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Review

Apoptotic cell death and cytokine dysregulation in human immunodeficiency virus infection: pivotal factors in disease progression

Mario Clerici[1,3], Apurva Sarin[2], Pierre A. Henkart[2] and Gene M. Shearer[2]

[1] Cattedra di Immunologia, Universita' degli Studi di Milano, Padiglione L.I.T.A., Ospedale L. Sacco, Via G.B. Grassi, 74, 20154, Milano, Italy
[2] Experimental Immunology Branch, NCI, NIH, Bethesda, MD, 20892, USA
[3] corresponding author: Mario Clerici, MD, Cattedra di Immunologia, Università degli Studi di Milano, Via Venezian, 1, 20133 Milano, Italy. tel: 39-2-3821-03-54; fax: 39-2-3821-0350; e-mail: mago@imiucca. csi.unimi.it

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Abstract

The progressive loss of CD4 T lymphocyte is patognomonic of Human Immunodeficiency Virus (HIV) infection and results in immunodeficiency and the appearance of acquired immunodeficiency syndrome (AIDS)-defining pathologies. Although a percentage of CD4 T lymphocytes is destroyed directly by HIV infection, a much higher proportion of lymphocytes remains uninfected and therefore must be destroyed by mechanisms not directly involving viral infection. One such mechanism is apoptotic T cell death (ATCD). ATCD in HIV infection has been shown to be: 1) secondary to cross-linking of CD4 by viral proteins; 2) mediated by both APO-1/Fas and lymphotoxin (LT); and 3) differentially modulated by type 1 and type 2 cytokines. We will briefly analyze the experimental evidences suggesting that ATCD contributes significantly to the immunopathogenesis of HIV/AIDS via depletion of CD4$^+$ T cells.

Keywords: apoptosis; programmed cell death; HIV; AIDS; immunology; cytokines; T lymphocytes

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ATCD, apoptotic T cell death; LT, lymphotoxin; SIV, simian immunodeficiency virus; CTL, cytotoxic T cell-mediated; TNF, tumour necrosis factor; IL, interleukin; IFNg, interferon gamma; TH, T helper; FasL, Fas ligand; sAPO-1/Fas, soluble form of APO-1/Fas; APC, antigen presenting cells; MLR, mixed lymphocyte reaction; PHA, phytohaemagglutinin; CEL, cell antiviral factor; TcR, T cell receptor; PCD, programmed cell death

Introduction

Apoptotic T cell death (ATCD) is an active process in which chromatin condensation and DNA fragmentation is associated with the death of T lymphocyte and other cell types (rev in Ameisen, 1994). ATCD has essential physiological roles in embriogenesis (rev. in Ellis *et al*, 1991; Cohen *et al*, 1992) including the regulation of positive and negative selection of immature thymocytes (rev. in Ransdell and Fowlkes, 1990), thus influencing and shaping the final T cell repertoire. In human immunodeficiency virus (HIV) infection, progression of disease classically results from the destruction of CD4$^+$ T lymphocytes. Despite years of investigation, the mechanism(s) responsible for the death of this subset of cells has not yet been completely elucidated. Different mechanisms have classically been suggested to be involved in the depletion of CD4 lymphocytes. Thus, CD4$^+$ T cell destruction can be provoked by direct viral infection of target cells resulting in: (1) HIV budding from infected cells with subsequent creation of pores and osmotic death; (2) generation of non-vital syncytia between HIV-infected and uninfected cells; and (3) toxic effects secondary to the presence of proviral DNA in the cytoplasm of host cells (rev. in Weiss, 1993; Levy 1993). Recently, elegant studies have highlighted the role that accelerated and extensive viral replication has in the destruction of CD4$^+$ lymphocytes (Wei *et al*, 1995; Ho *et al*, 1995). Thus, it was estimated that more than 10^9 new viral particles are formed every day in HIV infected individuals, and that approximately 5% of the circulating pool of CD4 T lymphocytes is destroyed and replenished daily as a consequence of such massive turn over (Wei *et al*, 1995; Ho *et al*, 1995). Even more recently, the half life of simian immunodeficiency virus (SIV) in macaques continuously infused with virus was calculated to be equal to 20–30 min (Ho *et al*, 1997). Despite raising some questions about the artificiality of the experimental model chosen, these data emphasize the important contribution of direct virus killing in HIV and SIV retroviral infections. Predictions from these mathematical models postulated that therapy that reduces HIV viral load to undetectable values would result in a quantitative reconstitution of the circulating pool of CD4 T lymphocytes (Wei *et al*, 1995; Ho *et al*, 1995). Despite the availability of such therapy, capable of inducing powerful and long-lasting reductions in HIV viral load, these predictions were not fulfilled (see further), raising questions about the role that other factors might play in the depletion of CD4 lymphocytes seen in disease progression.

