The Human Immunodeficiency Virus: Infectivity and Mechanisms of Pathogenesis

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Infection with the human immunodeficiency virus (HIV) results in a profound immunosuppression due predominantly to a selective depletion of helper/inducer T lymphocytes that express the receptor for the virus (the CD4 molecule). HIV also has tropism for the brain leading to neuropsychiatric abnormalities. Besides inducing cell death, HIV can interfere with T4 cell function by various mechanisms. The monocyte serves as a reservoir for HIV and is relatively refractory to its cytopathic effects. HIV can exist in a latent or chronic form which can be converted to a productive infection by a variety of inductive signals.

THE HUMAN IMMUNODEFICIENCY VIRUS (HIV), THE ETIOlogic agent of the acquired immunodeficiency syndrome (AIDS), has the capability of selectively infecting and ultimately incapacitating the immune system whose function is to protect the body against such invaders (*1, 2*). HIV-induced immunosuppression results in a host defense defect that renders the body highly susceptible to "opportunistic" infections and neoplasms. The immune defect appears to be progressive and irreversible, with a high mortality rate that may well approach 100 percent over several years. From the time that the first cases were reported to the Centers for Disease Control (CDC) in the summer of 1981 until 1 December 1987, there have been approximately 47,000 cases of AIDS in the United States and 58 percent of the patients have already died (*3*). It is estimated that between 1 and 2 million individuals in the United States are infected with HIV and are at present without symptoms (*4*). Given the fact that approximately 20 to 30 percent of infected individuals will develop AIDS within 5 years of infection, it is projected that there will be 270,000 cumulative cases of AIDS by 1991 (*4*). Although the majority of reported cases have occurred in the United States, AIDS is a worldwide epidemic including thousands of cases reported in Europe. Despite the difficulties in epidemiologic surveillance, it is estimated that there are millions of infected individuals in Central Africa (*5*).

HIV infection is spread by sexual contact, by infected blood or blood products, and perinatally by mother to infant (*6*). Regardless of the portal of entry of the virus, the common denominator of HIV infection is a selective tropism of the virus for certain cells of the immune system and the central nervous system (CNS), which results in immunosuppression and neuropsychiatric abnormalities (*1, 2*).

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The Virus

Nature of HIV. In order to fully understand the pathogenic mechanisms of HIV infection, one must consider the unique nature of the causative microbe. HIV is an RNA retrovirus that was originally designated human T lymphotropic virus (HTLV)-III (*7*), lymphadenopathy-associated virus (LAV) (*8*), or AIDS-associated retrovirus (ARV) (*9*). It shares many features with other members of the nontransforming and cytopathic lentivirus family of retroviruses. Of particular note are its morphological, biological, and molecular similarities to the visna virus of sheep (*10*), equine infectious anemia virus (*11*), and the recently described feline immunodeficiency virus (*12*). These viruses, including HIV in humans, cause a slowly progressive and inevitably fatal disease in their hosts. HIV is also related to other recently isolated primate retroviruses such as simian T lymphotropic virus (STLV)-III, which causes disease in captive macaques but is apparently not pathogenic for wild African Green monkeys (*13*). HTLV-IV has been isolated from healthy West Africans (*14*). Others have reported that this latter virus may be indistinguishable from STLV-III (*15*). HIV is increasingly referred to as HIV-1 to differentiate it from HIV-2 (or LAV-2), which shares serologic reactivity and polynucleotide sequence homology with STLV-III and has been isolated from West African patients with a clinical syndrome indistinguishable from HIV-induced AIDS and AIDS-related condition (ARC) (*16*).

