

REVIEW ARTICLE

MECHANISMS OF DISEASE

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THE IMMUNOPATHOGENESIS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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THE human immunodeficiency virus (HIV) is probably the most intensively studied virus in the history of biomedical research. A large number of distinct isolates have been cloned and sequenced, and the genes of the virus and several of the protein products of these genes have been characterized.¹ Furthermore, many of the pathogenic mechanisms associated with HIV infection that lead to clinical disease have been established, such as the functional abnormalities and quantitative depletion of CD4 T lymphocytes that cause the profound immunosuppression characteristic of advanced HIV infection.² It is generally agreed that HIV itself has the primary role in the initiation and propagation of the pathogenic process.³ Nonetheless, a number of important issues concerning the pathogenesis of HIV infection and disease from both a virologic and an immunologic standpoint remain unresolved. Foremost among them is the observation that the viral burden in peripheral-blood mononuclear cells is low at the same time that CD4 T lymphocytes are progressively depleted and immune function deteriorates in most patients.² Although a recent study demonstrated that in patients with HIV a substantial percentage of peripheral-blood mononuclear cells are infected with the virus,⁴ the body of evidence favors an extremely low viral burden in peripheral-blood mononuclear cells. The recent findings of a much greater viral burden and greater viral propagation in lymphoid tissue than in peripheral blood (see below) may help resolve this issue. The question has nonetheless stimulated investigation into additional mechanisms of immune dysregulation associated with HIV infection, and a series of immunologic and nonimmunologic mechanisms of immune-cell dysfunction and destruction have been proposed. In this article, we shall outline the available knowledge concerning the pathogenesis of HIV

infection and discuss information that has recently emerged in this area.

THE COURSE OF HIV INFECTION

Although the course of HIV infection may vary somewhat among individual patients, a common pattern of development has been recognized (Fig. 1).⁵ Primary infection with HIV is followed by the development of detectable humoral and cellular immune responses to the virus and a prolonged period (median, 10 years) of clinical latency, during which the patient is usually asymptomatic, followed by the appearance of constitutional signs and symptoms.⁵ Clinically apparent disease then develops, and even with treatment,⁶⁻⁸ death usually ensues within two years.⁹ The contributions of the different pathogenic mechanisms of HIV infection probably vary considerably during each stage of this infection.

Acute HIV Syndrome

In 50 to 70 percent of patients with primary HIV infection an acute mononucleosis-like syndrome develops approximately three to six weeks after initial infection (Fig. 2).¹⁰ This period is associated with high levels of viremia, and within one week to three months there is an immune response to HIV.^{11,12} HIV is widely disseminated during this early stage of infection,¹⁰ strongly suggesting that the subsequent course of HIV infection may be influenced by the seeding of virus, particularly in the lymphoid organs, during this short period. Furthermore, the HIV-specific immunity initiated during this stage is associated with a dramatic decline in viremia.^{11,12} However, this immunity is apparently inadequate to suppress viral replication completely, since HIV expression persists in lymph nodes even when plasma viremia is difficult to detect¹³ and HIV messenger RNA (mRNA) is virtually undetectable in peripheral-blood mononuclear cells.^{13,14}

Detectable viremia declines markedly or disappears weeks to months after the acute syndrome subsides, and the change is temporally associated with the emergence of an HIV-specific immune response.^{11,12} It is highly likely, however, that viral replication is never completely curtailed, since it is detectable in lymph nodes during apparently quiescent stages of infection.¹³ Although a substantial percentage of patients with HIV infection do not have a clinically recognizable acute syndrome after primary infection, the events described above probably occur even in the absence of symptoms.

Clinical Latency

After primary infection, viral dissemination, the appearance of HIV-specific immunity, and the apparent curtailment of viral replication, most patients

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have a period of "clinical latency" that lasts for years.⁵ The term clinical latency is misleading, however, since during this period virtually all patients have a gradual deterioration of the immune system, manifested particularly by the depletion of CD4 T cells.^{2,5} Furthermore, although a patient always has many more infected cells that are not expressing detectable HIV mRNA or protein than cells in which viral expression is readily detected,^{15,16} there is probably never a true state of complete microbiologic latency (i.e., no viral expression) during the course of HIV infection.

