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MINIREVIEW

Role of the Fas/Fas Ligand Apoptotic Pathway in Human Immunodeficiency Virus Type 1 Disease

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APOPTOSIS AND THE DEPLETION OF CD4$^+$ T CELLS

Infection with human immunodeficiency virus type 1 (HIV-1) is characterized by the gradual and inexorable depletion of CD4$^+$ T lymphocytes. The pathogenetic importance of the loss of these cells is unquestioned since it correlates with the loss of immune capabilities and the consequent occurrence and severity of opportunistic infections and neoplasias. Thus, it is axiomatic that understanding the pathogenesis of HIV-1 disease requires an appreciation for the mechanisms involved in the loss of CD4$^+$ T cells.

In 1991, several groups of scientists proposed that apoptosis is important in the pathogenesis of infection with HIV-1 (2, 32, 60). Most cogently, Amiesen and Capron hypothesized that the depletion of CD4$^+$ T lymphocytes in HIV-1 disease occurs by apoptosis secondary to inappropriate induction of activation-induced cell death (2). The incorporation of the concept of apoptosis into a reasonable conceptualization of HIV-1 infection was met with enthusiasm. The attractiveness of this model was due to its potential explanation of an organismal variable (the depletion of CD4$^+$ T cells in infected persons) in terms of a cellular mechanism (apoptosis). These scientists went on to propose the pharmacologic prevention of activation-induced apoptosis as a therapeutic modality for HIV-1-infected persons (2).

Soon after its publication, the hypothesis of inappropriate apoptosis in HIV-1 disease was supported by the findings of two independent groups (23, 39). They found that a greater proportion of T cells from HIV-1-infected persons died in culture than did T cells from healthy individuals. This greater propensity for apoptosis was observed for cells either left without any overt activation (spontaneous cell death) or for cells specifically activated (activation-induced cell death). Nevertheless, it should be noted that no correlation between these in vitro analyses and disease progression or virus levels has been subsequently found (40, 48).

THE FAS/FAS LIGAND APOPTOTIC PATHWAY IN HIV-1 DISEASE

In 1995, the molecular mechanism of activation-induced T-cell death was determined to involve a pair of complementary molecules called Fas (also known as CD95 and APO-1) and Fas ligand (1, 12, 18, 24). Moreover, the ligation of Fas with Fas ligand was recognized as an important homeostatic control mechanism for maintaining appropriate numbers of T cells (57). Thus, many investigators sought to test the possibility that the Fas/Fas ligand apoptotic pathway was accentuated in HIV-1-infected patients and thereby operative in depleting their CD4$^+$ T lymphocytes.

This suggestion appeared to be confirmed when several groups of scientists reported that the proportion of Fas-expressing T cells in HIV-1-infected persons increased with disease progression (5, 16, 22, 25, 52). Additionally, ligation of Fas with antibodies or with an active, soluble form of Fas ligand induced these cells to die by apoptosis (22, 25, 52). However, the implications of these findings in terms of CD4$^+$ T-cell depletion were not clear, since both CD4$^+$ and CD8$^+$ T cells demonstrated increased proportions of Fas expression and apoptosis upon ligation.

Further investigation concerning the possible involvement of the Fas/Fas ligand pathway in activation-induced cell death of T lymphocytes from HIV-1-infected persons has not produced a clear consensus. Some have found that activation-induced T-cell death is Fas dependent (10, 20), but others have not found any involvement of Fas and Fas ligand (26, 27). Recent data suggest that tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) but not Fas ligand mediates the apoptosis of activated T cells from HIV-1-infected persons (26).

The more important issue involves the possible role of the Fas/Fas ligand pathway in disease pathogenesis. However, the experiments reported thus far have not directly addressed this concern since the in vivo relevance of activating T cells in vitro has never been established. Moreover, there is no involvement of Fas and Fas ligand in the spontaneous apoptosis of peripheral blood cells from HIV-1-infected persons, which might reasonably be considered more reflective of in vivo events than activation-induced apoptosis (10, 27).

More relevant to the potential of Fas-dependent apoptosis acting in vivo was the finding that freshly isolated T lymphocytes from HIV-1-infected persons possessed Fas ligand message (10, 41, 50). Although this finding is important in considering the involvement of the Fas/Fas ligand pathway in vivo, these scientists did not observe spontaneous Fas ligand activity by blood cells in spite of the presence of the message. Consequently, the significance of the presence of the message in terms of HIV-1 disease pathogenesis is unclear.

While scientists were investigating Fas expression and activation-induced cell death, others discovered that in vitro exposure of monocytes or peripheral blood cells from healthy volunteers to HIV-1 enhanced Fas ligand mRNA and Fas ligand activity in these cells (7, 65). These data were used to support the contention that Fas ligand is involved in the depletion of T cells in HIV-1-infected persons. Additionally, simian immunodeficiency virus (SIV) infection of concanavalin A-stimulated peripheral blood mononuclear cells from healthy

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macaques enhanced Fas ligand expression, and this enhancement was related to expression of the Nef protein (68). However, the more direct demonstration that freshly isolated monocytes or other blood cells from the HIV-1-infected patients or from the SIV-infected macaques actually express cell surface Fas ligand protein and possess Fas ligand activity was not provided.

