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T Helper Cell Activation and Human Retroviral Pathogenesis

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INTRODUCTION

The understanding of disease caused by human retroviral infections has been hampered by our lack of understanding of the complexity of the interactions of these viruses with the human immune system. In fact, it is in part through the study of these infections that important insights into the workings of the immune system itself have been made. Human retroviruses have the common characteristics of causing chronic persistent infection and a long and variable asymptomatic period during which overt clinical disease is not frequently manifested. Substantial evidence exists documenting that the human retroviruses, human immunodeficiency virus (HIV) and human T-cell leukemia virus (HTLV), take advantage of activated T helper (Th) cells to initiate permanent infection (117, 312, 364). Furthermore, the transcriptional signals used by Th cells to regulate cell function are also used by these retroviruses to regulate virus production. In effect, after establishing infection, human retroviruses appear to benefit from an active immune system to subsequently proliferate. This is, however, not without consequences. The way in which these viruses respond to the intracellular signals produced in Th cells following contact with common antigens eventually leads to a distortion in Th-cell function, and depending on which virus is involved, this may lead to two extremely different disease outcomes. Infection with HTLV results in dysregulated Th-cell proliferation, sometimes causing a disease of excess Th cells commonly known as adult T-cell leukemia (ATL). In contrast, infection with HIV causes a disease of profound Th-cell loss, resulting in systemic immunosuppression and AIDS. Thus, in both instances, disease progression is intimately linked to a disturbance of normal Th-cell growth and function, although the disease outcome represents two different extremes in Th-cell numbers.

Activation occurs following the interaction of Th cells with specialized cells (antigen-presenting cells [APC]), which present foreign antigen. When appropriate costimulatory signals are delivered during this interaction, the Th cell becomes activated and can proceed to differentiate and proliferate. In addition to activation, two other normally occurring alternative outcomes of APC–Th-cell interaction, anergy and apoptosis, may occur. Anergy is a state of nonresponsiveness which may occur to protect the host from inappropriate Th-cell responses if the proper coregulatory signals are not available. Apoptosis is a fundamental process which assists in the regulation and normal physiologic development and balance of cell populations. In populations of immunologic cells, apoptosis is a natural process aimed at the regulated removal of unwanted or self-reactive cells. Apoptosis is also observed to be increased in a large number of disease states, often reflecting disturbances in normal physiological processes. In addition to anergic cells, highly elevated levels of apoptosis have, for instance, been observed in HIV-infected individuals, occurring in Th cells and other lymphocyte populations. In contrast, HTLV infection, which is also intimately linked to cellular activation, is associated with a protection from apoptosis, possibly culminating in the development of Th-cell cancer. In this review, the active involvement of immune activation, anergy, and apoptosis and specifically the consequences of dysregulated Th-cell functions in the pathogenesis of human retroviral infections will be discussed with particular regard to their significance to aberrant Th-cell function and disease progression.

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T HELPER CELL BIOLOGY

T Helper Cell Development and Maturation

Many activities of Th cells are to a large degree mediated by the production of cytokines. A number of events determine which type of cytokines these cells will produce, depending on the type of Th cell they become (Th0, Th1, Th2, or Th3). The events which determine this are largely influenced by the nature of the infectious agent, the type of APC involved and the local microenvironment. Depending on the costimulating signals that the Th cell receives, it may undergo appropriate activation, proliferation, and cellular differentiation into an antigen-specific Th1/0 or Th2 population. Current research in this area is revealing other subpopulations such as Th3 cells. However, for the purposes of simplifying this discussion, we will confine ourselves to Th1 and Th2 cells. If the appropriate costimulatory signals are not provided, the Th cell may enter a nonresponsive state (anergy) or undergo programmed cell death (apoptosis) (reviewed in reference 306). Activation, anergy, and apoptosis are all normal physiologic processes which regulate T-cell responses. Stimulation of Th cells with antigen presented by the class II major histocompatibility complex (MHC) APC, followed by appropriately polarized costimulatory signals and additional cytokines, commonly results in a specific proliferation and further development into a dichotomy of the two extremes referred to as Th1 or Th2 (143). The cytokines (type 1 and type 2) produced by Th1 and Th2 cells, respectively, serve to regulate the function of specific immune system effector responses of cytotoxic T lymphocytes (CTL) and antibodies by B cells, respectively, in response to foreign antigen. The Th phenotype produced is influenced by the cytokines in the microenvironment of the Th cell, where it interacts with particular APC, influenced by surrounding cell types and their cytokines at the time of antigen presentation (236, 348).

Differentiation of naive Th cells into the Th1 phenotype is promoted by gamma interferon (IFN-γ). Th1 cells are characterized by their ability to produce interleukin-2 (IL-2), IFN-γ and tumor necrosis factors alpha and beta (TNF-α and -β), which are not made by Th2 cells. In contrast, Th2 (but not Th1) cells synthesize IL-4, IL-5, IL-6, and IL-10 (reviewed in references 274, 285, and 297). Th1 and Th2 cells also differ markedly in the signals required for their development. IL-2 is required for the development of the Th1 population, and these cells drive the cell-mediated arm of the immune response, including transient antibody production, the activation of macrophages, and delayed-type hypersensitivity responses. The Th2 phenotype is induced by IL-4, and restimulation of these cells results in high-level IL-4 secretion (298, 322). The humoral arm of the immune response is driven by Th2 cells, resulting in sustained production of antibodies, including immunoglobulin E (IL-4) and activation of eosinophils (IL-5) and mast cells (IL-3, IL-4, and IL-10) (274, 285, 297). In the absence of clear polarizing signals, a Th cell designated Th0 may develop. These cells produce a cytokine profile intermediate between those of Th1 and Th2 cells and can undergo partial differentiation to the Th1 or Th2 phenotype (1, 93, 313). A Th3 phenotype which produces high levels of transforming growth factor β (TGF-β) has also been described (44).

The development of a particular Th phenotype may be favored depending upon the exogenous stimulus received by the host. In response to infections by intracellular organisms (viruses, bacteria, and protozoa), the Th1 population is favored (69, 129, 284, 287, 363). The induction of a Th1 response by intracellular bacteria and viruses reflects their ability to stimulate IFN-α/β and IL-12 production by macrophages (285). These cytokines induce IFN-γ production by natural killer (NK) cells and T cells, which in turn inhibits the development of IL-4-producing cells (65). When IFN-γ levels are absent or limited, IL-4 production favors the development of Th2 cells, which predominate in response to particulate antigens and extracellular organisms including allergens and helminth infections (69, 261, 284, 288). The conditions favoring a particular Th shift are thus dependent upon the cytokines elicited during the initial immune response to an exogenous agent, and this will affect any subsequent specific immune response.

Activation of T Helper Cells

Th cells are specialized in that they express cell surface receptors which recognize and bind foreign antigen in the form of short peptides displayed in the context of MHC class II by APC (B cells, macrophages, and follicular dendritic cells). Activation of the Th cell in the proper context results in the expansion of Th populations and the elimination of inappropriately responding Th cells by apoptosis. The new population, in the appropriate environment, provides the necessary cytokines for the proliferation and expansion of other populations of effector cells, such as B cells or CD8$^+$ CTL, enabling them to utilize their effector mechanisms to remove foreign antigen. Full activation requires T-cell receptor (TCR)-CD3 complex recognition of peptide antigens presented by APC, as well as nonantigenic costimulatory signals provided by the APC. Costimulation is provided by the engagement of the B7 molecule on APC with the constitutively expressed CD28 receptor on the Th cell (110, 132, 159). Activation profoundly induces the expression of cytolytic T-lymphocyte-associated sequence (CTLA-4) (29), a receptor which shares 28% amino acid identity with CD28 (133) and which binds B7 with a 20-fold greater avidity than CD28 does (207). B lymphocytes express three distinct CTLA-4 counterreceptors designated B7-1, B7-2, and B7-3 (25). While the interaction of B7 molecules at the CTLA-4 receptor can enhance proliferative responses of resting Th cells costimulated with anti-CD3 and anti-CD28 antibodies (208), anti-CTLA-4 antibodies inhibited proliferation when cross-linked or presented in an immobilized form together with anti-CD3 and anti-CD28 antibodies (9, 25, 135, 182, 202, 207). This inhibition results from a block in the transition from the G_1 to the S phase of the cell cycle (185). Furthermore, anti-CTLA-4 antibodies can induce cell death of activated T cells (120). The contribution of CTLA-4 to Th cell proliferation is thus more complex than was originally reported and is an area requiring further study. A novel receptor (SLAM) involved in T-cell activation has been reported to enhance the proliferation of and cytokine production by CD4$^+$ T cells in the absence of any other stimuli (57). Signalling via SLAM potentiates the development of a Th0/Th1 cytokine profile in a CD28-independent manner (57).