The most obvious and quantifiable aspect of the deterioration that occurs during the clinically latent stage is the depletion of peripheral-blood CD4 T cells. Although this depletion may occur even without large increases in plasma concentrations of virus (as manifested by p24 antigenemia or culturable virus), viral replication in lymphoid organs, together with the spectrum of immunologic events that are directly or indirectly triggered by the virus, may contribute to it. Thus, HIV disease is clearly progressive during the so-called latent period.

Clinically Apparent Disease

The inevitable outcome of the progressive deterioration of the immune system that occurs in most patients with HIV infection is clinically apparent disease or an acquired immunodeficiency syndrome (AIDS)—defining illness, either severe and persistent constitutional signs and symptoms or an opportunistic infection or neoplasm.^{5,17} Exceptions to the direct correlation between deteriorating immune function and clinically apparent disease are the progressive generalized lymphadenopathy that some patients have early in the course of infection and that may be caused by a vigorous immune response against HIV in the lymph nodes¹⁸; Kaposi's sarcoma, which can occur before the onset of severe immunosuppression¹⁹ and which may be influenced by a complex interplay of growth factors²⁰⁻²²; and neurologic disease that may reflect direct or indirect effects of the virus or its products on neurons and other cells of the nervous system.²³ The profound immunosuppression that occurs during this phase of HIV infection is the end stage of the immunopathogenic events that began at the time of primary infection, when the virus disseminated and seeded the lymphoid organs, and continued for years through the clinically latent but microbiologically active stages of infection.

IMMUNOPATHOGENIC MECHANISMS OF HIV INFECTION

Mechanisms of CD4 T-Lymphocyte Dysfunction

In patients with HIV infection, immunosuppression is due to quantitative as well as functional defects in CD4 T cells. The potential mechanisms of CD4 T-cell dysfunction are listed in Table 1. Several of these have been reviewed previously² and will be dis-

cussed only briefly here. Other, more recently proposed mechanisms will be discussed in greater detail.

Single-Cell Killing and Syncytia Formation

In vitro single-cell killing and syncytia formation occur through direct HIV-mediated cytopathic effects.²⁴⁻²⁶ Single-cell killing may result from the accumulation of unintegrated viral DNA or from the inhibition of cellular protein synthesis after HIV infection.²⁴ The formation of syncytia involves fusion of the cell membrane of an infected cell with the cell membranes of uninfected CD4 cells, which results in giant multinucleated cells. A direct relation between the presence of syncytia and the degree of the cytopathic effect of the virus in individual cells has been demonstrated in vitro,²⁷ and HIV isolated during the accelerated phase of infection in vivo has a greater capacity to induce syncytia in vitro.²⁸ Syncytia have rarely been seen in vivo, however. In vitro, their formation may be regulated by the leukocyte adhesion molecule LFA-1 (lymphocyte-function-associated antigen 1) produced by human CD4 T lymphocytes inoculated with HIV.^{27,29}

HIV-Specific Immune Responses

Both humoral and cellular immune responses contribute to antiviral immunity.⁵ The major antiviral effects of antibodies are attributed to their neutralizing properties.³⁰ However, antibodies directed against some regions of the envelope of HIV may have an additional protective function related to their ability to mediate antibody-dependent cellular cytotoxicity after binding to natural killer cells,⁵ leading to the killing of HIV-infected cells that express viral-envelope proteins on their surfaces. HIV-specific cytotoxic T lymphocytes may play an important part in the immune response against HIV, and they have been found in a substantial percentage of patients with HIV infection.^{5,31-33} These mechanisms of immunity and the effector cells involved may have a dual role, however. The first is a protective role in the initial immune response to HIV infection, at which time these mechanisms may help to control or even clear the infection. The second is a pathogenic role during the chronic phase of infection, when the same mechanisms may be involved in the elimination of HIV-infected cells (i.e., CD4 T cells, follicular dendritic cells, and macrophages) and may thus contribute to the progressive deterioration of the immune system.