The HIV genome. As visualized by electron microscopy, HIV has a dense cylindrical core whose structural elements are coded for by the viral *gag* gene and encase two molecules of the viral RNA genome (*17, 18*). The central core is surrounded by a lipid envelope acquired as the virion buds from the surface of an infected cell. Virus-encoded enzymes required for efficient replication, such as the reverse transcriptase and integrase, are also incorporated into the virus particle. The HIV proviral genome has been well characterized (Fig. 1). It is approximately 10 kb in length and comprises the flanking long terminal repeat (LTR) sequences that contain regulatory segments for HIV replication as well as the *gag*, *pol*, and *env* genes coding for the core proteins, the reverse transcriptase-protease-endonuclease, and the internal and external envelope glycoproteins, respectively (*17, 18*). HIV also has at least five additional genes, three of which have known regulatory functions (*17, 18*), and the expression of these genes almost certainly has an impact on the pathogenic mechanisms exerted by the virus. The *tat* gene plays an important role in the amplification of virus replication by encoding a protein that functions as a potent trans-activator of HIV gene expression (*19*). The *trs/art* gene also upregulates HIV synthesis by a trans-acting antirepression mechanism (*20*). In contrast, the *3' orf* gene may downregulate virus expression, as one group has reported that deletion of the gene results in an approximately fivefold increase in viral DNA synthesis and viral replication (*21*); however, others

have not seen such an effect (*22*). Although the *sor* gene is not absolutely required for HIV virion formation, it clearly influences virus transmission in vitro and is critical to the efficient generation of infectious virions (*23*). Finally, the *R* gene codes for an immunogenic protein whose function is currently unknown (*24*).

Immunopathogenic Mechanisms of HIV Infection

Scope of the immunologic defect. The critical basis for the immunopathogenesis of HIV infection is the depletion of the helper/inducer subset of T lymphocytes, which express the CD4 phenotypic marker (the T4 cell), resulting in profound immunosuppression (*1, 2*). Although a large number of immunologic abnormalities that accompany HIV infection have been described, all but a few can be attributed to the selective defect in the T4 subset of lymphocytes [reviewed in (*25*)]. The T4 lymphocyte is the focal and critical cell involved directly or indirectly in the induction of most immunologic functions (*25*) (Fig. 2). Hence, a functional defect of T4 cells would result in a decrease in inductive signals to multiple limbs of the immune response, and this would explain the apparent paradox of a selective defect in a single subset of cells causing a global immune defect.

HIV infection. HIV has a selective tropism for the T4 cell, and a convincing body of evidence has suggested that the CD4 molecule is, in fact, the high-affinity receptor for the virus (*26*). After HIV binds to the CD4 molecule, the virus is internalized and uncoated (Fig. 3). The precise mechanism of virus entry into the target cell is unclear. It has been suggested that receptor-mediated endocytosis plays a role in this process (*27*). However, it has recently been demonstrated that *p*H-independent fusion of the transmembrane portion (gp41) of the virus envelope with the cell membrane is required for virus entry (*28*). In addition, the inability of mouse cells transfected with the CD4 gene and expressing the human CD4 protein to be productively infected with HIV in the face of viral binding (*27*) suggests that other proteins expressed on the human T4 cell may be required for virus internalization.

Once internalized, the genomic RNA is transcribed to DNA by the enzyme reverse transcriptase (*18*). The proviral DNA, which can exist in a linear or circularized form, is integrated into the host chromosomal DNA in a process dependent on an endonuclease encoded by the viral *pol* gene (*18*). An unusual feature of HIV infection compared to most other retroviruses is the accumulation of large amounts of unintegrated viral DNA in the infected cells (*29*). When this phenomenon does occur in other retroviral systems, it is usually associated with a significant cytopathic effect (*18*) and has been suggested as an important factor in the cytopathicity of HIV (*29*).

After integration of provirus, the infection may assume a latent phase with restriction of the cycle until the infected cell is activated. Once cell activation occurs, the proviral DNA transcribes viral genomic RNA and messenger RNA (mRNA). Protein synthesis, processing, and virus assembly occur with budding of the mature virion from the cell surface [reviewed in (*2*)].

Mechanisms of cytopathic effect. When active replication of virus occurs, the host cell is usually killed. However, one of the critical unknowns in the immunopathogenesis of HIV infection is the precise mechanisms of the cytopathic effect in T4 cells. The potential role of accumulation of unintegrated viral DNA (*18*) has been discussed above. Another mechanism that has been proposed is a massive increase in permeability of the cell membrane when large amounts of virus are produced and bud off the cell surface (*30*). Others have speculated that HIV may induce terminal differentiation of the infected T4 cell, leading to a shortened life-span (*31*); however, the evidence for this is meager.