Apoptotic cell death plays a fundamental role in CD4$^+$ T cell depletion in HIV infection; experimental evidences

It is unlikely that a cytopathic effect of HIV on infected cells can account for the depletion of CD4$^+$ T cells that is

characteristic of HIV infection. Infact: (1) only a minority of T lymphocytes contains HIV genetic material; and (2) the percentage of CD4 loss attributable to direct HIV infection was recently evaluated to be roughly 10% of the circulating pool even in the most advanced phases of the disease (Haase, 1996). Additionally, the increases in the number of circulating CD4 in patients undergoing antiretroviral therapies that include the use of protease inhibitors, and in whom HIV viral load is virtually reduced to zero, are only partial (Kelleher *et al*, 1996; Connors *et al*, 1997). Additional discrepancies are observed in patients treated with these therapies. Thus: (1) the persistent suppression of HIV viral load, often under the limit of detectability, is associated with increases in $CD4^+$ T cell counts that are only observed in the first weeks or months of therapy (Kelleher *et al*, 1996; Connors *et al*, 1997); and (2) antiretroviral therapies are not associated with modification of *in vitro* susceptibility of peripheral blood mononuclear cells to apoptosis. These data suggest that mathematical models predicting viral replication to be the only factor responsible for CD4 depletion and disease progression have not taken in consideration other mechanisms that could be responsible for such processes.

Non-virally mediated mechanisms that have been known to be involved in the destruction of $CD4^+$ T cells in HIV infection include lysis of lymphocytes via antibody dependent complement cytotoxicity, and cytotoxic T cell-mediated (CTL) destruction of targets presenting either viral products or HLA alloantigens on their surface. These mechanisms have been reviewed elsewhere by others (Levy 1993; Zinkernagel and Hengartner, 1994) and will not be covered in this article. An alternate mechanism that could lead to CD4 depletion was recently presented by Wolthers and colleagues (1996). These authors have analyzed telomere length in CD4 and CD8 lymphocyte of HIV-infected individuals and have observed that the telomere length of the terminal restriction fragment was reduced in CD8+ but not in CD4+ T cells of HIV-seropositive individuals. The authors have thus put forward the hypothesis that depletion of CD4 T cells might be secondary not to an increased death of mature T cells, but rather to an interference of CD4 T cell renewal from progenitors. In this review we will nevertheless focus on the pathogenetic role of ATCD in the progression of HIV infection.