Autoimmune Mechanisms

Nonpolymorphic determinants of major-histocompatibility-complex (MHC) class II molecules, particularly HLA-DR and HLA-DQ, share some degree of structural homology with the gp120 and gp41 proteins of HIV type 1,³⁴ and antibodies to these HIV proteins could therefore cross-react with HLA class II molecules. In fact, antibodies that react with class II molecules have been found in the serum of pa-

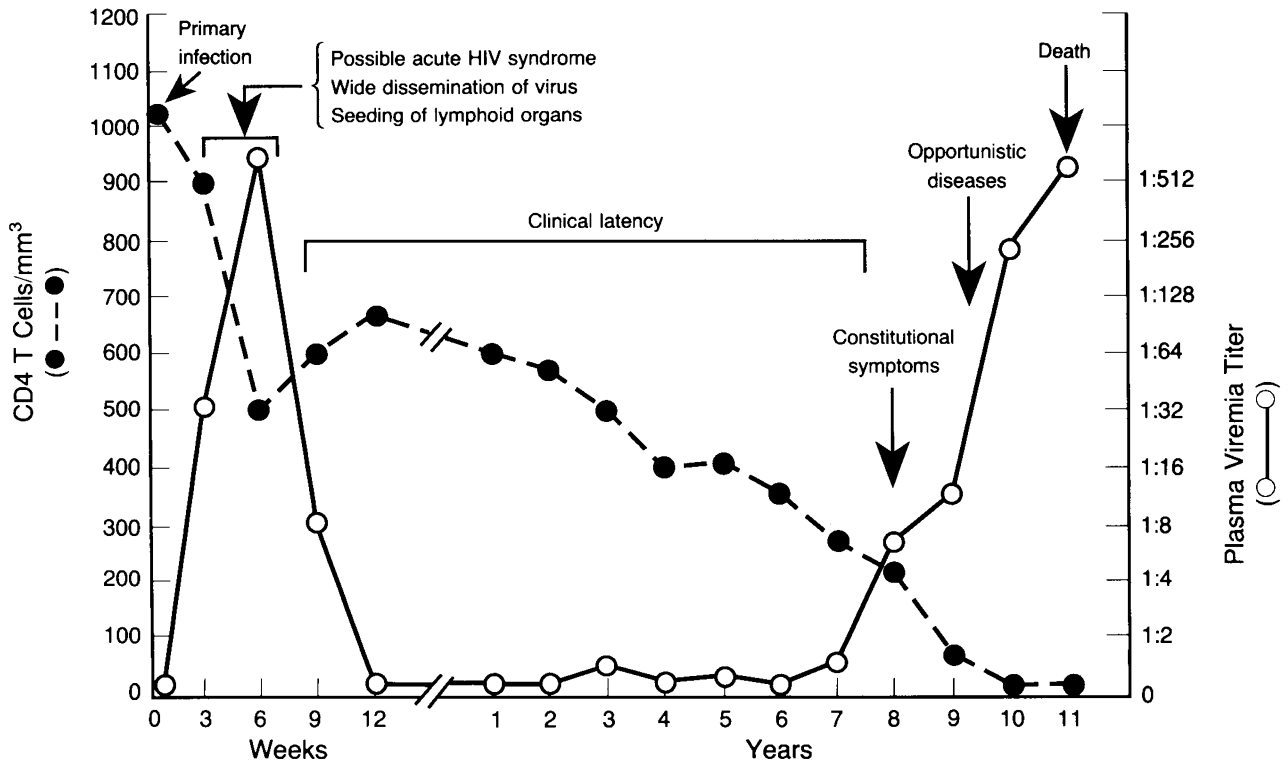


Figure 1. Typical Course of HIV Infection.

During the early period after primary infection there is widespread dissemination of virus and a sharp decrease in the number of CD4 T cells in peripheral blood. An immune response to HIV ensues, with a decrease in detectable viremia followed by a prolonged period of clinical latency. The CD4 T-cell count continues to decrease during the following years, until it reaches a critical level below which there is a substantial risk of opportunistic diseases.