The outcomes of APC–Th-cell interaction and the development of the Th1 and Th2 phenotypes are presented in Fig. 1. Appropriate costimulation results in a cascade of intracellular signalling pathways required for the induction of IL-2 and Th-cell proliferation. In one of these pathways, the activity of phospholipase C-γ1 is enhanced by phosphorylation, allowing the cleavage of membrane-bound phosphatidylinositol 4,5-bisphosphate to generate the second messengers inositol triphosphate and diacylglycerol (55). The production of inositol triphosphate triggers a dramatic bimodal elevation of free calcium levels within the cell (55, 102, 105). Diacylglycerol directly activates protein kinase C (PKC) (61). Both second-messenger signals are essential for the production of IL-2,

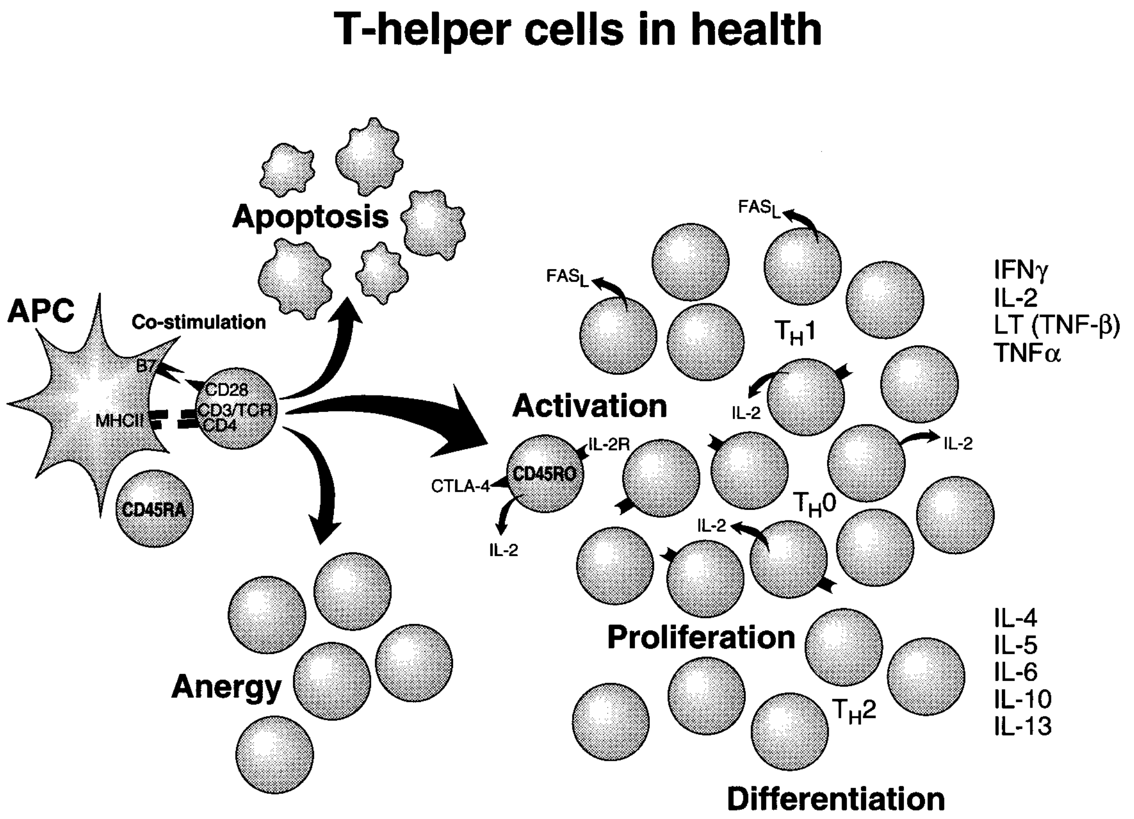

FIG. 1. Activation, proliferation, and differentiation to Th1 and Th2 phenotypes. The events following costimulation of a Th cell by interaction with an APC include activation, anergy, and apoptosis. Following appropriate costimulation, the Th cell proliferates and differentiates into Th subpopulations dependent upon the nature of the stimulatory signal and cytokines in the microenvironment.

which in turn is required for the proliferation of the activated cell and for the maintenance of memory. The availability of IL-2 allows the Th cell to remain in the cell cycle and also protects it against apoptosis. Repeated activation of T cells may result in a loss of IL-2 synthesis and the subsequent elimination of these cells by apoptosis.

While Th1 cells proliferate in response to IL-2, Th2 cells proliferate in response to IL-2 or IL-4, provided that IL-1 is made available by the APC (348). In contrast, Th1 cells express little or no IL-1 receptor (39). Mitogen stimulation results in much higher levels of cyclic AMP (cAMP) in Th2 cells than in Th1 cells (238). Inducers of cAMP inhibit Th1 cell proliferation but do not inhibit Th2-cell proliferation (131). Furthermore, agents which elevate cAMP levels block IL-2 and IFN-γ production by Th1 cells but not IL-4 production by Th2 cells (20). The level of cAMP generated in the Th cell may differentially regulate the lymphokines produced by Th cells, and the higher levels of cAMP induced in the activated Th2 cell may interfere with several transcription factors including NF-κB and AP-1. This could explain the contrasting cytokine profiles of Th1 and Th2 cells (8, 43, 247, 332). Lower NF-κB levels are noted in Th2 cells (198), and the cytokines produced by both Th1 and Th2 cells significantly modulate levels of the NF-κB inhibitor protein, IκBα (197). Furthermore, the relative abundance of the IL-4-inducible transcription factor STAT6 correlates with differentiation to the Th2 phenotype (199). The influence of cAMP levels on STAT production in Th2 cells has not been reported. Another Th2 lymphokine, IL-10, inhibits antigen-stimulated proliferation of Th1 cells (91, 92), probably by modulating the synthesis of B7 molecules (73). It seems likely that Th2 cells do not require costimulation via CD28/CTLA-4 for activation. Thus, the immune response generated to an external stimulus not only is limited by the lymphokines produced by the Th cell and their downstream effects on Th-cell activation genes but also may be influenced by the availability of accessory signals required during activation. Th-cell activation may result in the coupling of the Fas receptor (CD95) with its ligand. CD95 is a member of the TNF/nerve growth factor receptor superfamily, and ligation of CD95 with Fas ligand (FasL) causes rapid apoptosis (programmed cell death) in sensitive cells (315). Apoptosis is characterized by the activation of a Ca^{2+}-dependent endonuclease which cleaves chromosomal DNA between nucleosomes (301, 354). The preferential expression of FasL on Th1 cells (279) arms these cells to kill other cell types or other Th1 cells by apoptosis.

CONSEQUENCES OF RETROVIRAL INFECTION ON IMMUNE ACTIVATION

Human retroviruses cause persistent infections characterized by long, clinically asymptomatic periods prior to disease progression. HTLV is known primarily as the etiologic agent of ATL, a malignancy of mature Th lymphocytes (140, 141, 268, 361). A hallmark of HTLV infection is the induction and continuous high-level expression of IL-2 receptor (IL-2R) (Table 1) (71, 114, 149, 272, 317, 357). Infection with HIV, the etiologic agent of AIDS (14), is marked by a loss of $CD4^+$ Th cells, resulting in immune system dysfunction (Table 1). Both infections induce a general state of immune system activation and are associated with neurological disorders. As with other

TABLE 1. Human Th-cell tropic retroviruses and Th-cell diseases

Characteristic	Mechanism in:	
	Th-cell cancer	AIDS
Underlying lesion	Accumulation of Th cells	Loss of Th cells
Virus	HTLV-1	HIV-1
Characteristics in host	Persistent intracellular viremia; low viral load	Persistent intracellular and extracellular viremia; high virus load
Frequency of disease	Infrequent; approximately <1% infected develop ATL	Frequent; approximately >98% infected develop AIDS
Activation	Increase in IL-2R and IL-2 spontaneous proliferation; non-MHC-restricted responsiveness	Antigen-antibody complexes in germinal centers; infection of APC; aberrant cytokine production by APC and altered cytokine production by Th cells
Apoptosis	Resistance due to Tax	Increase in frequency and in susceptibility to Tat
CD3/TCR triggering	Decrease in HTLV-1 expression	Increase in HIV expression

viruses, these retroviruses have the potential to subvert the cellular transcriptional machinery with specific regard to utilizing Th-cell signals for their own replication. This subversion of the host cell machinery most often results in a dysregulation of normal Th-cell function and growth. While both viral infections result in a generalized increase in Th-cell activation, there is a profound divergence both in the subsequent Th-cell activation-related events and in the ensuing consequences of cell expansion versus cell loss. The alterations in Th-cell populations as a result of HIV-1 and HTLV-1 infection and the resulting dysregulation of normal cellular activation and proliferation are presented schematically in Fig. 2.

HIV Infection

HIV infection can be generally grouped into three clinical phases: (i) the acute infection period, which in some ways presents similarly to a mononucleosis-like syndrome; (ii) an asymptomatic period of variable duration; and (iii) the period of clinical disease during which multiple opportunistic infections and/or neoplasms are manifested. Recent studies have shown that HIV infection in vivo is a dynamic process involving continuous rounds of infection, replication, and cell death (144, 349). HIV predominantly infects CD4$^+$ T cells (Th cells) as well as CD4$^+$ cells of the monocytic lineage, which also express MHC class II. The turnover of CD4$^+$ T cells during HIV infection is thought to be rapid, with the entire population of peripheral CD4$^+$ T cells estimated to be replaced on average every 15 days (144). While the greater majority of infected individuals do not present clinical signs of disease for extended periods, virus replication remains high, especially in reservoirs such as the lymph nodes and spleen (74). In patients who die of AIDS-related illnesses, infection is extensive, targeting brain, lung, colon, and liver cells (74). Persistent and high levels of virus replication result in the loss and destruction of normal lymphoid architecture. As the immune system chronically deteriorates, virus and virus-infected cells are less efficiently removed by the host.