T lymphocytes of HIV infected patients were observed to undergo apoptosis without stimulation (Laurent-Crawfors *et al*, 1991; Gougeon *et al*, 1991; Ameisen and Capron, 1991; Meeyard *et al*, 1992) or when stimulated with antigens or mitogens (Groux *et al*., 1992; Oyazu *et al*, 1993; Banda *et al*, 1993; Clerici *et al*, 1994) and *in vitro* infection of HIV-seronegative lymphocytes induces apoptosis (Terai *et al*, 1991). Even more important, apoptotic death of HIV infected lymphocytes was shown to be dominant in uninfected, bystander cells and not in productively infected cells, both in the peripheral blood and in lymph nodes of HIV-seropositive individuals (Finkel *et al*, 1995; Piazza *et al*, 1997). Apoptotic death in HIV infection was subsequently established to be associated with at least two different components of the nerve growth factor/tumor necrosis factor (TNF) receptor family: lymphotoxin (LT) (Clerici *et al*, 1996) and APO-1/Fas (Fas) (Katsikis *et al*, 1995; Silvestris *et al*, 1996; Estaquier *et al*, 1996; Sloan *et al*, 1997). ATCD was also suggested to be reduced by soluble APO-1/Fas (sAPO-1/Fas), a soluble form of APO-1/Fas that prevents engagement of membrane-bound Fas and thus reduces Fas-mediated apoptosis (Cheng *et al*, 1994). Finally, susceptibility of lymphocytes to ATCD in HIV infection was observed to be differentially regulated by interleukin (IL)-2; interferon gamma (IFNg) and IL-12 (type 1 cytokines) as opposed to IL-4 and IL-10 (type 2 cytokines). Thus, type 1 cytokines were shown to have a protective role in preventing ATCD whereas type 2 cytokines were not protective, and augmented ATCD of peripheral lymphocytes in some HIV infected individuals (Clerici *et al*, 1994, 1996; Radrizzani *et al*, 1996; Estaquier *et al*, 1996). The potential relevance of ATCD in disease progression was illustrated by the following observations: (1) the percentage of lymphocyte spontaneously undergoing apoptosis is directly proportional to the reduction in $CD4^+$ T cell counts (Gougeon *et al*, 1996); (2) susceptibility of antigen- and mitogen-stimulated peripheral lymphocyte to apoptosis increases with disease progression (Gougeon *et al*, 1996); (3) serum concentration of LT and sAPO-1/Fas are predictors of disease progression independent of HIV viral load (Medrano *et al*, 1997); and (4) apoptosis is not present in HIV infected chimpanzees in whom $CD4^+$ T cell depletion, alteration of T helper (TH) cell function, and the development of AIDS are not observed (Heeney *et al*, 1993; Gougeon *et al*, 1993, 1996), but is observed in macaques infected with pathogenic strains of SIV (Estaquier *et al*., 1994).

The Fas/Fas ligand system and apoptosis in HIV infection

Activation of Fas by it ligand (FasL) can trigger T cell proliferation and cytokine production or can induce apoptosis in susceptible cells (Yonehara *et al*, 1989; Ito *et al*, 1991; Alderson *et al*, 1995; Dhein *et al*, 1995; Force *et al*, 1995; Ju *et al*, 1995; Nagata and Golstein, 1995). This system is finely regulated as it was recently shown that a soluble form of Fas (sAPO-1/Fas) can prevent the interaction between Fas and FasL thus reducing apoptosis (Cheng *et al*, 1994).

Because different pathologic conditions are associated with reduction in the serum concentration of sAPO-1/Fas (Tanaka *et al*, 1996), this is an approach by which Fas-dependent ATCD can be modulated. Surface expression of Fas was found to be increased on lymphocytes of HIV-infected individuals (Debatin *et al*, 1994; McCloskey *et al*, 1995; Silvestris *et al*, 1996). Additionally, the interaction of Fas with its ligand in HIV-infected cells provokes ATCD in a much higher percentage of lymphocyte (Katsikis *et al*, 1995; Sloan *et al*, 1997). Thus, lymphocytes of HIV-seropositive individuals express Fas in higher quantities and are more prone to undergo ATCD upon ligation of this receptor. Recent data suggest that activated CD4 T lymphocytes can kill CD8 effector T cells via Fas/FasL mediated apoptosis (Piazza *et al*, 1997). If these data can be extended to the setting of HIV infection, it is possible that such a mechanism could explain selective killing of

Table 1 Experimental evidences (*in vitro*) suggesting a role for alterations of the Fas/Fas ligand (FasL), soluble APO-1/Fas (sAPO-1/Fas) system in HIV infection