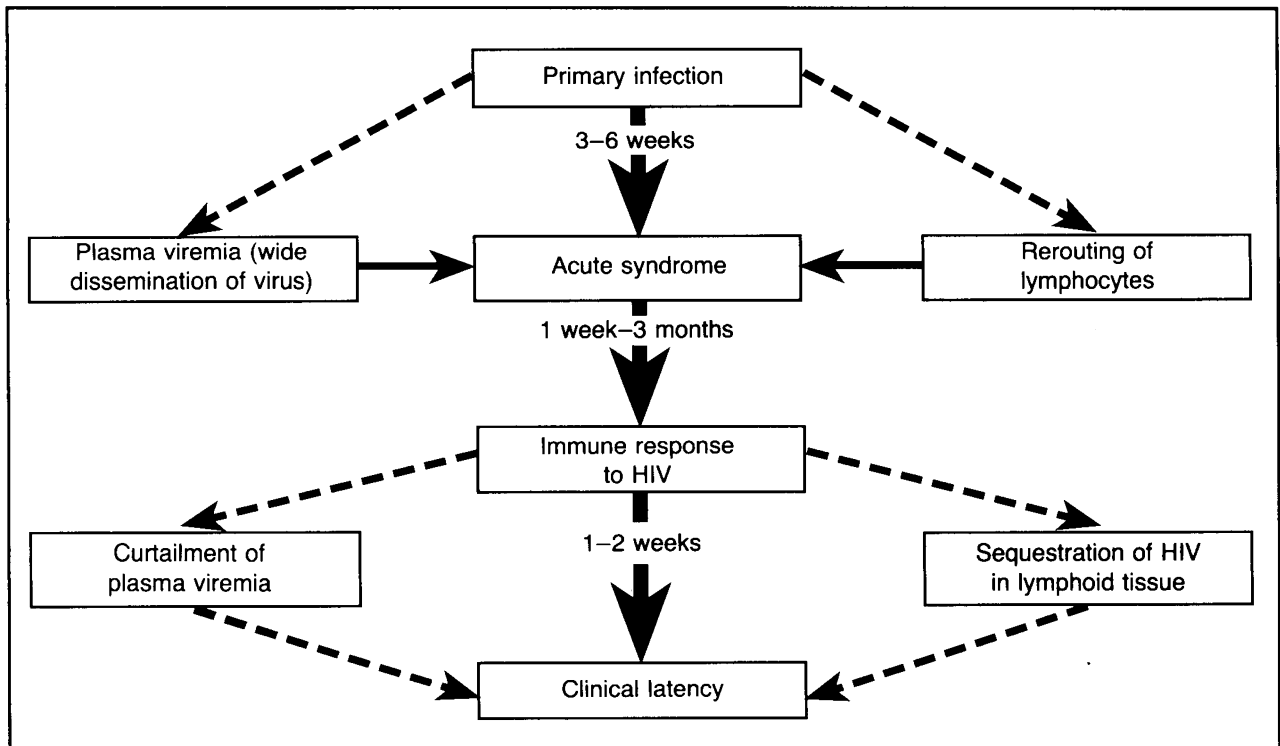


Figure 2. The Progression of HIV Infection from Primary Infection through the Acute HIV Syndrome to the Stage of Clinical Latency.

tients with HIV infection. These antibodies could prevent interaction between CD4 and class II molecules expressed on the antigen-presenting cells, thus impairing the cellular interaction required for efficient antigen presentation and inhibiting antigen-specific functions mediated by helper CD4 T cells.^{34,35}

The hypothesis that gp120 functions as an "alloepitope"^{36,37} is also based on the homology between HLA-DR and HLA-DQ molecules and this HIV-envelope glycoprotein. It has been suggested that gp120 bound to the CD4 molecules of T cells may trigger a long-term allogeneic immune response. Both of these possibilities, however, need to be substantiated with more convincing experimental evidence before their role in the pathogenesis of HIV infection can be determined.