The spread of HIV infection to brain cells may result in an AIDS dementia complex, represented by a variety of mild to severe neurological disorders, including neoplasms, peripheral neuropathies, and myopathies (reviewed in reference 310). Neurotoxins produced by infected cells and induced by viral proteins may contribute to cellular damage, resulting in neurologic disorders. Neurotoxic activity has also been demonstrated for the viral regulatory proteins Tat and Nef in a variety of cell lines and animal models (reviewed in reference 204). Virus replication can be measured in brain tissue (180) and the central nervous system (340) in patients with AIDS dementia disorders. However, there is no evidence to suggest that the development of AIDS dementia is associated with increased viral load. In fact, one study of children with severe AIDS-related encephalopathy indicated low viral replication in brain tissue (340). However, vigorous CTL activity directed toward HIV-1 Env, Gag, Pol, and Nef proteins has been reported to occur in the cerebrospinal fluid of patients with AIDS dementia (157).

Persistence of virus in the host in the presence of ineffective immune system clearance results in a state of chronic immune system activation. Activation of cells in the course of the immune response further favors the spread and establishment of HIV in new target CD4$^+$ Th cells and in macrophages. In addition, virus replication is potentiated both by activation signals and by cytokines such as IL-6 and TNF-α (270, 288). Cell-mediated and humoral immune responses are detectable early in infection. These include virus-specific neutralizing antibodies, antibody-dependent cellular cytotoxicity, CTL and NK cells, and complement-dependent lysis (reviewed in reference 257). In addition, within the CD8$^+$ population is a subset of cells which induce an activation-dependent, nonlytic suppression of virus replication (347). Studies of long-term nonprogressors infected with HIV-1 suggest that low viral load is associated with apparently effective neutralizing antibody and CD8$^+$ lymphocyte responses (31, 258).

The asymptomatic period associated with HIV-1 infection is characterized by a high-level state of immune system activation, as is evident by the expression of related activation markers (Table 2). These include β_2-microglobulin, serum and urinary neopterin, soluble IL-2R, soluble CD8 molecules, and soluble TNF-α receptors. The increase in the levels of many of these markers during disease progression is paralleled by the development of immune system dysfunction, which may result in an anergy-like loss of proliferative potential (191, 263, 299, 300) or in cell death by spontaneous or activation-induced apoptosis (4, 12, 115, 122, 227). A deficiency in extracellular cysteines and intracellular glutathione occurs early in HIV infection and has been associated with a decline in CD4$^+$ Th cells and with progression to disease (77, 79). While cysteine

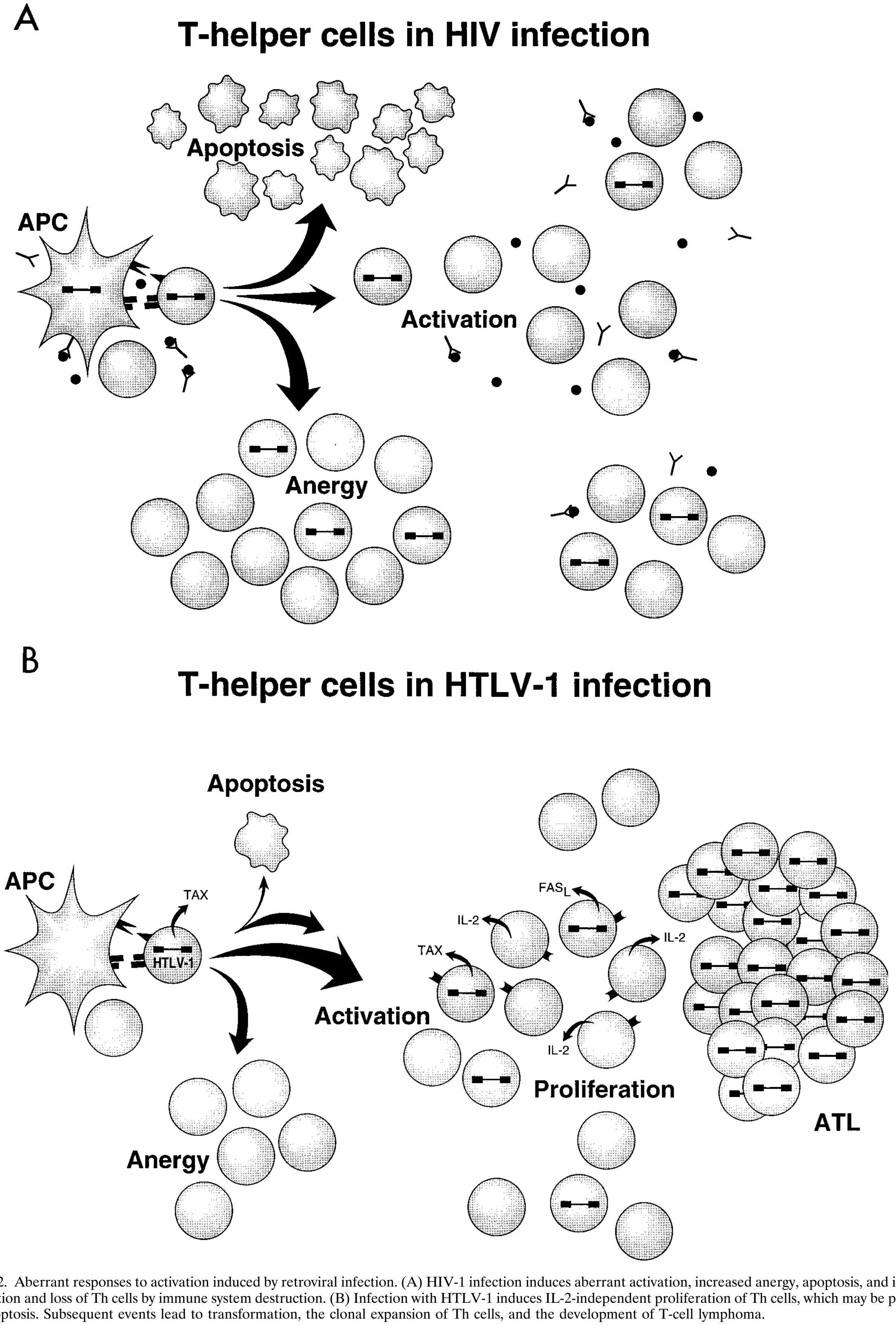

FIG. 2. Aberrant responses to activation induced by retroviral infection. (A) HIV-1 infection induces aberrant activation, increased anergy, apoptosis, and impaired proliferation and loss of Th cells by immune system destruction. (B) Infection with HTLV-1 induces IL-2-independent proliferation of Th cells, which may be protected from apoptosis. Subsequent events lead to transformation, the clonal expansion of Th cells, and the development of T-cell lymphoma.

TABLE 2. Markers of activation in HIV and HTLV infection

Marker	Marker expression in[a]: HIV infection ASY[b]	HIV infection AIDS	HTLV infection ASY	HTLV infection HAM/TSP	HTLV infection ATL	Reference(s)
β_2-Microglobulin	↑					64, 85, 187, 195, 253, 370
Neopterin	↑	↑			↑	64, 97, 121, 195, 250, 290
Soluble CD8	↑		↑	↑		253, 292, 331
IL-2	↑	↓	↑	↑	↓	296, 325
Soluble IL-2R	↑		↑	↑	↑	126, 148, 251, 296, 303, 309
TGF-β				↑		245, 326
TNF-α	↑	↓		↑		188, 195, 251, 296, 335
TNF-β					↑	96, 326
TNF-αR (RI, RII)	↑					113, 163, 164
IFN-α		↑				221
IFN-γ	↑	↑	↑	↑	↑	245, 326
HLA-DR	↑			↑	↑	108, 171
HLA class II			↑	↑		200
CD38	↑					168
CD28		↓				49
CD45RO	↑					265
Soluble CD2	↓	↑				291
Immunoglobulins	↑ IgA	↑ IgG2		↑ IgA		80, 242, 277, 290, 341
	↑ IgM	↑ IgG4		↑ IgM		45, 211, 337, 341
	↑ IgG1			↑ IgG		277, 341
	↑ IgG3					213
	↓ IgG2					277
	↓ IgG4					211
Lipoproteins	↑					307
Cholesterol	↑					307
Fas (CD95)	↑	↑			↑	66, 67, 84, 168, 308

[a] ↑, increased; ↓, decreased.

[b] ASY, asymptomatic phase.

metabolic dysfunction is evident in species highly susceptible to AIDS such as humans with HIV infection and rhesus macaques with simian immunodeficiency virus (SIV) infection, no decreases in cysteine or glutathione levels are evident in HIV-infected chimpanzees or SIV-infected African green monkeys (77).