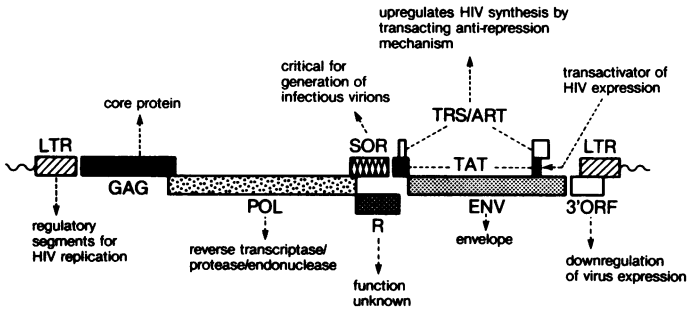

Fig. 1. HIV proviral DNA genome. The eight identified genes of HIV and their recognized functions are illustrated.

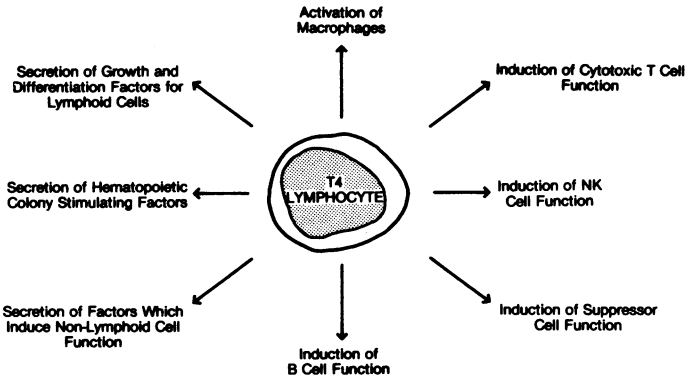

Fig. 2. Critical role of the T4 lymphocyte in the human immune response. The T4 cell is responsible directly or indirectly for the induction of a wide array of functions of multiple limbs of the immune response as well as certain nonlymphoid cell functions. This is effected for the most part by the secretion of a variety of soluble factors that have trophic or inductive effects (or both) on the cells in question.

There is mounting evidence that both the CD4 molecule and the virus envelope play a role in the cytopathic effect in infected T4 cells. Certain subsets of monocytes and macrophages express the CD4 molecule (*32*) and these cells can bind to and be infected with HIV (see below); however, HIV does not induce a significant cytopathic effect in monocytes. Since the level of expression of CD4 on the monocyte is considerably less than that on the T4 cell (*33*), it is possible that the density of this receptor is important in determining the presence or degree of cytopathic effect of the bound and internalized virus. Furthermore, superinfection of HTLV-I–infected T cell clones of either the T4 or T8 phenotype with HIV resulted in a productive infection and accumulation of unintegrated HIV DNA. However, a cytopathic effect was seen only in the T4 clones; the T8 clone was resistant to the cytopathic effect (*34*).

A potentially important mechanism of cell death in HIV infection involving CD4-envelope protein interaction is cell fusion. The high level of HIV *env* gene expression in infected T4 cells, as manifested by the budding of viral particles from the plasma membrane, results in cell fusion with neighboring uninfected T4 cells and leads to the formation of multinucleated giant cells (syncytia) that comprise both infected and uninfected cells (*35*). Depending on the virus isolate in question, cytolysis and death of the fused cells occurs, usually within 48 hours. It is also possible that intracellular complexing of CD4 and envelope proteins may play a role in the cytopathic effect of HIV (*36*).