Anergy

Complexes of gp120 antigen and antibody bind to CD4 molecules, and the CD4 cells become refractory to further *in vitro* stimulation through the activation of their CD3 molecules.³⁸ Similarly, *in vitro* peripheral-blood mononuclear cells inoculated with HIV no longer respond to stimulation with anti-CD3 antibodies.³⁹ These findings led to the hypothesis that a negative signal is delivered to CD4 cells after their component CD4 molecules react with gp120 or gp120-anti-gp120 complexes. In this regard, anti-gp120 antibodies have recently been detected on CD4 T lymphocytes in patients with AIDS.⁴⁰

Superantigens

Considerable attention has been given to the possibility that a superantigen, either retrovirally encoded or unrelated to HIV, may play an important part in the immunopathogenesis of HIV infection.⁴¹ Superantigens are microbial or viral antigens that are capable of binding to nearly all T cells that have a specific variable region of the β chain of the T-cell antigen receptor (Fig. 3). Unlike conventional antigenic peptides that bind in the groove of the MHC class II molecules, require interaction with specific variable components (variable α , joining α , variable β , diversi-

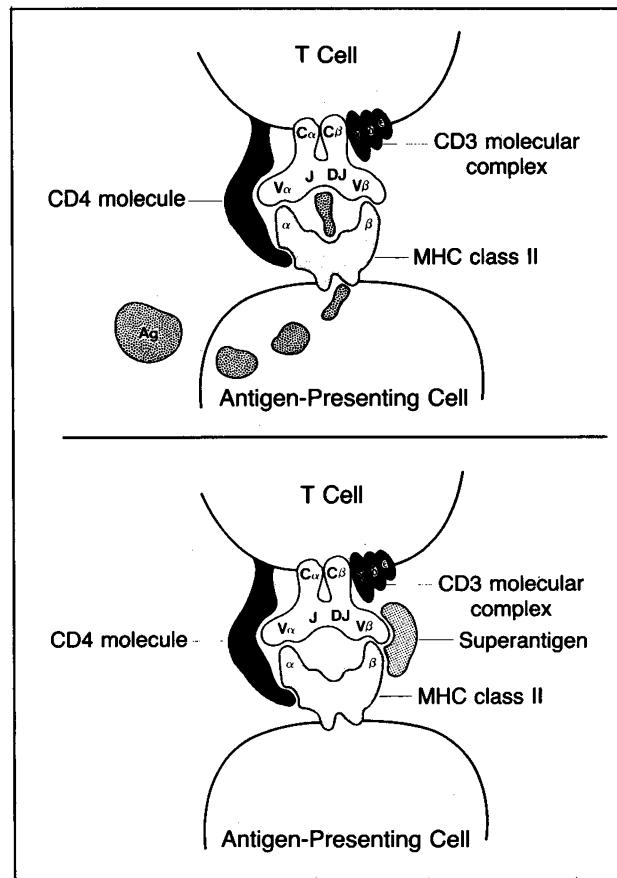


Figure 3. Recognition of Conventional Antigens and Superantigens by CD4 T Cells.

In the upper panel, all the variable elements of the α and β chains of the T-cell antigen receptor are involved in the recognition of conventional antigenic peptides in the groove of a particular MHC class II molecule. In the lower panel, the recognition of superantigens involves predominantly the variable region of the β chain of the T-cell antigen receptor and virtually any MHC class II molecule. V denotes variable, J joining, D diversity, and Ag antigen.

ty β , and joining β) of the α and β chains of the T-cell antigen receptor, and thus result in the stimulation of only a tiny fraction of T cells, superantigens bind only to the variable- β region of the T-cell antigen receptor. These superantigens therefore induce massive stimulation and expansion of T cells bearing the specific variable- β regions, followed by deletion or anergy.⁴² The superantigen hypothesis regarding HIV infection stems from the observations that endogenous or exogenous retroviral-encoded superantigens stimulate murine CD4 T cells *in vivo*, leading to the anergy or deletion of a substantial percentage of CD4 T cells that have the specific variable- β regions.⁴³⁻⁵⁷ In line with this hypothesis, there have been reports that patients with HIV infection have perturbations of T-cell subgroups bearing certain specific variable- β regions.^{58,59} However, rather than cause deletions of specific subgroups of T cells, it is more likely that superantigens, if present in HIV infection, serve as

Table 1. Potential Mechanisms of the Functional and Quantitative Depletion of CD4 T Lymphocytes.