HTLV Infection

The asymptomatic period of HTLV-1 is associated with low virus expression in peripheral blood T cells and low levels of virus in leukemic cells of ATL patients (95, 107, 149, 174, 316). In vitro culture of ATL cells results in virus production, whereas in vivo culture does not (95). This would suggest that such cells producing high levels of virus in vivo become targets of the immune system and are either removed by CTL, antibody-dependent cellular cytotoxicity, or NK cells or are down-regulated in vivo by other cells so that virus is not expressed. In contrast, expression of the virus-encoded *trans*-activating protein, Tax, has been demonstrated in peripheral blood mononuclear cells (PBMC) of seropositive carriers of HTLV-1 prior to the onset of ATL (325). The inflammatory disease induced in HAM/TSP (106, 252) is associated with higher levels of virus expression, and virus is easily detected in PBMC and spinal fluid (21, 237). The level of HTLV-1 detected in central nervous system tissues from HAM/TSP patients is greater than in brain tissue from ATL patients, indicating that there is an increased viral load in HTLV-1-associated neurological disease (82). The contribution of viral burden to ATL and/or HAM/TSP is a neglected area requiring in-depth study.

The frequency of HTLV-1-specific CTL in HAM/TSP patients is markedly higher than in asymptomatic patients (82). These CTL recognize target cells expressing the Tax protein (82, 155, 167, 181, 259, 260), and in some patients CTL specific for Gag and Env can be detected (82). Naturally occurring variants of Tax impair its recognition by CTL, and these variants have severely reduced transactivation potential (249). While variation in the principal target epitope may contribute to the persistence of the virus, this could, under some conditions, limit virus expression. Higher frequencies of CTL in HAM/TSP patients may correlate with the high viral load, which is not observed in ATL patients (176). While the frequency of Tax-specific CTL is lower in asymptomatic patients (259), the demonstration of such CTL raises speculation about their role in the pathogenesis of HAM/TSP.

HTLV-1 infection is associated with the constitutive expression of IL-2R (71, 114, 136, 230, 233, 360, 362) and in some cases with the production of IL-2 by infected cells (71, 272, 357). In addition, HTLV-1 carriers demonstrate large numbers of activated T cells and a high degree of spontaneous proliferation of in vitro-cultured T cells (71, 272, 357). The level of immune system activation observed in asymptomatic HTLV-1 patients is not likely to be induced by Tax, because it has been shown previously that Tax cannot activate lymphocytes on its own. Activation can be induced by cell-to-cell contact with HTLV-1-infected cells (172). The maintenance of this state of activation is probably dependent on the ability of Tax and subsequently influenced cellular proteins to up-regulate cellular gene expression. HTLV-1-mediated Th-cell activation, combined with virus-mediated induction of cellular gene expression, may permit the virus to both initiate and maintain the lymphoproliferative process. However, this does not explain the quiescence of the virus in the infected, activated Th cell. Alternatively, the down-regulation of CD3 on leukemic cells

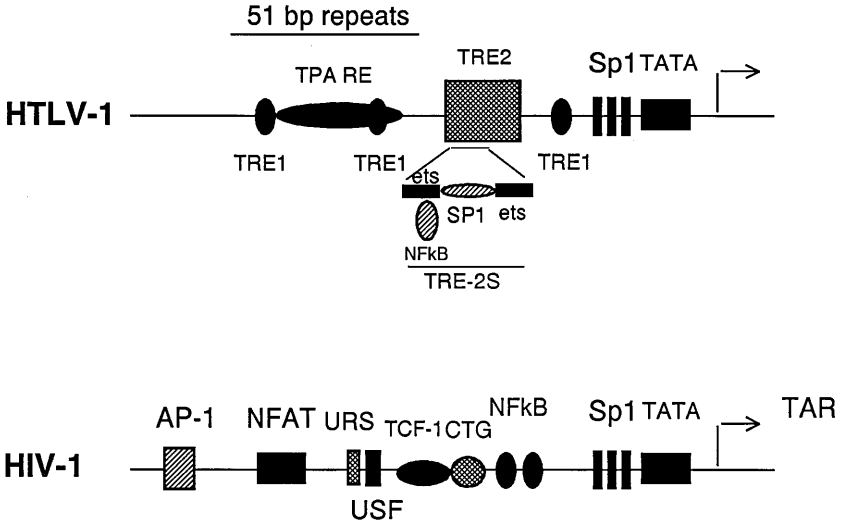

FIG. 3. Schematic representation of the LTR of HTLV-1 and HIV-1. The binding locations of cellular transcription factors are indicated and are further discussed in the text. USF, upstream stimulatory factor; URS, upstream responsive sequence; TCF, T-cell-specific transcription factor. Arrows indicate the start site of transcription.

(152, 330, 363) may suggest that Th-cell activation occurs more continuously in infected cells, perhaps during the asymptomatic period, or may be a reflection of adaptation of the developing tumor cells to immunologic pressures. Infected cells respond indiscriminately to antigen and with no HLA-DR restriction (271). Furthermore, ATL cells have recently been reported to evade NK cell-mediated cytolysis in mice with severe combined immunodeficiency (scid mice), and this evasion appears to be dependent upon low virus expression (89). Th-cell activation and cell proliferation may be a mechanism for the virus infection to be propagated while maintaining a protective intracellular location, thus avoiding detection by immune responses outside of host cells.

EFFECT OF T HELPER CELL ACTIVATION ON RETROVIRAL EXPRESSION

Figure 3 depicts the structure of the long terminal repeat (LTR) regions which mediate replication of HTLV-1 and HIV-1. The striking feature of the LTR regions is how few similar functional promoter elements are shared between HIV-1 and HTLV-1. The HTLV-1 TRE-1 sequences are responsive to activation mediated by the virus-encoded *trans*-activating protein Tax. The response of one TRE-1 to Tax-mediated *trans*-activation is further enhanced by a sequence of four pentanucleotide repeats (TRE-2) located between the second and third TRE-1 sequences (223). A 25-bp sequence (TRE-2S) within TRE-2 is required for cooperative Tax *trans*-activation (324). Mutagenesis studies indicate that the Ets- and NF-κB-binding sites in TRE-2S are dispensable to the cooperative effect (324). Tax does not bind to these enhancer sites but can interact with a number of families of transcription factors to induce gene expression (16, 35, 98, 111, 142, 143, 193, 262, 320, 321, 345, 368). In fact, Tax expression induces phosphorylation and turnover of the inhibitory protein IκBα, resulting in constitutive NF-κB activity (186). In addition, Tax activates many cellular genes including IL-2 and its receptor alpha chain (reviewed in references 119, 359, and 360). This deregulation of the expression of cellular genes has been suggested to contribute to alterations in the phenotype of infected cells and the subsequent development of HTLV-1 leukemogenesis via transformation (317, 360). However, the pleiotropic action of Tax is not explained by viral quiescence observed in vivo, unless early T-cell activation genes can support short periods of viral replication and, hence, Tax expression periodically.

The pathways by which Tax exerts its *trans*-activating function appear to be independent of both PKC (278) and cAMP (273) pathways. Up-regulation of transcription by the PKC-stimulating phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate (TPA) is determined by a 60-bp element (TPA RE) which overlaps with one TRE-1 (278). In addition, the integrity of the two 51-bp repeated elements which overlap the first two TRE-1 regions is required for optimal response to phorbol ester (278). Induction by activators of adenylate cyclase (243, 273) is mediated via the octameric cAMP-responsive element located within the TRE-1 sequences and is dependent upon the availability of PKA (162). Thus, HTLV-1 expression may be up-regulated by Tax and by cellular pathways which may be induced in the activated Th cell upon infection.

In comparison with the HTLV LTR, the core elements required for HIV LTR gene expression include the Sp1-binding sites, the TATA box, and the Tat responsive element (TAR element) (Fig. 1) (17, 18, 101, 134, 160, 161). HIV expression is positively regulated by binding of the HIV-encoded Tat *trans*-activating protein to the TAR element found at the 5′ end of all mRNAs (19). The HIV-1 promoter also has several *cis*-acting regulatory elements in common with cellular gene promoters including NFAT-1, NF-κB, AP-1, and Sp-1. Two NF-κB-binding sites act as a major enhancer of LTR-mediated gene expression and are important for basal LTR activity (18, 150, 241). Deletion of the Sp-1 binding sites results in a marked decrease in Tat-mediated activation (18, 134). Deletion of both NF-κB- and Sp-1-binding sites abolishes Tat-mediated transcription, indicating that Tat may interact with cellular transcription factors to stabilize elongation and to initiate transcription (17, 165, 166, 210). Binding of the nuclear factor of activated T cells (NFAT) is dependent upon Th-cell activation (304). The NFAT-1-binding site falls within a region of the LTR called the negative regulatory element, and deletion of this region results in higher levels of virus expression (212). However, the HIV-1 LTR responds to agents which induce

Th-cell activation, including TPA, phytohemagglutinin, and monoclonal antibodies to the cell surface receptors CD3 and CD28 (7, 123, 130, 169, 222, 241, 293, 327). The LTR is also responsive to several cytokines (IL-1, IL-6, and TNF-α) which are up-regulated in the cell during Th cell activation and which may also be provided by accessory cells (11, 78, 153, 175, 184, 225, 253, 344).