It has been proposed that autoimmune phenomena play a role in the cytopathicity associated with HIV infection. Some examples are the immune clearance of infected T4 cells expressing envelope

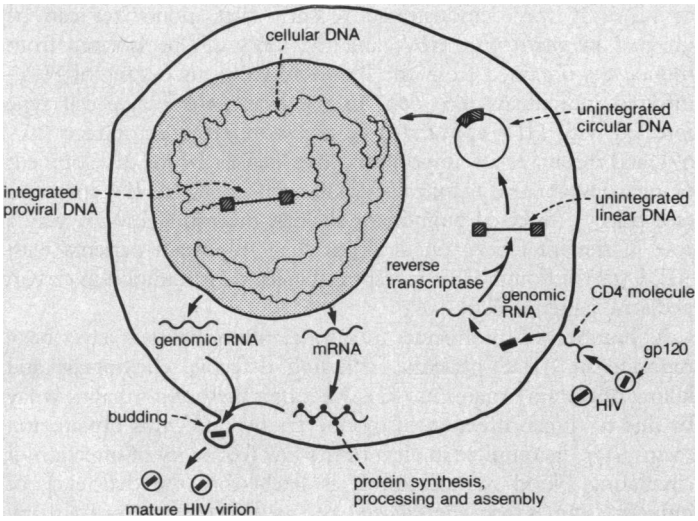

Fig. 3. The life cycle of HIV.

proteins on their surface that are recognized as non-self, or, alternatively, the binding of free envelope protein (gp120) to the CD4 molecule of uninfected T4 cells, resulting in similar immune clearance (*37*) or the elimination of such cells by antibody-dependent cellular cytotoxicity (*38*). Others have reported an AIDS-related cytotoxic antibody reacting with a specific antigen on stimulated T4 cells (*39*). Another hypothesis is autoimmunization with class II–like antigens (*40*). This theory is based on the fact that the CD4 molecule on the T4 cell recognizes a portion of the class II major histocompatibility complex (MHC) molecule. Since the HIV envelope binds to the CD4 molecule, it can mimic the configuration of a portion of the class II MHC antigen. Hence, antibodies and cytotoxic lymphocytes directed against the HIV envelope can potentially cross-react with class II MHC antigens. The extent if any to which these autoimmune phenomena are involved in cytopathicity of HIV infection is unclear at present.

Quantitative deficiency of T4 lymphocytes. The most conspicuous immunologic abnormality resulting from HIV infection is a quantitative deficiency of T4 lymphocytes (*25*). The question arises whether the depletion of T4 cells can be explained totally by the direct cytopathic effects discussed above or whether other indirect mechanisms contribute. The use of fluoresceinated antibodies against viral encoded proteins (*41*) and in situ hybridization techniques (*42*) to detect cells expressing viral proteins or mRNA, respectively, has shown that only an extremely small percentage of cells (in the range of 1 in 10^5) in the peripheral blood of HIV-infected individuals are expressing virus at any given time. It should be pointed out, however, that somewhat larger proportions of cells might be latently infected (see below). These cells are not expressing virus and therefore are not readily detectable by currently available techniques. Nonetheless, although the precise half-life of T4 cells is not known, in view of the normal turnover of T lymphocytes in the body (*43*), it would seem that the T cell pool would be able to compensate for such a seemingly low rate of T4 cell destruction. Thus, it has been hypothesized that in addition to a direct HIV-induced cytopathic effect on a given T4 cell, other potential mechanisms of T4 depletion may be operable (*44*). For example, it is possible that HIV infects a T4 cell precursor or stem cell and that this leads to lack of production of mature cells. In addition, HIV might infect and selectively deplete a subset of T4 cells or even $CD4^+$ nonlymphoid cells that are critical to the propagation of the entire T4 cell pool. In this regard, it is known that T4 lymphocytes elaborate factors, including interleukin-2 (IL-2), that are trophic for lymphocytes (*45*) as well as for cells of the myeloid series (*46*). Finally, another potential mechanism of T4 cell depletion is the induction by HIV or the secretion by HIV-infected cells of soluble factors that are toxic to T4 lymphocytes (*47*).