Direct HIV-mediated cytopathic effects (single-cell killing)
HIV-mediated formation of syncytia
Virus-specific immune responses
HIV-specific cytolytic T lymphocytes
Antibody-dependent cellular cytotoxicity
Natural killer cells
Autoimmune mechanisms
Anergy caused by inappropriate cell signaling through gp120-CD4 interaction
Superantigen-mediated perturbation of T-cell subgroups
Programmed cell death (apoptosis)

potent activators of T cells, rendering them more susceptible to infection with the virus.

Apoptosis

Programmed cell death, or apoptosis, is a normal mechanism of cell death that was originally described in the context of the response of immature thymocytes to cellular activation.⁶⁰⁻⁶² It is a mechanism whereby the body eliminates autoreactive clones of T cells.⁶⁰⁻⁶³ It has recently been suggested that both qualitative and quantitative defects in CD4 T cells in patients with HIV infection may be the result of activation-induced cell death or apoptosis.⁶⁴⁻⁶⁷ Since apoptosis can be induced in mature murine CD4 T cells after cross-linking CD4 molecules to one another and triggering the T-cell antigen receptor,⁶⁸ there has been speculation that cross-linking of the CD4 molecule by HIV gp120 or gp120-anti-gp120 immune complexes prepares the cell for the programmed death that occurs when an MHC class II molecule in complex with an antigen binds to the T-cell antigen receptor (Fig. 4).^{66,67} Thus, the mere activation of a prepared cell by a specific antigen or superantigen could lead to the death of the cell, without direct infection by HIV. However, programmed cell death occurs spontaneous-

ly in vitro in the absence of an antigenic stimulus and occurs in CD8 cells.^{69,70} If confirmed, the apoptosis hypothesis, like the superantigen hypothesis, would help explain the depletion of CD4 T cells without requiring that each depleted cell be infected with HIV.

INDUCTION OF HIV EXPRESSION

Although HIV in vitro can infect both resting and activated CD4 T cells equally well,⁷¹ its ability to replicate in T cells is strictly dependent on the state of activation of the cells.⁷¹⁻⁷³ Furthermore, efficient viral replication in monocytes or macrophages depends on both the activation and the differentiation states of these cells.⁵ The role of these cells as reservoirs of HIV and as effectors of tissue damage in organs such as the brain has been reviewed elsewhere.^{2,5,74}

Models of coinfection or simultaneous cotransfection of cells with HIV and other viruses have demonstrated that certain viruses, such as cytomegalovirus, herpes simplex virus, hepatitis B virus, human herpesvirus 6, and human T-cell lymphotropic virus type I can up-regulate the expression of HIV.⁷⁵ For the purpose of this discussion, viral expression refers to the production of viral mRNA or protein and may not reflect complete viral replication. In addition, the