Experimental observation
Up-regulation of Fas on lymphocyte of HIV-infected individuals
Augmented susceptibility of lymphocyte of HIV-infected individuals to undergo apoptosis upon ligation of Fas
Correlation between expression of Fas/susceptability of Fas ligation to apoptosis and clinical stage of HIV infection
Monocyte- CD4/Fas-FasL 'Kiss of death'
CD4-CD8/Fas-FasL 'Kiss of death'
Prevention of Fas-induced apoptosis by IL-12
Reduced serum concentration of sAPO-1/Fas in progressing HIV infection

HIV-specific CTL, allowing viral mutants to escape immune recognition and control. Another recent set of data shows that up-regulation of Fas on monocytes is observed in HIV infection, and postulates the augmented expression of Fas on these cells to be responsible for the destruction of uninfected CD4 T lymphocyte subsequent to antigenic presentation and Fas interaction, via a classical 'kiss of death' mechanism (Badley *et al*, 1997). Different experimental findings support a role for the quantitative/qualitative alterations of the Fas/FasL system in the progression of HIV infection to AIDS (Table 1).

In summary: (1) surface expression of Fas is augmented in disease progression and individuals with AIDS and opportunistic infections express significantly more Fas than asymptomatic patients (Debatin *et al*, 1994; McCloskey *et al*, 1995; Sivestrisn *et al*, 1996); (2) ATCD induced by engagement of Fas on the surface of CD4 lymphocyte is higher in symptomatic than in asymptomatic HIV-infected individuals (Katsikis *et al*, 1995; Sloan *et al*, 1997); (3) the magnitude of anti-Fas-induced ATCD inversely correlates with absolute CD4 cell counts (Katsikis *et al*, 1995); and (4) IL-12 (the generation of which decreases in the progression of HIV infection) prevents Fas-mediated apoptosis of lymphocyte of HIV-seropositive individuals (Radrizzani *et al*, 1995). A different set of data further supports the importance of Fas/FasL in the pathogenesis of HIV infection. Low serum concentrations of sAPO-1/Fas were recently shown to have a strong independent predictive power for progression to AIDS in a multivariate conditional logistic regression model that included among other variables, HIV viral load at entry (Medrano *et al*, 1997). Thus, complex alteration of the Fas/FasL/sAPO-1/Fas system are present in HIV infection and are likely to be involved in $CD4^+$ T cell depletion and in the progression of HIV infection.

Cell mediated immunity is defective in HIV infection

The progression of HIV infection is also characterized by a complex dysregulation in the function of TH cells (Lane *et al*, 1985; Giorgi *et al*, 1987; Miedema *et al*, 1988; Clerici *et al*, 1989). At least two different types of functional defects have been observed in HIV-infected individuals. Thus, defects in both TH-antigen presenting cells (APC) interactions and in cytokine production were described. The defects associated with the interaction between TH and APC are multiple and sequential, and can be summarized as follows: (1) TH defects (analyzed as the ability of TH lymphocytes to proliferate and to secrete IL-2) to soluble antigens appear early in the disease (Clerici *et al*, 1989). Because soluble antigens need to be processed and presented on the surface of autologous APC in association with MHC class II to CD4 T lymphocyte (rev. in Naor, 1992), this is the most sensitive index of dysfuction of these lymphocyte. That is defect is not secondary to an impairment in the capacity of APC to process/present antigenic peptides was shown by experiments in which soluble antigen-sensitised APC from HIV-infected monozygotic twins were able to stimulate CD4 TH of the HIV-uninfected twins (Clerici *et al*, 1990; Blauvelt *et al*, 1995); (2) Defects in TH function in response to stimulation with allogeneic lymphocytes in a mixed lymphocyte reaction (MLR) appear next, in patients in whom the ability to respond to soluble antigens was lost earlier (Clerici *et al*, 1989). Because both CD4 and CD8 T lymphocytes are stimulated in MLR and both autologous and heterologous APC can stimulate lymphocytes (Via *et al*, 1990), this TH defect is less specific for CD4 TH lymphocytes; (3) PHA-stimulated proliferation and IL-2 production can become defective in HIV-seropositive individuals in whom TH defects to soluble antigens and alloantigens are observed. Because both CD4 and CD8 T cells are stimulated by PHA and because the ability of this mitogen to stimulate lymphocyte is only marginally dependent on APC, the inability to respond to mitogens is an index of a profound and massive impairment in TH function in HIV infected patients (Clerici *et al*, 1989). These functional defects are: (1) observed in the majority of HIV-seropositive individual even during the phase of clinical latency; (2) sequential (i.e. loss of response to soluble antigens preceeds loss of response to alloantigens which preceeds the inability to respond to PHA); and (3) independent of changes in CD4 cell counts (Clerici *et al*, 1989). From a practical standpoint, these functional defects were shown to be predictive for three major clinical endpoints: (1) destruction of CD4 T lymphocytes and disease progression (Lucey *et al*, 1991); (2) time to AIDS (Dolan *et al*, 1995); and (3) time to death (Dolan *et al*, 1995). Thus, a recent publication analyzed time to AIDS diagnosis and survival time in a group of HIV seropositive individuals and observed significantly longer disease-free time and survival in those individuals in whom no *in vitro* TH defects to either soluble antigens, alloantigens, or PHA were detected at the time of entry into the study (Dolan *et al*, 1995).