We have previously observed, using Jurkat T-cell clones containing integrated LTR–β-galactosidase constructs, marked differences between activation-mediated induction of HIV-1 and HTLV-1 (61). While the HIV-1 LTR was up-regulated by single signals such as CD3 or CD28 pathways, the HTLV-1 LTR was not induced by these pathways. HIV-1 LTR-mediated transcription was increased by TPA, and this response was further enhanced by the calcium (Ca^{2+}) ionophore ionomycin. In contrast, the induction of the HTLV-1 LTR by TPA was inhibited by ionomycin (58, 59, 61), suggesting that the triggering of Ca^{2+}-dependent pathways in the cell could adversely affect virus expression. Further experiments revealed that the ionomycin-mediated inhibition was not restricted to TPA-induced activation mechanisms, since basal LTR activity and Tax-mediated activation were also compromised by ionomycin. The immunosuppressive drug cyclosporin A suppresses the proliferation of HTLV-1-infected T-cell lines (244). In our experiments, the suppression of Ca^{2+}-dependent phosphatase activity by cyclosporin A caused LTR responses in ionomycin-treated cells to recover to levels above those obtained in the absence of ionomycin (59), suggesting a complementation of ionomycin and cyclosporin A in HTLV-1 activation. Increased levels of free Ca^{2+} in the presence of cyclosporin A may provide a greater affinity of transcription factors for the LTR and an enhanced LTR induction.

These findings suggest that Th-cell activation, while up-regulatory to HIV-1 LTR function, can be inhibitory to HTLV-1 expression and may contrast two different survival strategies within the human host. In this respect, the presence of proviral DNA and of low levels of viral products, such as Tax, may be sufficient for the expression of IL-2R by the infected T cell. An elevated state of activation resulting in the expression of IL-2R and activation of the IL-2/IL-2R autocrine loop could concurrently provide conditions allowing for the expansion of HTLV-1 provirus-infected cells while suppressing virus expression and cell destruction by the host immune response. This may provide one of several likely events which contribute to the quiescence of the virus during the asymptomatic period of ATL.

T HELPER CELL ACTIVATION AND DISEASE PROGRESSION

HIV and AIDS

Immune dysfunction is a characteristic common to human retrovirus infection, reflecting the central role of Th cells in orchestrating a broad array of immune responses. There are several theories regarding the mechanisms responsible for progression to AIDS, and these are summarized in Table 3. One of many mechanisms suggested to account for the loss of CD4$^+$ lymphocytes during progression to AIDS centers on the dysfunctional activation of Th cells. In contrast to HTLV infection, HIV infection is characterized by high virus loads and waves of extracellular viremia due to recurring periods of neutralization and escape. Consequently, there is substantial deposition and trapping of antigen-antibody complexes in the follicular centers of lymph nodes. This saturation of MHC class II-rich regions with virus is likely to substantially impair APC–Th-cell interactions (138). Further contributing to Th-cell dysfunction is the loss of APC function of monocytes and dendritic cells in AIDS patients (215, 229). This is supported by the reduced production of IL-12 by macrophages in HIV infection (40) and the ability of IL-12 to restore T-cell responses to recall antigen in HIV-infected individuals (51).

TABLE 3. Theories regarding mechanisms mediating disease progression to ATL versus AIDS

ATL	AIDS
Multiple mechanisms singly or combined	Multiple mechanisms singly or combined
IL-2-independent activation resistant to TGF-β regulation of apoptotic removal	Persistent waves of extracellular viremia and high virus load
Persistent activation of Th cells	Impaired APC–Th-cell interaction
Reduced expression of β-polymerase and impaired DNA repair	gp120-impaired Th-cell function
	Anergy
Increased reactive oxygen intermediates and increased DNA damage	Loss of CD4 renewal capacity
	Loss of proliferative responses
Survival of unfit Th cells, accumulation of rare mutational events, and eventual ATL	Increased anergy and apoptosis
	Shift in Th-cell population to Th2-predominant response
	Increased oxidative stress and apoptosis

Prior to a significant decline in CD4$^+$ cell numbers, immune dysfunction (124, 190, 191, 194, 258, 264, 305, 311), demonstrated by a sequential suppression of activation in response to signalling by antigen, mitogen, and pokeweed mitogen (190, 191, 263, 299, 300) and an increased number of T cells programmed for cell death (227), is evident. These abnormalities in T-cell response are progressive, demonstrated by the loss of proliferative responses to recall antigens and lectins in later stages of infection (226, 305). Th-cell dysfunction may be mediated by the interaction between the CD4 receptor and soluble gp120. In fact, gp120 inhibits the proliferation of PBMC stimulated via the TCR (46, 206) and the expression of IL-2 mRNA in CD4$^+$ T cells (254). Proliferation was restored by the addition of exogenous IL-2 (206). A recent report by Schols and Declercq demonstrated that gp120 inhibited CD4$^+$ and CD8$^+$ T-cell functions by inducing IL-10 production by monocyte/macrophage cells (294). Elevated levels of IL-10, TNF-α, and IFN-γ have been demonstrated in vivo in individuals infected with HIV-1 (87). The impaired response of normal PBMC (294) and Th1 cells (86) cultured with gp120 was relieved by stimulation through the CD28 receptor. The partial restoration of proliferative responses by CD28 stimulation of Th1 cells also restored IFN-γ and IL-2 production (86). The expression of CD28 is low in HIV-infected individuals (27), and the loss of this recovery route may permit the maintenance of Th-cell dysfunction. Recovery may be further compounded by the fact that IL-10 appears to induce an inhibition of antigen-stimulated proliferation of Th1 cells (91, 92) by down-regulating the synthesis of B7 molecules (73).

The induction of Th-cell unresponsiveness is not exclusive to gp120. The HIV Tat protein inhibits T-cell responses to phytohemagglutinin and pokeweed mitogen (343) and to anti-CD3 stimulation (314). Tat directly binds to CD26 to evoke this inhibition (127, 314), which can be overcome, similarly to gp120-induced unresponsiveness, by exogenous IL-2 or by costimulation via CD28 (314). If Tat and gp120-CD4 interactions are able to induce a state of anergy in T cells, this might result in an eventual loss of T-cell subsets. Additionally, if a shift from Th1 to Th2 occurs, IL-2 levels may not be sufficient to effect recovery.

Progression to disease is marked by an increase in virus expression concurrent with a decrease in the number of CD4$^+$ T cells (125). This may be due to transcriptional activation of the virus by cytokines such as TNF-α and IL-6, whose levels are also elevated at this time (26, 269, 328). However, lower proliferation rates by Th1 cells would be expected to contribute to a lower replicative efficiency, which could not support the observed increase in virus expression associated with progression to AIDS (287). A lower efficiency of Th1 cells to support virus replication could be due to the presence of IFN-γ or to the release of suppressive factors by CD8$^+$ T cells. Replication-suppressive factors produced by CD8$^+$ T cells include the β-chemokines MIP-1α, MIP-1β, and RANTES (56). The entry of HIV-1 into a CD4$^+$ cell is dependent upon the coexpression of specific fusion factors. Infection by primary and macrophage-tropic isolates requires the G-protein-coupled seven-transmembrane-domain coreceptors, CC CKR3 and CC CKR5 (3, 48, 70, 75, 76), while infection with T-cell-line-adapted isolates and syncytium-inducing primary isolates requires fusin (88), another G-protein-coupled seven-transmembrane-domain coreceptor whose ligand has not yet been identified. Binding of the replication-suppressive chemokines to the coreceptor has been shown to inhibit cell fusion mediated by the HIV envelope glycoproteins (3, 70). However, CD8$^+$ suppressive factors also potently suppress HIV LTR-mediated gene expression (42, 62, 63, 216), and this occurs before the onset of RNA transcription (178). In addition, the ability of CD8$^+$ T cells to suppress LTR-mediated gene expression does not appear to correlate with improved clinical status (63a). Two distinct CD8$^+$ T-cell suppressor activities have been reported, one which is lost upon disease progression and a second which is maintained at all stages of disease (13). Thus, while virus replication is enhanced during progression to disease, there are mechanisms supporting a down-regulation of virus expression by the preferentially infected Th cell, including suppressive cytokines, chemokines, and a disruption in the normal Th-cell responses to activation. Enhanced virus replication may reflect a change in the phenotype of cells which are infectable and presumably the infection of new cell types brought on by a change in the phenotype of the virus.

