can bind to and cross-link CD4. The interaction of the gp 120 with the CD4 molecule can prime $CD4^+$ and $CD8^+$ T cells for apoptosis (106, 117-122). Thus, contact of primary uninfected $CD4^+$ T cells with HIV-infected or HIV envelope glycoprotein-expressing cells results in apoptotic cell death (123). Cytoskeletal components play a major role in HIV-1 infection. In fact, it has been shown that gp120 is able to induce cytoskeleton-driven polarization, thus sensitizing T cells to CD95-mediated apoptosis. In particular, an early and stable ezrin activation through phosphorylation, consistent with a role of ezrin in CD95 sensitization was reported (124). The HIV envelope protein has also been reported to cause apoptosis by binding to chemokine co-receptor (125-128). We demonstrated that incubation of resting $CD4^+$ T cells from healthy donors with HIV-1 or macaque cells with SIVmac251, even in the presence of an inhibitor of the viral replication, is sufficient to prime $CD4^+$ T cells for apoptosis (62, 129, 130) and sensitizing T cells to CD95-mediated apoptosis. It has been shown that apoptosis can be induced by conformationally noninfectious HIV particles suggesting that immunopathogenesis may not depend solely on direct cytopathic effects of HIV replication but that HIV-1 virions may also contribute importantly (131, 132).

Individual variations in chemokine receptor expression (133, 134) may also determine $CD4^+$ T cell death because the sensitivity of $CD4^+$ T cells to die *in vitro* depends on the levels and on the nature of the chemokine receptors expressed (117, 129, 130, 135, 136). In peripheral blood mononuclear cells, syncytium-inducing (SI, X4-tropic strains) human immunodeficiency virus type 1 (HIV-1) infects and depletes all $CD4^+$ T cells, including naive T cells. Non-SI HIV-1 infects and depletes only the CCR5-expressing T-cell subset. This may explain the accelerated CD4+ T cell loss after SI conversion in vivo, and associated with a poor prognostic and aids outcome. It has been proposed that ligation of the CXCR4 molecule, the main coreceptor of syncytia inducing (SI) virus, alone causes p38 activation and apoptosis ("direct effect") (137). Moreover, we found that a strain of SIV that uses CCR5 and BOB/GPR15 as co-receptors causes also death of noncycling primary CD4+ T cells (62). Thus, the extent of in vivo expression of BOB/GRP15 and of CCR5 could impact on disease outcome. Strategies involving the use of molecules which block viral binding to CCR5 have been assessed in the past few years in the macaque model for their ability to prevent SIV infection or to induce a decrease in viral load but their efficacy is incomplete (138), suggesting either that the levels of CCR5 differ between individuals or that an alternative co-receptor is involved in cell death induction such as BOB/GRP15. Paradoxically, its dynamics is unknown. Finally, given that the engagement of co-receptors may induce the release of interleukins that have been reported to exert pro-apoptotic activities, such as IL-10 (18, 97) and more recently type 1 interferon through a TRAIL-dependent pathway (139, 140), an indirect effect may be also operating.

Therefore, as most of the HIV particles produced are non infectious, the simple fixation and/or penetration of viruses, without integration, may be sufficient to prime T cells for apoptosis in quiescent cells.

7. CYTOKINES REGULATE MEMORY CD4 T CELL APOPTOSIS

In keeping with the idea that costimulatory signals and cytokines play a key role in the control of T cell survival and T cell death during HIV infection, we and others have found that several cytokines exert a preventive effect on T cell death of HIV-infected individuals (18, 97, 98, 141-144). 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. Moreover, IL-12, which up-regulates TH1 functions and prevents TCR-mediated $CD4^+$ T cell apoptosis, also prevents Fas-mediated apoptosis of $CD4^+$ T cells from HIV-infected persons (97, 98). 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. 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 from HIV infected individuals. IL-15 can also inhibit T cell apoptosis and enhances the function of HIV-specific $CD8^+$ T cells. Similarly, these cytokines prevent apoptosis of T cells from SIV-infected macaques (111). In humans, interleukin 7 (IL-7) is involved in normal T lymphopoiesis, but also acts as a survival factor for peripheral T lymphocytes (145, 146). IL-7 prevent activated T cell death *in vitro* via a signal thought to be mediated by the gamma chain receptor (147). IL-7 is a key cytokine in HIV pathogenesis and is associated with an unfavorable prognosis (148-150). Serum IL-7 concentrations are inversely correlated with $CD4^+$ and $CD8^+$ T cell counts during HIV infection. *In vitro* treatment of naive T cells with IL-7 may favor the replication of X4 and R5 HIV strains (151, 152) and the emergence of X4 variants (148). We found that *in vitro* treatment with IL-7 favors X4-mediated $CD4^+$ T cell apoptosis through Fas (136). Moreover, IL-7 not only sensitized T lymphocytes to undergo apoptosis (153) but also neurons (154). Altogether these data suggest that IL-7 may have a deleterious effect on HIV pathogenesis and that exogenous IL-7 must be used with caution during HIV infection.