More recently, alterations in cytokine production were reported to be associated with the progression of HIV infection (rev. in Clerici and Shearer, 1993, 1994a; Klein *et al*, 1997). A series of reports analyzed the production of two functionally distinct families of cytokines: type 1 cytokines (IL-2; IFNg; IL-12; IL-15) that are mainly aimed at the activation of cell mediated immunity and the destruction of intracellular parasites; and type 2 cytokines (IL-4; IL-5; IL-6; IL-10; IL-13), more targeted toward the activation of B lymphocyte and protection against extracellular microorganisms. A progressive decline in type 1 cytokines and a parallel increase in the generation of some type 2 cytokines, and a subsequent shift away from cell mediated

immunity and in favor of humoral immunity were suggested to characterize the course of HIV infection (rev. in Clerici and Shearer, 1993; 1994a; Klein *et al*, 1997). This hypothesis was confirmed by different lines of investigation. To summarize: (1) IL-2 and IL-12 production are reduced in HIV-seropositive patients and both IL-12 and IL-15 restore *in vitro* defective soluble antigen-stimulated proliferation of TH cells from HIV-infected individuals (see above) (rev. in Clerici and Shearer, 1993; 1994a; Seder *et al*, 1995); (2) increased IL-4, IL-6, IL-10, and/or IL-13 production are present in HIV infection, and anti-IL-4 as well as anti-IL-10 neutralizing antibodies increase antigen-stimulated proliferation of HIV-infected lymphocyte (rev. in Clerici and Shearer, 1993; 1994a); (3) a strong production of IL-2 and IFNg and weak production of IL-4 and IL-10 are observed in both adult and pediatric long-term non-progressing HIV seropositive individuals, whereas a specular cytokine pattern is detected in patients who progress towards AIDS (Vigano' *et al*, 1995; Clerici *et al*, 1996); (4) the ability to respond to common antigens *in vivo* in a delayed type hypersensitivity reaction, a classical type 1 cytokines-driven reaction, is lost in, and predictive for, disease progression (Blatt *et al*, 1993; Dolan *et al*, 1995); (5) *in vivo*, the presence of hematological parameters associated with a type 2 cytokine production such as IL-4 driven hyper-IgE (Lucey *et al*, 1991; Israel-Biet *et al*, 1993) and IL-5 driven hypereosinophilia (Fleury-Feith *et al*, 1992; Smith *et al*, 1994, Caterino-de-Araujo, 1994) are unfavorable prognostic factors and are clinically associated with rapid disease progression.