It has been suggested that during infection with HIV, the Th-cell population becomes skewed with a loss of Th1/0 cells and a predominance of Th2 cells. This proposed shift from a Th1 to a Th2 profile is associated with decreased cell-mediated immunity (53, 218). The Th1 to Th2 shift hypothesis and its importance in HIV infection remains controversial (118, 218). Taken together with this theory are data which demonstrate preferential replication of HIV-1 in Th2-like cells (218). Elevated levels of soluble CD30 have been detected in HIV-1-infected subjects (266). CD30, a member of the TNF/nerve growth factor receptor superfamily, is strongly expressed on activated Th2 clones but not Th1 clones and has been shown to up-regulate HIV-1 expression (68, 286). Strong cell-mediated immunity is detected in HIV$^+$ long-term nonprogressors (31, 258), while a type 2 cytokine profile is found in progressors (54, 342). Taken together, the above evidence suggests that HIV can subvert both the cell-mediated and humoral arms of the immune response by causing increased Th-cell dysfunction and decreased Th cell numbers and antigen-specific Th-dependent responses, resulting in skewed cytokine profiles, conditions favoring virus replication, and ultimately Th-cell loss.

Vigorous CTL activity has been reported in HIV-1-infected individuals (reviewed in reference 204), and it has been speculated that this activity may be important in the control of viremia during primary infection (23, 183). The numbers of these HIV-1-specific CTL are reduced in HIV-1-infected subjects with low CD4$^+$ T-cell counts (34), and this decrease correlates with disease progression (189). Thus, it appears that a stable pool of CTL is required for the control of HIV-1 infection. A reduced pool of CTL in late-stage disease may be the result of HIV-mediated apoptosis, since CTL specific for Epstein-Barr virus are maintained (34). A reduction in HIV-1-specific CTL activity may contribute to increased viral expression and a reduced clearance of infected cells. In contrast, CTL activity may contribute to the immunopathogenesis of HIV-1 infection through persistent function to inappropriate targets such as Th-APC (54, 138, 204). Insights into the role of CTL in HIV infection have been gleaned through the study of long-term nonprogressors and exposed seronegative individuals (reviewed in reference 54). Indeed, lack of progression is associated with low viral load and with anti-HIV CD8$^+$ CTL directed against Gag, Pol, and Env (282). In exposed seronegative individuals, HIV-specific T-cell responses including CTL activity can be detected (54), indicating that limited exposure to the virus may be sufficient to engage a cell-mediated immune response in the absence of HIV-specific antibodies.

HTLV and ATL

On the basis of studies of HTLV-1 transmission, it appears that ATL develops preferentially in individuals infected early by their mothers through breast milk (240). This suggests a link between disease progression and an incubation period spanning many years. It has been suggested that infection with HTLV-1 subtly alters the normal immune system development, such as during ontogeny, and that such events may favor the later development of lymphoma (219). Few infected peripheral blood T cells express HTLV-1 (173), however, infected cells can activate uninfected cells via cell-to-cell contact (353). In this way, a small number of infected cells may maintain a persistent level of immune system activation, possibly precipitating the development of ATL or HAM/TSP. This condition of immune system activation is further supported by the ability of the infected Th cell to maintain the activated state for prolonged periods in an IL-2-independent manner (146, 353). We have postulated that Th-cell activation down-regulates HTLV expression (59, 61). Hollsberg et al. (145) have reported that HTLV-1 mediates T-cell activation through a pathway which is insensitive to the immunosuppressive cytokine TGF-β1. In addition, HTLV-1 infection induces a resistance in previously activated cells to immune suppression by TGF-β1 (145).

While HTLV-1 preferentially infects CD4$^+$ Th cells, many cell types may be infected in vitro, including cells of the monocyte-macrophage lineage (72). In addition, Osame et al. (252) reported on the production of a colony-stimulating factor with myelinotoxic activity that is produced in patients with HAM/TSP. Infection of macrophages with HTLV-1 in vivo has not been clearly demonstrated. However, given the low level of virus expression by infected cells in peripheral blood, detection of virus in monocytes has been problematic. It has been suggested that infected macrophages could secrete neurotoxic agents mediating demyelination and inflammation. While this remains to be proven scientifically, it is possible that aberrant activation of Th cells by HTLV-1 will provide the potential for macrophages to present an altered cytokine profile. Similarly, HIV-infected or gp120-stimulated macrophages produce neurotoxic products as well as inflammatory cytokines, such as TNF-α and IL-1β, which can further potentiate neurotoxin production (50, 302).

The molecular and cellular events that drive the asymptomatic infected individual to ATL or HAM/TSP remain controversial, however, the low frequency of disease among infected individuals (140) suggests that a rare event or combination of events are required for progression. Some of the current hypotheses postulated to explain the progression from a carrier state to ATL are listed in Table 3. The HTLV-1-encoded Tax protein has been demonstrated to have oncogenic potential (246, 272, 275, 323, 362), and it has been proposed that HTLV-1 infection is a necessary but insufficient step and that secondary or tertiary random, mutational events are required for cellular transformation to ATL. The oncogenic potential could also occur only under specific, possibly rare, cellular conditions when simultaneous Tax expression is present. One mechanism postulated is the development of a prelymphoma state caused by the continuous triggering of T-cell activation (224, 362). However, since progression to disease is uncommon, other mechanisms for the shift to cancer, including previous or subsequent host cell damage, have been proposed (362). The reduced expression of the DNA repair enzyme β-polymerase (158) is a Tax-mediated event which may allow for the accumulations of random, nonlethal, and eventually oncogenic mutational events which could lead to the development of ATL. This model is strengthened by the observation that a variety of different chromosomal abnormalities are frequently found in ATL patients; however, no specific aberration appears to be related to the development of ATL (37, 100, 231). Tax has been shown to activate NF-κB and the HIV-1 LTR by a mechanism which depends upon the production of reactive oxygen intermediates (295; reviewed in reference 356). In addition, mice transgenic for HTLV-1 develop an inflammatory arthropathy which correlates with Tax expression in joints (154). In contrast, Tax also induces the expression of adult T-cell leukemia factor, which is the human homolog of the bacterial coenzyme thioredoxin (147, 356). Thus, while Tax may induce conditions of oxidant stress, which favor gene expression, this condition can be reversed to protect cells from oxidative damage. This type of feedback mechanism may be another way in which virus persists. However, continued rounds of oxidative stress and recovery have the potential to induce irreversible genetic damage to HTLV-infected cells. Given their Tax-related resistance to apoptosis (60), the survival of these cells may allow for the accumulation of mutations, eventually leading to their transformation to ATL cells. As described above, oxidative stress has also been proposed as one of several cellular conditions significant in the progression to AIDS (77, 79).

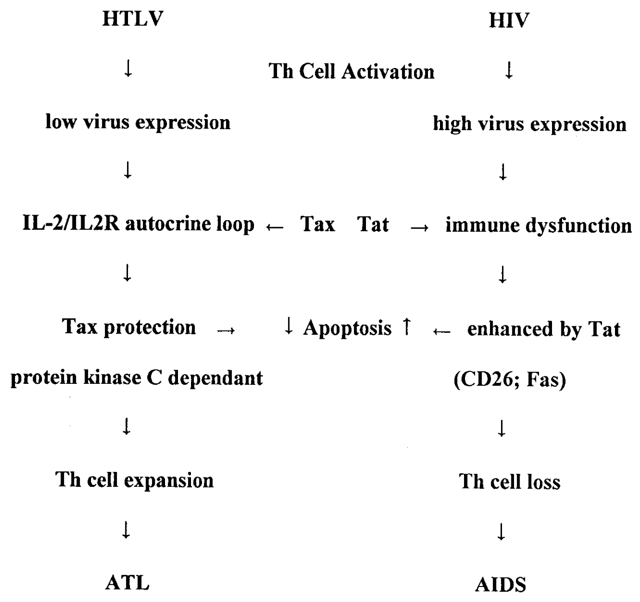

FIG. 4. Infection of Th cells by HTLV or HIV and the consequences of activation on apoptosis.

EFFECT OF HUMAN RETROVIRUS-ENCODED PROTEINS ON APOPTOSIS

The mode of stimulation and the intensity and duration of stimulation of the Th cell determine its subsequent proliferative response. Appropriate engagement of the TCR results in proliferation and IL-2 production. Inappropriate stimulation by engagement of the TCR in the absence of a costimulatory signal may result in a functionally paralyzed or anergic cell or a cell programmed for death by apoptosis (reviewed in reference 306). It has been well documented that one outcome of the in vitro activation of CD4$^+$ and CD8$^+$ T cells in HIV-1-infected individuals is apoptosis (4, 12, 115, 122, 227, 228). The induction of apoptosis by HIV is multifaceted, being mediated by specific virus-encoded proteins and also by altered cellular pathways, which result from the effects of infection on immune responses. The HIV Tat protein and interactions between the CD4 receptor and gp120 are known mediators of altered T-cell responses; thus, it is not surprising that these mediators have also been identified as apoptotic agents. Apoptosis is induced in T-cell lines by the expression of the HIV *env* gene (196, 213), and anti-gp120 antibodies can block apoptosis mediated by HIV infection of T cells. Apoptosis induced by cell-to-cell transmission of HIV requires CD4-Env interactions and is not dependent upon new HIV replication (220). Cross-linking of CD4 with gp120 and anti-gp120 or with anti-CD4 antibodies can prime uninfected cells for apoptosis (12, 248). Apoptosis is also induced by cross-linking with gp120 followed by ligation of the TCR, and this sequence of binding events has been suggested as a mechanism of apoptosis in HIV-infected individuals (12, 122). The susceptibility of CD4$^+$ T cells to this route of apoptosis depends upon the period between the binding of gp120 and the subsequent encounter with antigen (333). In addition, resistance to gp120-mediated apoptosis is characterized by a down-modulation of CD4 concurrent with a high expression of the anti-apoptosis protein Bcl-2 and is not dependent upon the level of Fas expression by the cells (334). Ligation of CD2 and CD28 in combination with TCR occupancy can rescue CD4$^+$ T cells from gp120-mediated apoptosis, and a similar rescue can be provided by IL-4 and IL-2 (334). However, the importance of TCR occupancy can be questioned, since recently activated cells can undergo gp120-mediated apoptosis in the absence of TCR ligation (94).