Functional abnormalities of T4 lymphocytes. Although quantitative depletion of T4 lymphocytes is the most obvious immunologic abnormality in HIV-infected individuals, a qualitative or functional defect of a selective subset of T4 cells is also a consistent finding. It has been clearly demonstrated that the subset of T4 cells that recognizes and responds to soluble antigen is selectively deficient in patients with AIDS and that this deficiency occurs early in the course of the disease (*48*). This defect is not due to an abnormality of antigen-presenting cells required for such responses. In a series of studies of identical twins, one of whom had AIDS and the other of whom was seronegative and healthy, monocytes from the seronegative twin, when co-cultured with his autologous T cells supported good proliferative responses to tetanus toxoid (TT) in vitro. However, monocytes from the seronegative twin failed to reconstitute the defective TT response when co-cultured with T4 cells from the twin with AIDS (*49*). Furthermore, we recently studied a large cohort of asymptomatic, seropositive homosexual men and noted the absence of an in vitro proliferative response to TT even after booster immunization in a substantial proportion of the subjects, many of whom had normal numbers of circulating T4 lymphocytes (*49*). This observation could be explained by a selective depletion of this functional subset of T4 cells, a functional abnormality of the subset, or both. Since this defect has also been seen with other test antigens (*50*), it is likely that it reflects abnormalities across the scope of the antigen-specific T cell repertoire. If this were explained completely by a depletion of this repertoire, one would have expected a significant quantitative deficiency in the total T4 cell pool, as was not noted in the above study. Hence, it is highly likely that a functional defect of T4 lymphocytes contributes to the observed abnormalities.

Functional abnormalities of T4 cells directly related to HIV can be explained by a noninfectious exposure of the T4 cell to HIV or by a noncytopathic infection of the T4 cell. We demonstrated earlier that exposure to HIV without infection of T4 cells results in a negative or tolerance-inducing signal, with the result that these cells are markedly defective in their responses to the subsequent exposure to soluble antigen and, to a lesser extent, mitogen (*51*). Other studies have also shown that subunits of HIV, particularly the envelope, which certainly cannot induce infection, are capable of inhibiting cell function (*52*).

There are a number of potential mechanisms of direct inhibition of T4 cell function by HIV in the absence of infection of the cell. Antigen-specific responses of T4 cells require the interaction of the CD4 molecule of the T4 cell with the class II major histocompatibility complex (MHC) molecule of the antigen-presenting cell during presentation of processed antigen to the CD3-Ti antigen receptor complex on the T4 cell (*53*). Since the envelope of HIV binds avidly to the CD4 molecule of the T4 cell (*26*), this could readily block the critical interaction with the class II MHC molecule. Responses of T4 cells to mitogens are not critically dependent on this CD4–class II MHC molecule interaction, and therefore mitogens might override the block seen with antigen responses (*49*). This hypothesis is consistent with the observation that mitogen responses are normal in certain circumstances in which a selective defect in antigen responses is seen (*48*).

Another hypothesis is that noninfectious interaction of HIV with the T4 cell results in a defect in postreceptor signal transduction, either after ligand binding at the level of the CD4 molecule or at the level of antigen receptor (CD3-Ti complex) itself. Since triggering of cells by certain mitogens occurs through a different activation

pathway than that of the cell's antigen receptor pathway (*54*), this again might explain in part the discrepancy between suppression of antigen responses as opposed to mitogen responses (*48*).

Functional impairment of T4 cells may also occur after noncytopathic infection with HIV. After infection with HIV, T4 cells no longer express CD4 molecules on their cell surfaces (*36*). The lack of expression of CD4 on these infected antigen-responsive T4 cells could interfere with the required interaction of CD4 molecules and class II MHC molecules described above. Finally, infected Jurkat T cells surviving cytopathic infection with HIV not only fail to express CD4 molecules on their surfaces, but also have decreased expression of the IL-2 gene in the face of normal expression of the IL-2 receptor gene (*55*). A functional defect in IL-2 gene expression may well contribute to the antigen-specific defect that requires IL-2 for amplification of response.

B cell abnormalities. Persons with AIDS also have significant abnormalities of B cell function as manifested by polyclonal activation, hypergammaglobulinemia, circulating immune complexes, and autoantibodies (*56*). Despite the heightened spontaneous responsiveness of the B cell repertoire of these individuals, there is a deficient antibody response to new antigens such as keyhole limpet hemocyanin (KLH) (*56*). Although certain T cell–dependent B cell responses may be abnormal as a result of defects in helper function of the T4 cell, as described above, it is clear that other defective responses result from abnormalities at the B cell level. The humoral defect is manifested most obviously in an inability to mount an adequate immunoglobulin M (IgM) response to antigenic challenge. This has most severe consequences in infants and children infected with HIV who have not had previous exposure to a variety of pathogenic bacterial organisms and who must rely on an initial IgM response for adequate host defenses (*57*). However, certain adult patients also manifest an increased susceptibility to various pyogenic bacteria, and this may also be related to the defect in humoral immune responses (*58*). In addition, the defective humoral response may render the serologic diagnosis of certain infections unreliable.