Additionally, it was shown that cytokine impairment and defects in TH cell function are not present in HIV-infected chimpanzees, in which infection and seroconversion are not accompanied by disease progression (Heeney *et al*, 1993; Gougeon *et al*, 1993, 1996). More recent results from experiments in which macaques were infected with either normally pathogenic SIV strains or with non-pathogenic Nef-deleted strains of SIV showed infection with the latter strains of virus to be associated with the preferential development of a type 1 cytokine pattern, and this pattern to be predictive of disease outcome (Zou *et al*, 1997). Finally, the C-C chemokines MIP-1α, MIP-1β and RANTES as well as a CD8-secreted cell antiviral factor (CAF), were observed to prevent HIV infection of target lymphocyte *in vitro* (Walker *et al*, 1986; Cocchi *et al*, 1995). The syntesis of both families of soluble antiviral factors was shown to be associated with a type 1 immune response and the generation of IL-2 and IFGγ, but not of IL-4, IL-5 or IL-10 (rev. in Levy *et al*, 1996).

Cytokines influence susceptibility of lymphocytes to ATCD in HIV infection

In an attempt to correlate seemingly independent observations, the possible association between HIV disease progression, impairment of cytokine production, and destruction of $CD4^+$ T lymphocytes (ATCD) was analyzed by a number of investigators. Background for this line of research stems from results showing that cytokines can influence T cell receptor (TcR) programmed cell death (PCD), as IL-2 was capable of blocking α-CD3- induced PCD of both $CD4^+CD8^-$ and $CD4^-CD8^+$ resting thymocytes (Nieto *et al*, 1990; Groux *et al*, 1993). Additionally, other researchers have shown that exogenously supplemented IL-2 results in Bcl-2-mediated increased survival of memory T cells, and removal of IL-2 from activated T cells results in down-modulation of Bcl-2 and apoptosis. In summary: (1) after antigen recognition via their T cell receptor (TcR) normal T cells, instead of classically becoming activated to proliferate can undergo PCD (rev. in Golstein *et al*, 1991, Cohen *et al*, 1992, Ameisen, 1994); (2) lymphocytes of HIV infected patients are particularly susceptible to TcR-induced ATCD (rev. in Ameisen, 1994); (3) loss of type 1 cytokine and increase in type 2 cytokine are observed in HIV infection (rev. in Clerici and Shearer, 1993). Results of these investigations have shown that *in vitro* antigen- and mitogen-stimulated ATCD of lymphocytes in HIV-infected individuals is influenced by cytokines. Thus, the addition of exogenous type-1 IFNg, IL-2, and IL-12 blocks T lymphocyte ATCD (Clerici *et al*, 1994, 1996; Radrizzani *et al*, 1996; Estaquier *et al*, 1996). In contrast, the type-2 lymphokines IL-4 and IL-10, have either no effect or enhance *in vitro* T cell ATCD (Clerici *et al*, 1994, 1996; Estaquier *et al*, 1996). Additionally, antigen- and mitogen-stimulated ATCD can be inhibited by antibodies against IL-4 and IL-10, and enhanced by anti-IL-12 (Clerici *et al*, 1994, 1996; Estaquier *et al*, 1996). In particular, it was shown that: (1) IL-12 inhibits apoptosis induced in human Th1 clones by three different methods: gp120-CD4 cross-linking, CD3-TcR activation, and IL-2 deprivation (Radrizzani *et al*, 1996); (2) IL-12 as well as neutralizing antibodies to IL-4 and IL-10 prevent activation-induced and Fas-mediated apoptosis of $CD4^+$ T lymphocytes of HIV-infected patients (Estaquier *et al*, 1996); and (3) *in vitro* stimulation of T cells via the TcR induces extensive apoptotic death of both the CD4 and CD8 subsets (Clerici *et al*, 1994), whereas antigen-stimulated apoptotic death is limited to CD4 lymphocyte of HIV-infected individuals (Clerici *et al*, 1996). Nevertheless, ATCD is blocked in both cases by type 1, but not by type 2 cytokines (Clerici *et al*, 1994, 1996); and (4) type 1 but not type 2 cytokines can prevent LT-mediated ATCD of antigen-stimulated CD4 lymphocyte of HIV-infected indivi-

Table 2 Effects of type 1 and type 2 cytokines on susceptibility to apoptosis of peripheral lymphocyte in HIV infection. Experiments were performed *in vitro*