Several mechanisms for gp120-induced apoptosis can be proposed. Binding of gp120 may interfere with normal T-cell regulatory pathways which protect the cell from apoptosis. These pathways include a decrease in p56^{lck} activity (38) or the activation of phosphatidylinositol 3- and 4-kinase activity (276). Alternatively, a disturbed microenvironment in which cytokines normally protective against apoptosis, such as IL-2 and IL-4, are down-regulated by HIV infection could render cells sensitive to apoptosis. In addition, interaction of HIV gp120 with CD4 can induce the production of a number of cytokines by T cells and macrophages, including TNF-α, IL-6, IL-1, granulocyte-macrophage colony-stimulating factor, and IFN-β (reviewed in reference 256). Finally, apoptosis could reflect the absence of proper accessory cell functions or their costimulatory signals. Underlying all of these proposals is the aberrant activation of cells in the presence of HIV infection.

Recent reports have indicated that infection with HIV-1 results in a greater sensitivity to Fas-mediated apoptosis in human $CD4^+$ and $CD8^+$ T cells and in macrophages (168, 352). Indeed, infected macrophages can induce Fas-mediated destruction of lymphocytes (10). In addition, HIV-1 Tat has been shown to induce enhanced expression of the Fas receptor, CD95, thus accelerating Fas-mediated apoptosis (352). The ability of Tat to induce apoptosis in various cell types requires nanomolar levels of Tat, while picomolar levels appear to be protective against apoptosis (109, 367). The protective effect of Tat may be mediated by Bcl-2 expression in human cell lines and PBMC (366). However, in contrast to this, infection of Bcl-2-expressing T-cell clones with HIV resulted in an accelerated spreading infection and rapid loss of cell viability (289). Thus, Bcl-2 expression enhanced the ability of T cells to support HIV replication. A similar result was observed in HIV-infected T cells treated with the adenovirus antiapoptosis protein E1B (6). On the other hand, the induction of apoptosis by Tat occurs in the absence of changes in Bcl-2 expression (205) and is associated with the activation of cyclin-dependent kinases (205), which could prevent cells from returning to a quiescent state. A Tat-induced protection from apoptosis could potentially provide conditions required for the lymphoproliferation of cells, leading to neoplasms associated with AIDS (366). In support of this proposal is the finding that Tat acts as a growth factor for cells derived from Kaposi's sarcoma lesions (83).

The contrasting effects of Tat in the studies described above could depend on whether conditions provide for the uptake of Tat, whether Tat is endogenously produced, or whether Tat is acting extracellularly at cell membrane receptors. Tat binds with high affinity to both soluble CD26 and cell surface CD26 on Th cells (127) and, in doing so, inhibits the activity of this receptor (343). CD26 is a surface protease, expressed by $CD4^+$ T cells, which mediates recall antigen responses. Although CD26 has been reported to serve as a coreceptor for HIV entry (30), this result could not be confirmed by other laboratories. Additionally, HIV preferentially infects $CD4^+$ $CD26^-$ T cells (22). There is a selective loss of $CD26^+$ cells, including both Fas^+ and Fas^- populations (104), during the progression to AIDS (22). The loss of both these populations suggests that the binding of Tat to CD26 may activate an alternate apoptotic pathway. Further to this, Morimoto et al. (234) have demonstrated that an inhibition of CD26 enzymic activity in $CD26^+$ cell lines results in an enhanced sensitivity to apoptosis induced by anti-CD95 antibody.

The Tat protein induces oxidative stress in human T cells (352) which can be abrogated by both inhibitors of Tat and agents which inhibit oxidative stress (81). Ehret et al. examined the ability of Tat to induce oxidative stress and apoptosis in chimpanzee T cells (81). Chimpanzees are susceptible to infection with HIV-1 but are relatively resistant to disease progression (137). While Tat was effectively taken up by chimpanzee T cells, neither oxidative stress nor apoptosis was observed (81). As previously mentioned, unlike HIV-1-infected humans, cysteine metabolic dysfunction is not evident in HIV-infected chimpanzees. The mechanism underlying the resistance of chimpanzee cells to the effects of Tat is not understood but may provide another avenue to a closer understanding of disease progression in HIV-1-infected individuals.

In addition to Tat, HIV-1 encodes several regulatory proteins, including Rev, which regulates viral mRNA expression, Nef, which induces CD4 internalization, Vpu, which is required for nuclear targeting, and Vpr, which is required for virus release (reviewed in reference 235). While apoptosis has not been demonstrated as an end point, Tat, Rev, Nef, and gp120 possess cytotoxic properties in vitro which may be involved in the pathogenesis of AIDS dementia (112, 209, 214, 351). Vpu, Nef, and Env participate independently in the down-modulation of CD4 in primary cells in vitro (41). The down-modulation is temporal, with Nef acting early and Env and Vpu acting late in the viral life cycle. Further contributing to T-cell dysfunction in HIV infection is the Vpr accessory protein, which has been reported to induce cell cycle arrest in the G_2 phase (15, 267). Vpr expression in the infected cell may protect the cell from apoptosis by preventing entry into the mitotic cycle, further contributing to viral persistence. Thus, apoptosis resulting from HIV-1 infection is a dynamic process, which could be mediated by viral proteins acting independently or in cooperation to undermine the normal function of the Th cell.

In contrast to HIV-1, human T-cell lines infected with HTLV-1 or expressing Tax are protected from Fas-mediated apoptosis (60). This protection is conferred to uninfected activated PBMC by the HTLV-1 Tax protein but not the HIV-1 Tat protein, and it shows a dependence upon basal PKC production in the infected cells (60). In another study, Tax was found to induce apoptosis in Jurkat cells bearing an estrogen-inducible fusion protein containing Tax (47); however, apoptosis of these cells required extended Tax expression (9 days). Other reports of the enhancement of apoptosis by Tax used non-T-cell models (99, 355). These contrasting effects of Tax on apoptosis could be, as with Tat, dependent upon the concentration of Tax used. Cell cycle position and regulatory pathways active in the Th cell upon the introduction of Tax could also contribute to the outcome of Tax treatment. This is particularly important to consider, given the pleiotropic effects of Tax on cellular gene activation and suppression.

APOPTOSIS AND DISEASE PROGRESSION

The loss of $CD4^+$ T cells is a hallmark of HIV infection. While several mechanisms probably account for this decline, cell death by the normal physiological process of apoptosis is significant in that it can be induced by several pathways (Fig. 4). The effects of HIV on the immune system provide the appropriate conditions for this process. Apoptosis can be mediated by HIV envelope proteins (12, 196, 350), TCR/CD3 interactions (12, 248), expression of Tat (205), cross-linking of CD4 (12, 255), and possibly superantigen (151). The contribution of HIV to the markedly elevated levels of apoptosis is generally believed to occur in HIV-infected lymphoid tissue and PBMC, both in infected and predominantly in uninfected bystander cells (90). Further, a direct correlation between apoptosis and disease progression has recently been demonstrated (116). Apoptosis in lymph nodes of infected individuals is associated with a general state of immune system activation, but earlier reports did not find an association with disease progression or viral load (239). Evidence indicates that pathways mediating apoptosis are up-regulated by HIV infection and may further be associated with disease progression. The role of the Fas pathway in the apoptosis observed in HIV infection has recently been the subject of vigorous study. An increase in Fas-mediated apoptosis in symptomatic HIV-1-

infected individuals which appears to correlate with an overexpression of Fas antigen during infection has been reported (168). Overexpression of Fas is evident in advanced disease (66, 84, 168, 308); however, the loss of CD4$^+$ cells during disease progression is independent of whether the cells are Fas$^+$ or Fas$^-$ (104). This indicates that HIV-associated apoptosis is not exclusive to the Fas pathway. Importantly, Fas$^+$ CD8$^+$ T-cell numbers are increased during HIV infection, including the CD8$^+$ CD28$^-$ subpopulation of these cells (36). A selective targeting of Fas$^+$ CD4$^+$ Th cells might explain the increase in Fas$^+$ CD8$^+$ T-cell number.