The polyclonal hyperactivity of the B cell limb of the immune response is likely due to multiple factors. The high incidence of infection with Epstein-Barr virus (EBV) and cytomegalovirus (CMV), both of which are polyclonal B cell activators, certainly contributes to this phenomenon. Of importance is the fact that the HIV itself or subunits of the virus can polyclonally activate B cells in vitro (*59*). In this regard, it has been demonstrated that a stretch of amino acids from a conserved region of the HIV envelope is partially homologous to neuroleukin, a factor than enhances B cell growth and differentiation (*60*). However, it is unclear at present whether this is related to the HIV-induced polyclonal B cell activation.

Natural killer cells. The number of circulating natural killer (NK) cells is not significantly diminished in HIV-infected individuals, including patients who have developed AIDS, and these cells bind normally to their target cells (*61*). However, their cytotoxic capability is diminished compared to that of normal individuals (*62, 63*) but can be normalized when activated in vitro with a variety of inductive signals such as IL-2, concanavalin A, or phorbol ester and calcium ionophore (*63, 64*). These findings are in accord with the model of relative selectivity of defect at the level of the inductive T cell population, with secondary effects on those cell populations that rely on these inductive signals for functional integrity.

Monocytes in HIV infection. Evidence is accumulating to support the concept that monocytes and macrophages play a major role in the propagation and pathogenesis of HIV infection. These phagocytic cells can engulf the virus. Certain subsets of monocytes express the CD4 surface antigen (*32*) and therefore can bind to the envelope of HIV. It was demonstrated recently that monocytes can be infected in vitro with HIV, and the virus can be isolated from monocytes obtained from the blood and various organs of HIV-infected individuals (*65, 66*). In the brain, the major cell type infected with HIV appears to be the monocyte/macrophage (*67–69*), and this may have important consequences for the development of neuropsychiatric manifestations associated with HIV infection (see below). Infected pulmonary alveolar macrophages may play a role in the interstitial pneumonitis seen in certain patients with AIDS (*66*) although EBV is responsible for this condition in certain pediatric patients (*70*).

A number of monocyte functional abnormalities have been reported in AIDS patients, including defective chemotaxis and killing of certain organisms (*71*). Although these abnormalities may be due to direct infection of monocytes by HIV, this explanation seems to be incomplete in view of the low frequency of infection of circulating blood monocytes. It is likely that the deficiency of inductive signals from the T4 cell (see above) is responsible for many of the functional defects of monocytes, a hypothesis that is supported by the fact that interferon-γ produced by T4 cells is capable of reconstituting certain defective functions of monocytes (*72*).

It is also possible that secretion of monokines is directly or indirectly influenced by HIV infection. Monocytes from some AIDS patients spontaneously secrete increased amounts of IL-1, even though the induction of secretion of this factor is deficient (*73*). It is quite possible that certain of the fevers and the wasting syndromes seen in AIDS patients are related to increased secretion of monokines such as IL-1 and tumor necrosis factor (cachectin) (*74*).