Cytokine	Biologic effect on apoptosis of peripheral lymphocytes
Type 1 cytokines	
Interleukin-2	Reduction
Interferon gamma	Reduction
Interleukin-12	Reduction
Type 2 cytokines	
Interleukin-4	No effect or augmentation
Interleukin-10	No effect or augmentation
Neutralizing antibodies to type 1 cytokines	
anti-interleukin-2	No effect or augmentation
anti-interleukin-12	No effect or augmentation
Neutralizing antibodies to type 2 cytokines	
anti-interleukin-4	Reduction
anti-interleukin-10	Reduction

duals (Clerici *et al*, 1996). These data indicate that cytokines are able to modulate apoptosis mediated by the three major known mechanisms: Bcl-2; Fas; and LT (Table 2).

From the evidences presented above, it appears that ATCD is a major contributor to the destruction of $CD4^+$ T lymphocytes in HIV disease via mechanisms independent of actual infection of the target cells, and that the profound dysregulation of the immune response present in this infection influences the phenomenon. But, how can HIV uninfected lymphocyte be sensitised to undergo ATCD? The finding that stimulation with CD4-dependent antigens such as gp120 peptides increase ATCD in the CD4 but not in the CD8 subset, suggests *in vivo* antigenic stimulation through infections to initiate extensive apoptotic death that is selective for CD4 T cells specific for antigens other than those used to initiate the death signal. Exposure of CD4 T