VIRAL REGULATION OF APOPTOSIS

While the concept of apoptosis in HIV-1 disease was being promulgated, a different perspective on the role of programmed cell death in viral infections was developed. Virologists were finding that viruses actively regulate apoptosis in a complex way. Viruses require live, functional cells for their own replication. An indication of the importance of cellular viability for viruses is the prevalence of viruses that have been shown to inhibit physiological cell death upon infection (47, 59, 63, 64).

Although viruses require live cells to replicate, they also have the potential to kill cells through a variety of different mechanisms (47, 59). Viruses and viral replication are often deleterious to cells and consequently can enhance apoptosis. Thus, massive viral replication, as in syncytium formation induced by HIV-1, can result in cell death (36, 56). Also, viruses produce various proteins that are noxious such as (i) the HIV-1 Tat protein, which by itself has been shown to induce apoptosis in uninfected T lymphocytes (34, 46); (ii) HIV-1 gp120, which cross-links CD4 and thereby primes cells for apoptosis (9, 35); and (iii) HIV-1 Vpr, which has a cytostatic or cytotoxic effect on cells (6, 44, 54).

It may seem paradoxical and self-contradictory to suggest that the same virus can both prevent apoptosis and induce apoptosis. Perhaps it is most clearly understood by suggesting that viruses regulate apoptosis for their own purposes which relate to their own life cycles. Thus, viruses may prevent apoptosis early in infection before viral replication has proceeded and induce apoptosis late in infection as a means of releasing viral particles. Similarly, some viruses may induce death in cells responsible for immunity but prevent death in cells that are actively infected.

Many viruses have been found to both inhibit and enhance apoptosis, including adenovirus (3, 17, 37, 59, 61, 67), baculovirus (14, 15, 45), vaccinia virus (19, 28, 33), and poliovirus (62). It is clear that HIV-1 can also regulate physiological cell death in a complex way. Some of the molecular and cellular mechanisms that mediate the various effects on apoptosis have been investigated (Table 1), and pleiomorphic effects of specific HIV-1 proteins on cell death have been found. For instance, although HIV-1 Tat can induce apoptosis (34, 38, 46), the protein also has the capacity to protect cells from dying (38, 69). Recently, HIV-1 Vpr has been shown to induce the physiological cell death of T lymphocytes in the absence of cellular activation, but the apoptosis of activated cells, which may be considered targets of viral infection, is inhibited by Vpr via IκB-mediated suppression of NF-κB (6). Understanding the complex regulation of apoptosis by viruses is key to understanding the pathogenesis of the diseases they cause.

TABLE 1. HIV-1 modulation of apoptosis

Viral protein involved	Mechanism	Reference(s)
Inhibition		
Tat	Increased Bcl-2 expression	38, 69
Vpr	IκB-mediated inhibition of NF-κB	6
p24/p17	Production of antagonistic epitopes that inhibit cytotoxic T lymphocytes	29
Not known	Inhibition of Fas ligand expression	50
Enhancement		
Tat	Increased activation of cyclin-dependent kinases	69
	Inhibition of manganese-dependent superoxide dismutase	66
	Enhanced Fas-dependent signal transduction	31
gp120/gp41	Syncytium formation	36, 56
	CD4 cross-linking	9, 35
	Cell death enhancement without hallmarks of apoptosis	31
Vpr	Not known	54

REGULATION OF APOPTOSIS IN HIV-1 DISEASE

Several findings in the last few years have suggested that the role of apoptosis in HIV-1 disease pathogenesis is more complex than is accounted for by simply proposing that the Fas/Fas ligand apoptotic pathway inappropriately induces the death of $CD4^+$ T cells. As with other viruses, HIV-1 most likely regulates apoptosis in an intricate way for the benefit of its own replication and transmission. The currently prevalent hypothesis that virus-induced, Fas/Fas ligand-dependent apoptosis is responsible for the depletion of $CD4^+$ T cells in HIV-1 disease does not take into account the varied and complex uses of apoptosis that other viruses have enlisted for their life cycles. It also does not adequately explain several relevant experimental results.

We have demonstrated that freshly isolated blood cells from HIV-1-infected patients have a deficiency in Fas ligand cell surface expression and activity compared to blood cells from uninfected, healthy volunteers (50). We tested these cells directly ex vivo for the presence of Fas ligand activity without any stimulation in vitro. Although this finding may seem paradoxical considering the presence of Fas ligand mRNA (10, 41, 50), we propose that there may be an active suppression of Fas ligand expression in HIV-1 disease as we have seen in cells infected with herpes simplex virus type 2 (51).

This suggestion is interesting in light of a recent finding indicating that cross-linking CD4 inhibits anti-CD3-induced apoptosis by inhibiting Fas ligand expression (43). Thus, virus-associated HIV-1 gp120 may be responsible for affecting Fas ligand surface levels. Another mechanism that could explain the decrease in Fas ligand expression is excessive enzymatic removal of the molecule from the cell surface. Soluble Fas ligand has been demonstrated to be elevated in the plasma of HIV-1-infected persons (8, 53). Moreover, recent findings have indicated that soluble Fas ligand inhibits the activity of the membrane-bound form of the molecule (55, 58).