Perhaps the most important implication of the infectivity of monocytes with HIV is the possibility that the monocyte serves as the major reservoir for HIV in the body. Unlike the T4 lymphocyte, the monocyte is relatively refractory to the cytopathic effects of HIV so that not only can the virus survive in this cell but it can be transported to various organs in the body such as the lung and the

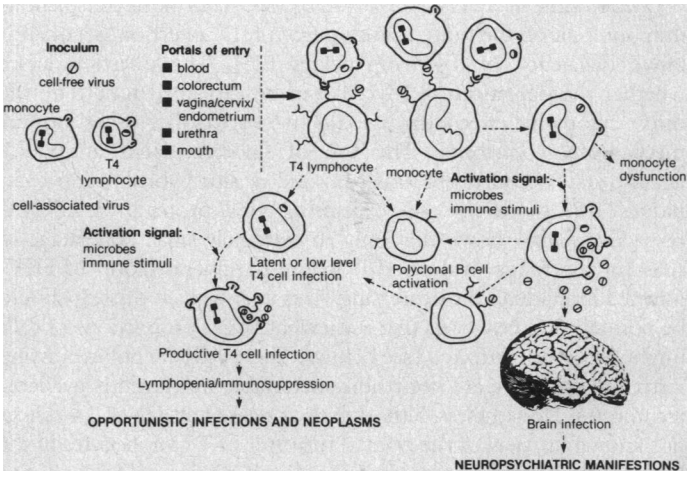

Fig. 4. Potential mechanisms of pathogenesis of HIV infection. Virus enters the body through a variety of portals of entry either as cell-free virions or in a cell-associated form. The virus binds to and infects $CD4^+$ cells and monocytes. The monocytes may also phagocytize virus. HIV infection can exist either as a latent or a low-level or chronic form. Upon activation of the infected cell, virus is produced resulting in a cytopathic effect on T cells and to a much less extent on monocytes. The monocyte can serve as a reservoir for HIV, transporting the virus to various parts of the body, particularly the brain, thereby leading to neuropsychiatric abnormalities. In addition, monocytes can pass the virus to T4 cells. Cytopathicity follows upon activation of the T4 cell, with resulting cell death and immunosuppression leading to the development of opportunistic infections and neoplasms.

brain. We recently developed cloned promonocyte cell lines derived from U-937 cells chronically infected with HIV (*75*). One of these clones (U1) does not constitutively express virus but is latently infected with two integrated copies of provirus per cell and can be induced to express virus by certain cytokines (*75*) (see below). Thus, monocyte precursors may be noncytopathologically infected and capable of secreting virus upon appropriate induction. In addition, HIV infection of the U1 clone results in the upregulation of IL-1β expression, an indication that HIV infection may have important influences on the expression of certain cellular genes.

Of particular interest is the recent finding of Gendelman *et al.* (*76*) that not only can monocytes harbor virus, but under certain circumstances they can actually serve as a major source of virus production in vitro. If this holds true in the in vivo situation, the monocyte may not only serve as a reservoir for the virus, but may be a major contributor to the viral burden of an infected host. The noncytopathic, low-replication infection of monocytes with HIV is somewhat analogous to infection with other lentiviruses such as the visna virus of sheep (*77*) against which effective immune surveillance does not develop. Similarly, persistence of HIV in human monocytes may explain in part the inability of an HIV-specific immune response to completely clear the body of virus (*78*).

Latency or low-level chronicity of HIV infection. It is clear that upon infection of susceptible cell cultures with HIV, certain cells survive that are either latently (integrated provirus without virus expression) or chronically (low-level virus expression) infected. This can be demonstrated with infection of human peripheral blood lymphocytes (*79*) or $CD4^+$ T cell lines (*80*). It is also clear that activation signals are required for the establishment of a productive HIV infection in vitro (*81*). Given the extended time frame (up to 5 years or longer) from initial infection with HIV to clinically detectable immunologic abnormalities and disease manifestations, it is highly likely that the virus exists for prolonged periods in a latent or chronic form in both lymphocytes and monocytes. Gradual attrition of the T4 cells usually occurs in a linearly progressive fashion. However, intermittent bursts of virus production may result in accelerated killing of infected T4 cells and spread of infection to other T4 cells and monocytes. The length of time for clinically relevant immunosuppression to occur will depend upon the rate of this process, which might vary greatly from individual to individual. Since activation signals are required for the establishment of a productive HIV infection in vitro (*81*), it is likely that various activation signals in vivo contribute to conversion of a latent or chronic infection to a productive one. Phytohemagglutinin (PHA) has been used to induce productive infections in vitro (*81*). For the HIV-infected individual, the wide range of in vivo antigenic stimuli would serve as more physiologically relevant cellular activators than the global stimulation observed in vitro with mitogens. In this regard, when cultures of human lymphocytes were exposed to HIV in the presence or absence of soluble antigens such as TT or KLH, virus production as measured by reverse transcriptase activity was noted in the cultures exposed to antigen, whereas no virus was expressed in the absence of antigenic stimulation (*51*).