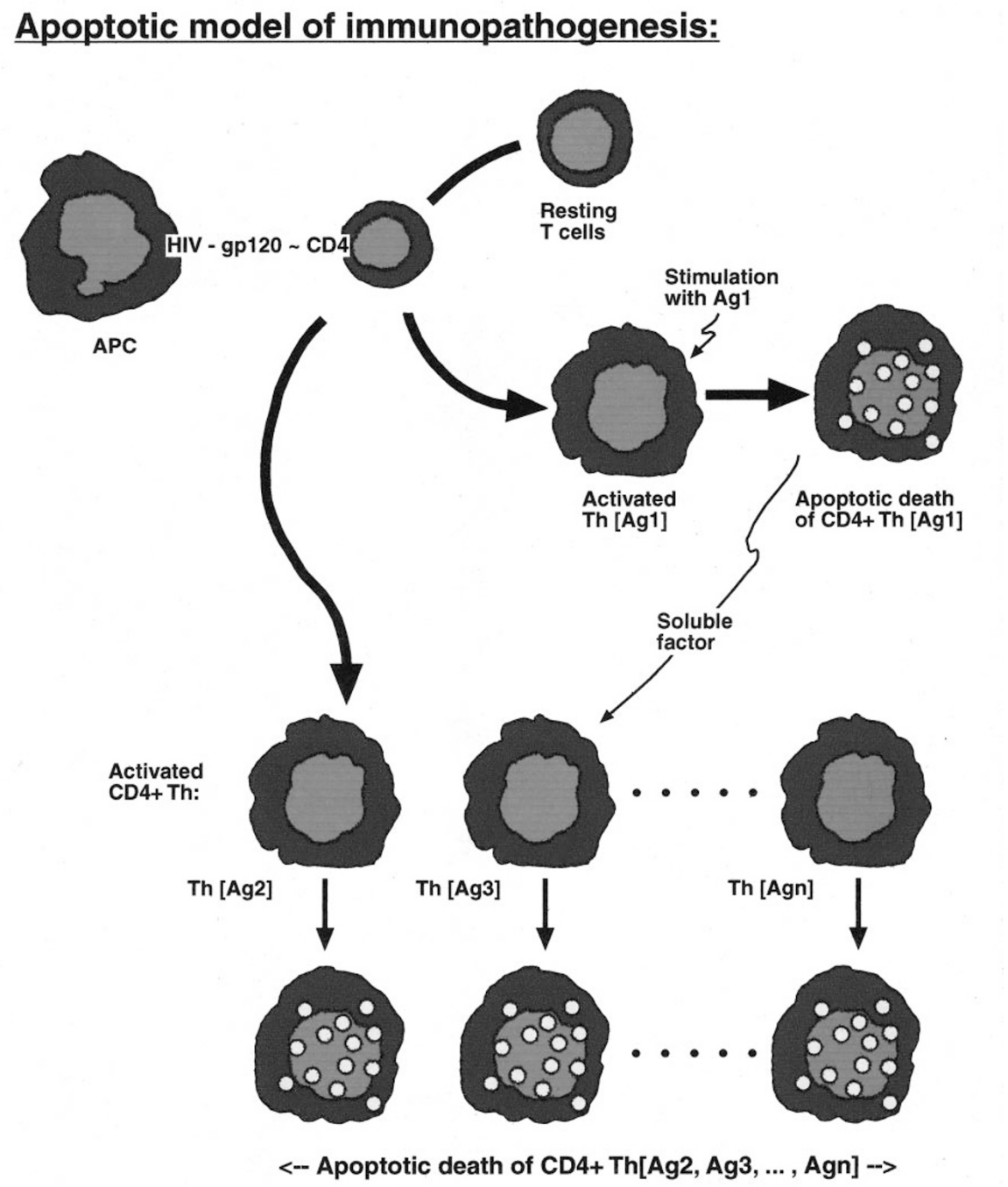

Figure 1 Model of extensive T cell activation via gp120 (presented by APC) interaction with CD4 on T lymphocytes. Activated T cells of different specificities are then susceptible to ATCD that is effected by LT (or Fas) released by antigen stimulation (with Ag 1) of an activated T cell clone

cells to HIV or HIV products could activate or sensitize T cells for a secondary ATCD - inducing stimulus, resulting in extensive T cell death (Figure 1). In this context, gp120 protein crosslinked to uninfected CD4 T cells followed by T cell receptor signaling has been reported to induce apoptotic T cell death, and Tat was similarly shown to sensitize uninfected CD4 T cells for antigen-stimulated apoptotic death (extremely interesting in this regard is the observation by Ehret *et al*., 1996, showing that T cells form chimpanzees resist Tat-induced apoptosis). More recently (see above) interaction between APC-expressing Fas and uninfected $CD4^+$ T cells was shown to deliver a 'kiss of death' to such cells. These non-infectious interactions between CD4 T cells and HIV or its products are likely to contribute appreciably to the depletion of CD4 T cells in HIV disease, without the need for infection of such cells. This mechanism would result in pan-depletion of activated T cells expressing a broad spectrum of antigen specificities. This depletion was shown to be reduced by cytokines such as IL-2, IL-12 and IFNg, and enhanced by IL-4 and IL-10. The observation that type 1 cytokines (protective against ATCD) are reduced, whereas type 2 cytokines (non protective against ATCD) are augmented in disease progression, accounts for the continuous and massive destruction of CD4 lymphocyte and, ultimately, to the appearance of AIDS. This model is shown in Figure 1.

Conclusions

Increased susceptibility of peripheral lymphocytes to ATCD characterizes the progression of HIV infection to AIDS. ATCD in HIV infection is dominant in virus-uninfected cells and appears to be mediated by at least two pathways, the first dependent of Fas and the second on LT. Progression of HIV disease to AIDS is also accompanied by alterations in the imbalance between the production of type 1 and type 2 cytokines. These apparently unrelated observations were linked by recent reports showing that the tendency of $CD4^+$ T lymphocytes of HIV infected individuals to undergo apoptosis is differently modulated by type 1 cytokines (protective against both Fas- and LT-mediated apoptosis) that decline, and type 2 cytokines (not protective and possibly enhancing ATCD) that augment in in disease progression. The recent reports of consistent increases in CD4 counts in patients receiving intermittent IL-2 therapy (Kovacs *et al*., 1995) support these experimental findings and reinforce the suggestion that rational end efficient drug therapy in HIV infection would possibly combine three distinct classes of drugs, namely antiretrovirals; immunomodulants; and agents targetted at preventing apoptosis of uninfected cells.

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