The protein PD-1 (programmed death 1) was originally isolated from a cytotoxic T-cell line CTTL-2 following IL-2 deprival that promote apoptosis (155). During HIV infection, it has been proposed a defect in IL-2 expression coincident with the progressive depletion of $CD4^+$ T cells and disease outcome. Recently, in HIV-infected individuals, it has been shown greater expression of PD-1, and that blocking the interaction between PD-1 and PD-L1 increases the capacity of peripheral blood HIV-specific T cells to proliferate and survive (156-158). We found in SIV-infected RMs that PD-1 is more abundantly expressed on T cells from Mesenteric LNs than in peripheral blood. Most importantly, PD-1 is higher expressed on cell surface of T cells from individuals that progress more rapidly to AIDS ("non-controllers"). Interestingly, we found that PD-1 expression is enhanced by incubation in the presence of TGF-ß (159), an immunosuppressive cytokine highly expressed in the tissues of SIV-infected monkeys. In fact, PD-1 signaling inhibits Akt phosphorylation by preventing CD28-mediated activation of phosphatidylinositol 3-kinase (PI3K) favoring cell death (160). In addition to PD-1, it has been shown that the inhibitory immunoregulatory receptor CTLA-4 signaling inhibits Akt phosphorylation. CTLA-4 was selectively upregulated in human immunodeficiency virus (HIV)-specific $CD4^+$ T cells but not CD8 T cells and CTLA-4 expression correlated positively with disease progression and negatively with the capacity of $CD4^+$ T cells to produce interleukin 2 in response to viral antigen (161). Thus, several molecules expressed on the surface of T cells that may impact cell signaling in inducing apoptosis.

8. DEATH OF MEMORY CD4 T CELL IS ASSOCIATED WITH MITOCHONDRIAL PERMEABILIZATION

Spontaneous T cell apoptosis is associated with a loss of the inner 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 (162) and in SIV-infected RMS (62, 111). Thus, the rate of spontaneous $CD4^+$ T cell apoptosis early after SIV infection post-infection is predictive of progression towards AIDS, and that this apoptotic process follows the intrinsic (rather than the extrinsic) cell death pathway (62). Indeed, the broad caspase inhibitor zVAD-fmk has no preventive effect on T cell death (62, 111). AIF has been proposed as a major effector released from the mitochondria into the cytosol in a caspase-independent pathway (163). However, this observation remains controversial (164). During SIV-infection, no major changes in the release of AIF from the mitochondria was observed (62). Bax and Bak, in the regulation of death-by-neglect and loss of mitochondrial homeostasis, represent the main actors controlling mitochondria (165). Because Bax and Bak affects the mitochondria electron transport (following cytochrome c release and loss of ATP), which results in the disruption of the mitochondrial membrane potential (166), this may provide at least one mechanism leading to the death of the $CD4^+$ T cells during primary infection. Alteration of mitochondria has been observed in peripheral blood mononuclear cells from HIV-infected individuals (167). During SIV-infection, both during the acute and the chronic phase, greater expression of Bak in $CD4^+$ T cells was observed (62, 111). Although, it has been reported in HIV-infected individuals that p53 phosphorylation on serine 15 is correlated with plasma viral load and death (168) as well p38 MAP kinase**,** we do not observed a correlation with p53ser15 in $CD4^+$ T cells but in $CD8^+$ T cells (62). The level of p53ser15 in $CD8^+$ T cells is predictive of disease progression and viral dissemination in the body (159). Interestingly, IL-2 and IL-15 reduced the death rate of $CD4^+$ and $CD8^+$ T cells from SIVmac251-infected macaques suggesting that cytokines prevent mitochondrial outer membrane permeabilization (169, 170).

Bim is required for efficient death-by-neglect (growth factor deprival), as Bim-/- mice have lymphoid hyperplasia and lymphocytes display partial resistance to death-by-

neglect (171, 172). The cell death observed in multiple tissues of Bcl-2-/- mice also require Bim activity, because Bim deficiency can rescue some aspects of Bcl-2-deficiency. Bim is localized to intracellular membranes to regulate Bcl-2 and Bcl-XL. More recently, a cooperation between Bim and CD95 has been proposed in the shutdown of autoimmunity (173-175). During SIV infection of RMs, we found that in addition to the extrinsic pathway involving Fas, Bim is increased in T cells from SIV-infected monkeys (111). More recently, it has been proposed a role of the transcription factor Foxo3a in the regulation of Bim and T cell apoptosis in HIV-infected individuals (176). However, the authors proposed a role of Bim in preventing Fas-mediated cell death which is a non classical cascade of event. An increased lymphocyte susceptibility to apoptosis, that is though to be related to heightened levels of immune activation, has been proposed as one of the main mechanisms responsible for the $CD4^+$ T-cell depletion *in vivo* during pathogenic HIV and SIV infections (22, 111, 177). Thus, in non-progressing hosts such as SMs or AGMs, it has been shown during the chronic phase that the level of the immune activation remains relatively low when compared to RMs (19, 32, 33, 50, 51). Similarly, a further and early divergence between SIV-infected RMs and AGMs was also observed during the acute phase in terms of dynamics of T and B cell proliferation in lymph nodes, with RMs showing significantly higher levels of $Ki67^+$ cells in the T cell zones, whereas AGMs displayed a low frequency of $Ki67^+$ (59). Therefore, Fas and Bim could represent the two main components controlling the balance between survival and death of activated memory T cells during HIV and SIV infection.

In conclusion, altogether these results demonstrate that early after infection, the death of effector memory $CD4^+$ T cells is a key event in further progression to AIDS. At this stage, based on animal models, we can conclude that viral replication by itself can not support the extent of cell death, and therefore involves indirect mechanisms (for i.e. immune activation, immunosuppressive cytokines, or apoptogenic factors). Clearly, CD95 and Bim may represent potent targets to prevent T cell apoptois during HIV infection and must be used with caution due to the risk of autoimmunity. Therapies based on the used of cytokines or inhibitors of immunosuppressive factors as well represent alternative approaches to modulate the death of $CD4^+$ T cells. Since the quality of the $CD4^+$ T cells affects the cytotoxic $CD8^+$ T cell response, it is likely that inhibiting the death of effector memory $CD4^+$ T cells early after infection could favor the control of infection and prevent AIDS.

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This work is dedicated to the memory of BH.

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