It has been postulated that other concomitant viral infections—for example, with EBV, CMV, hepatitis B, or herpes simplex virus (HSV)—could induce HIV expression (*49*). When HIV-susceptible cells were simultaneously cotransfected with a plasmid containing the HIV LTR linked to the chloramphenicol acetyltransferase gene along with plasmids containing the *tat-III* gene and the immediate early genes from a variety of heterologous DNA viruses, it was clear that the presence of genes of these other viruses such as HSV in the presence of *tat-III* upregulated the expression of HIV (*82*).

In addition to mitogens, antigens, and heterologous viruses, physiologic cellular inductive signals that might be encountered as part of the normal immune response might play a role in the induction of virus expression. We recently showed that cytokine-containing delectinized supernatants of PHA-stimulated human mononuclear cells as well as recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) are capable of inducing expression of virus in a chronically infected cloned promonocyte cell line (U1), which did not constitutively express virus (*75*) (see above). Although this phenomenon was observed in a cloned promonocyte cell line and may not be generally reflective of the total mononuclear cell repertoire, it nonetheless serves as a model to delineate the normal physiologic mechanisms that might be operable in the induction of virus expression from a latent or chronically infected state, with resultant cytopathicity, immunosuppression, and disease manifestations. A schematic diagram of the potential mechanisms of pathogenesis in HIV infection is shown in Fig. 4.

Pathogenesis of Neuropsychiatric Manifestations of HIV Infection

Neurologic abnormalities are quite common in AIDS and occur to varying degrees in at least 60 percent of patients. Details of the clinical and pathologic manifestations are reviewed elsewhere (*83*) and in this issue (*84*). At least three currently recognized potential pathogenic mechanisms can explain the neuropsychiatric manifestations of HIV infection.

Monocyte/macrophage–induced pathogenic effects. It appears that the predominant cell type in the brain that is infected with HIV is the monocyte/macrophage (*67–69*). We previously demonstrated by simultaneous in situ hybridization and immunohistochemical staining that HIV mRNA was expressed selectively in multinucleated giant cells exhibiting monocyte markers in the brains of two patients with AIDS encephalopathy (*67*). Similar results were reported when immunoperoxidase techniques were used (*69*). Others have also reported infection of mononuclear cells and multinucleated giant cells, as well as endothelial cells and, rarely, astrocytes and neurons, in the brain (*68*). It is likely that the virus enters the brain through infected monocytes and releases monokines and enzymes that are toxic to neurons, as well as chemotactic factors that lead to infiltration of brain substance with inflammatory cells.

Direct infection of neuronal tissue. It has been difficult to demonstrate direct infection of neuronal cells with HIV. Nonetheless, there are scattered reports of the demonstration of virus in neurons, oligodendrocytes, and astrocytes (*68, 85*). A number of studies have demonstrated the presence of CD4 molecules or mRNA for CD4 in neurons and glial cells from various areas of the brain (*25, 86*) and so the potential exists for the binding to and infection of brain cells by HIV. The precise role of direct infection of the neuronal cells of the brain with HIV remains to be determined.

Inhibition of neuroleukin. Finally, of particular interest is a recent report that the gp120 of the HIV envelope inhibited the growth of neurons in the presence of neuroleukin, but did not inhibit their growth in the presence of nerve growth factor (*87*). It was postulated that the inhibition was due to the partial sequence homology between the gp120 and neuroleukin.

In conclusion, an extraordinary amount has been learned about the pathogenic mechanisms of HIV infection, particularly with regard to its effects on the human immune system. Certainly, further delineation of the nature of HIV-induced immunopathogenesis will be critical to the study, treatment, and prevention of HIV-related conditions and will also serve as a model for further understanding of the precise mechanisms of immunoregulation of the normal immune response.

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