Th1 cells can be induced to express FasL, whereas Th2 cells express little or no FasL (279). Thus, while cross-linking of gp120-CD4 complexes by antibody would stimulate both Th1 and Th2 cells, FasL would be expressed primarily by Th1 cells with the potential to induce activation-dependent cell death or undergo apoptosis themselves. A clonal expansion of FasL-expressing Th1 cells might lead to a loss of the CD95$^+$ Th1 population, thus possibly increasing the proportion of Th2 cells. Naive T cells (CD45RA$^+$) express little or no cell surface Fas, but Fas expression can be induced upon activation, while mature (CD45RO$^+$) T cells express high levels of Fas (177, 232). Fas-mediated signalling under specific conditions results in an enhanced proliferation of Th cells and increased production of IL-2, IFN-γ, and TNF (2). Not all Fas-expressing cells are susceptible to apoptosis (358); thus, the expression of apoptogen receptors such as Fas alone is not sufficient for apoptosis to occur. Apoptosis may require specific cellular conditions, such as down-regulation of protective genes (i.e., Bcl-2), changes in redox potential, or exhaustion, for cell death to proceed. For instance, one study has demonstrated a high sensitivity of T cells of HIV-1-infected individuals to Fas stimulation by using an antibody unreactive to the apoptotic domain of Fas (308). During progression to AIDS, Th cells are in a high-level state of activation and Fas expression is increased. In the latter stages of the immune response, signalling via Fas may lead to a reduction in the number of T cells via apoptosis. This could result in a change in cytokine profiles as a result of the loss of antigen-specific helper activity. In addition, anergy induced by inappropriate activation may further compound the problem of the apoptotic role of Fas and possibly result in further T-cell loss. Thus, in advanced disease, the Th1 population expressing high levels of Fas could become a target for removal rather than activation. This could be mediated in several ways, including binding of Tat to CD26 or by a Th1-to-Th2 shift in cytokine profile. Study of the participation of cytokines in the promotion of activation-induced apoptosis in HIV-1-infected lymphocytes has revealed that type 1 cytokines (IFN-γ, IL-2, and IL-12) are protective against apoptosis (52). In contrast, the Th2 cytokines IL-4 and IL-10 either have no effect or enhance apoptosis (52). Thus, a decline in CD4 counts could represent a shift from a protective Th1 profile to a Th2 cytokine profile, which would permit further apoptosis. The Th1-to-Th2 shift would be further supported by the preference of macrophages to present antigens to Th1 cells. An infected macrophage might deliver an altered activation signal during antigen presentation, which could result in anergy or apoptosis. In this regard, it is important to note that infection of human macrophages results in the de novo expression of FasL and the ability of these cells to induce the Fas-mediated cell death of human PBMC (10).

While CD4$^+$ T-cell depletion is central to the development of AIDS, other cell types are also committed to apoptosis throughout the course of infection. CD8$^+$ T cells, B cells, and hematopoietic progenitor cells from HIV-1-infected individuals also undergo apoptosis (32, 33, 115, 156, 227, 281). One of the earliest events following HIV infection is an expansion of the population of activated, memory (CD45RO$^+$) CD8$^+$ T cells (170, 369). Accompanying the activation and expansion of the CD8 compartment, however, are functional defects in CD8$^+$ T-cell responses to activation and recall antigen (123, 339). Associated with the increase in the number of CD8$^+$ T cells is the advent of HIV-specific CTL, which are present throughout the asymptomatic period (179, 283, 338). Peripheral CD8$^+$ T cells of infected individuals undergo spontaneous and activation-induced apoptosis following a short period of in vitro culture (115, 227). A direct correlation was found between the intensity of spontaneous and anti-CD3-induced apoptosis in both CD4$^+$ and CD8$^+$ T cells from patients and their ex vivo activation state, as evaluated by CD45RO, HLA-DR, and CD38 expression (116). An activation-associated cell death has been observed for the Fas$^+$ CD45RO$^+$ T-cell population in asymptomatic infection (156). The chronic activation state of the immune system induces a down-regulation of Bcl-2 and an up-regulation of Fas in a fraction of CD8$^+$ T cells, which primes these cells for in vitro apoptosis (24). Further to this, in vitro studies indicate that increasing virus load and apoptosis are associated with a shift toward the selective death of CD8$^+$ T cells (33). In vivo, a progressive depletion of CD8$^+$ T cells and a decline in CD8$^+$ T-cell effector function occur upon disease progression (5, 28, 192, 217, 346). Thus, HIV infection induces anergy and apoptosis in the CD8$^+$ T-cell compartment. CD8$^+$ T cells expressing Fas and CD28 and demonstrating a Th0 profile (IL-2 and IL-10) have been suggested to be associated with long-term survival. While the susceptibility of this cell population to apoptosis and the potential of these cells for protection from apoptosis by CD28 stimulation remain to be determined, CD8$^+$ T cells of patients with progressive disease show reduced Fas expression, loss of CD28 expression, and loss of the production of IL-2 and IL-10 (365). Loss of CD28 expression, combined with lack of IL-2 production, could result in a loss of HLA-1-restricted cytolytic activity and could negatively affect the production of virus-suppressive factors (204).

HTLV-1 is mitogenic to resting T cells via the CD2 activation pathway (103), and this effect is mediated by cell-to-cell contact (173). In HTLV-1-infected T-cell lines, CD2 cross-linking induces a cyclosporin A-resistant apoptosis (128). Serum starvation-induced apoptosis of ATL cells is prevented by IL-2 but promoted by glucocorticoid and the activation of PKA (329). Examination of thymic tissue of rabbits infected with a lethal HTLV-1 T-cell line (but not a nonlethal T-cell line) showed evidence of apoptosis (201).

CTL-induced apoptosis has been observed in active spinal cord lesions in patients with HAM/TSP (336). Cells undergoing apoptosis were identified as CD45RO$^+$ T lymphocytes. These authors observed Bcl-2 expression in many of the T cells in the inflammatory lesions but not those susceptible to apoptosis, suggesting that infiltrating T cells could be resistant to apoptosis. This is particularly relevant, since Bcl-2 blocks Tax-mediated apoptosis in rat cells (230). In addition, HTLV-1-infected individuals with ATL have been reported to undergo a spontaneous remission which was paralleled by a decrease in CD45RO expression by PBMC (318). In another study, the CD45RO cell populations in HTLV-1 carriers and infected individuals with ATL were examined (319). This study found two patterns of CD45RO expression. One was a combination of CD45RO with both high and intermediate fluorescence intensity, but the second pattern, which was exclusively high fluorescence intensity, was associated with disease progression. The intermediate-intensity population expressed far lower levels of Fas antigen than did the high-intensity cells, further suggesting that intermediate-intensity CD45RO cells may be protective against apoptosis and disease progression (319).

Virus-mediated inhibition of apoptosis has been observed for adenovirus (280), Epstein-Barr virus, (139), and Sindbis virus (203). The dysregulation of cell suicide pathways by virus infection may help to favor the establishment of viral infection of the host by temporarily and partially impairing immune responses. In an HTLV-1-infected person, a limited amount of Tax expression could render infected cells protected from apoptotic elimination during routine immune responses and surveillance. Thus, expansion of the populations of cells expressing HTLV-1 proviral DNA may occur, predisposing these cells to possibly develop into Th-cell cancer. Protection from apoptosis in HTLV-1 infection may be afforded by low-level expression of Tax and the subsequent activation of the IL-2/IL-2R autocrine loop (Fig. 4). In ATL, protection from apoptosis may eventually allow the more aggressive development of lymphomas over time. Also contributing to the establishment of this type of cancer is the ability of ATL cells to evade immune responses such as NK-cell cytolysis (89). Given the extended asymptomatic period of HTLV-1 infection and the infrequent development of ATL, progression to disease probably depends on the accumulation of a complex series of events including persistent T-cell activation, fluctuating viral quiescence, and lifelong genetic mutations and alterations over time.

CONCLUSIONS

The specific events which affect Th cells and determine the onset of the progression to ATL and AIDS are still not precisely defined. However, a growing body of evidence supports a central role of T-cell activation in the contrasting pathogenesis of AIDS versus ATL. The differences found in the Th-cell responses to T-cell activation pathways between HTLV-1 and HIV-1 suggest that these two viruses have evolved very different strategies for utilizing and residing in the same host cell type. They both abrogate T-cell activation signals to control their own replication, as well as influencing factors affecting the depletion and expansion of Th-cell populations. However, they differ in the Th-cell activation pathways they abrogate. Those differences must be contrasted in the context of the central biological function that Th cells have and of the loss versus expansion of these cell populations in the pathogenesis of HIV and HTLV infection, respectively. Because progression to ATL occurs infrequently in infected individuals, the events that trigger progression may be rare. In addition, it seems likely that, as with HAM/TSP, higher virus expression may be required for progression to disease. It must also be considered that certain events may need to occur, possibly in a specific order during infection. The observation that T-cell activation limits HTLV expression in vitro may indicate that infrequent events are required during the asymptomatic phase for the stepwise progression to ATL. In contrast, the course of clinical progression to AIDS is more predictable, despite the small population of long-term nonprogressors. This group may be critical to defining the relationship between immune system activation, immune system suppression, and Th-cell loss during HIV infection. A focus on understanding the impact of retroviral infection on Th-cell population dynamics during infection and disease progression is important to further our knowledge of these contrasting human retrovirus-mediated diseases.

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