Regardless of the mechanism for decreased membrane Fas ligand expression in HIV-1 disease, the suggestion that an inappropriate accentuation of the Fas/Fas ligand apoptotic pathway accounts for the depletion of $CD4^+$ T lymphocytes in HIV-1-infected persons is not likely. Our findings suggest that the Fas/Fas ligand pathway is suppressed by the viral infection in these patients (50).

Other observations also suggest that Fas-dependent apoptosis is not accentuated in HIV-1 disease. Patients preferentially accumulate T cells that express Fas and that are susceptible to killing by Fas ligand agonists (5, 16, 22, 25, 52). The accumulation of these cells suggests that they persist in infected persons instead of being depleted by apoptosis. Moreover, one group of investigators has shown that blood cells from HIV-1-

infected persons expressed high levels of Fas and Fas ligand mRNA, but they did not observe spontaneous cell death in these patient samples (41). Other groups observed spontaneous T-cell death from HIV-1-infected patients but failed to inhibit it by suppressing the Fas/Fas ligand pathway (10, 27). Consequently, there is no definitive indication that the Fas/Fas ligand apoptotic pathway is operative in HIV-1-infected patients.

Additional findings have suggested that HIV-1-mediated regulation of apoptosis is likely to have complex effects. Inhibition of apoptosis of cells infected in culture has been found to markedly enhance HIV-1 production and to facilitate persistent infection (4, 13, 49). In these experiments, inhibition of apoptosis was achieved by the constitutive expression of Bcl-2 (49) or adenovirus E1B 19K (4) via transfection and by the addition of inhibitors of the proapoptotic interleukin-1β-converting enzyme-like proteases (13). Thus, the inhibition of apoptosis in cells infected with HIV-1 has an enhancing effect on viral replication in culture. Moreover, we have shown that the reconstitution of Fas ligand activity in culture results in a marked decrease in virus production (50). These results suggest that the regulation of apoptosis in HIV-1-infected persons could have profound implications in terms of virus levels. Since virus levels are important for the HIV-1 life cycle, especially in terms of the likelihood of transmission, it seems reasonable to consider the possibility that the virus inhibits apoptosis of infected cells.

We hypothesize that HIV-1 regulates apoptosis in a way that is beneficial for itself in terms of the requirements of its own life cycle, especially those involving virus production and transmission. This regulation is likely to be complex since it involves both the inhibition and the induction of apoptosis. We propose that the complexity of apoptosis regulation in HIV-1 disease may be reflected in part by differential effects with respect to time so that newly infected cells are prevented from dying and with respect to different types of cells so that some uninfected cells—perhaps cells that have the potential to mediate an effective immune response against the virus—are induced to die.

The complex interaction of apoptosis and HIV-1 pathogenesis is also likely to be reflected by the various apoptosis-inducing molecules such as Fas ligand, TRAIL, and TNF, which have differential activities and implications with regard to HIV-1 production. For instance, it is known that TNF induces apoptosis as well as stimulates HIV-1 production, whereas Fas ligand induces apoptosis without the stimulation of concomitant viral replication (11, 30). The activity of TRAIL in terms of HIV-1 production is not yet known.

It is also important to consider apoptotic events in different anatomical locations. It is known that lymph nodes from HIV-1-infected persons demonstrate enhanced levels of apoptosis compared to lymph nodes from seronegative individuals and that the level of apoptosis is correlated with the activation status of the cells (21, 42). Moreover, in one study no correlation was found between apoptosis and either disease progression or viral burden (42). The molecular and cellular mechanisms of physiological cell death in lymph nodes from infected persons have not been investigated.

At the same time that HIV-1 manipulates apoptosis in its favor, the host uses various mechanisms of programmed cell death to counteract the virus. For instance, the cytotoxic immune response can be conceived of as a means to provide an exogenous trigger for the apoptosis of infected cells. In order to relate the organismal phenomena of $CD4^+$ T-cell depletion to the cellular mechanism of apoptosis, scientists must account for the many, different, independently regulated pathways of cell death. The capacity of infected cells to kill themselves in order to protect the organism from viral infection, the propensity of immune cells to mediate immunity by cytotoxic mechanisms, the requirement of viruses to inhibit or at least delay apoptosis so that virus replication can occur, and the production of viral proteins that induce cell death combine to form a complex set of events that may together help to explain variations in organismal parameters such as fluctuations in $CD4^+$ T-lymphocyte levels as well as virus levels. Integration of these various components of cell death is most likely to produce a greater understanding of HIV-1 infection at an organismal level.

The regulation of apoptosis has profound implications for both the virus and the human host. It has the potential of significantly influencing virus levels and transmission as well as the host immune response and consequently health. A greater appreciation of the intricately choreographed regulation of apoptosis in HIV-1 disease pathogenesis will likely provide new opportunities in developing diagnostic, prognostic, and therapeutic modalities and thus may eventually help us advance the care of infected persons.

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