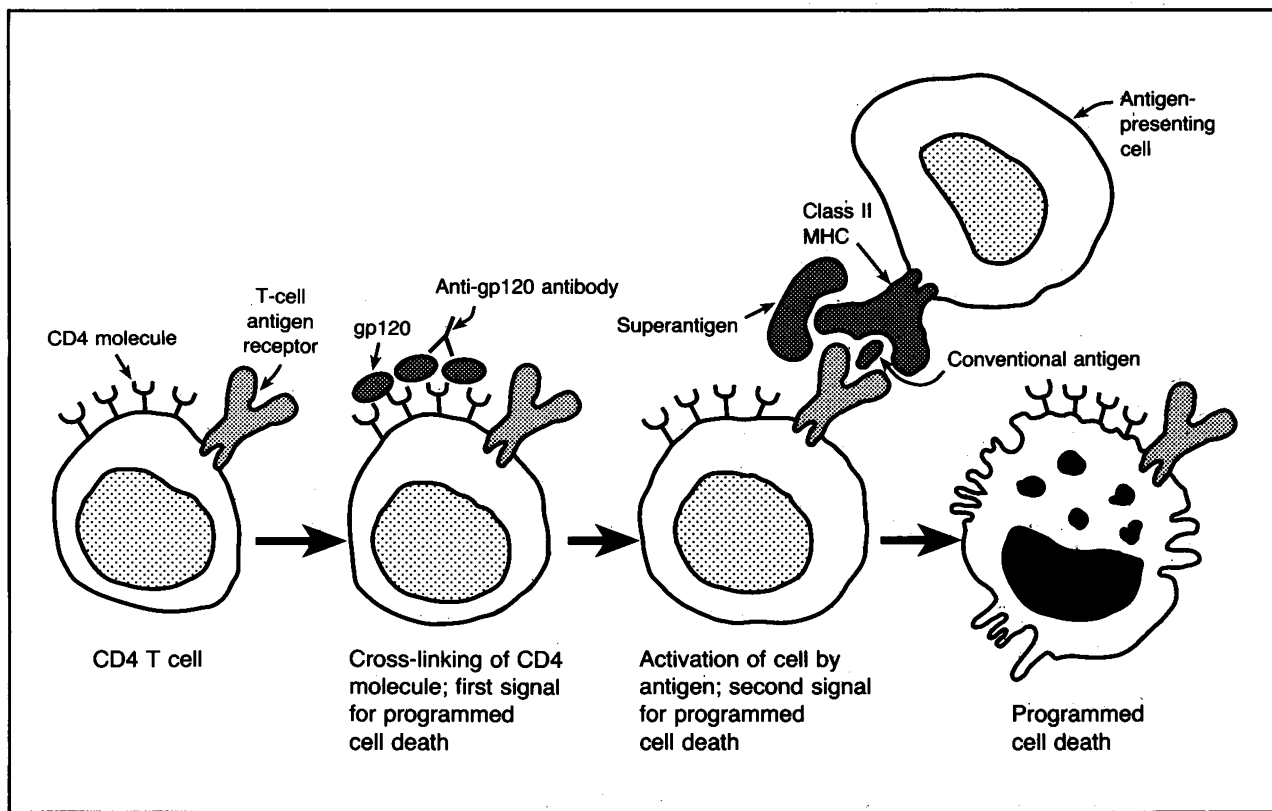


Figure 4. Apoptosis (Programmed Cell Death) in HIV Infection.

In this model, the cross-linking of CD4 molecules to one another by gp120 alone or gp120 in complex with anti-gp120 antibodies provides the first of two signals required for programmed cell death. Activation of the cell through the T-cell antigen receptor by either conventional antigen or superantigen is the second signal.

presence of other microbes, such as mycoplasma, may induce the expression of HIV.⁷⁶ Of particular relevance was the demonstration that a group of cytokines is capable of regulating the induction of HIV expression from the state of latent or chronic infection to active viral expression.⁷⁷ Many of the cytokines involved in the homeostatic regulation of the human immune response, such as interleukin-1, interleukin-3, interleukin-6, tumor necrosis factor (TNF)- α and TNF- β , interferon gamma, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor, stimulate HIV replication in cell lines of monocyte-macrophage lineage with chronic infection and in primary cultures of cells of the same lineage.^{75,77-80} In addition, TNF- α and TNF- β may induce the expression of HIV in T-cell lines with chronic infection.⁷⁵ In contrast, interferon alfa and interferon beta exert a suppressive effect on HIV infection,⁸¹⁻⁸⁵ as may interleukin-4 and transforming growth factor- β .^{75,86-88} Since cytokines may be produced and may act locally in tissues, without entering the circulation, their plasma concentrations need not be elevated for them to have an important role in the modulation of HIV expression at the tissue level. The complex immunoregulatory network of cytokines that maintains immune homeostasis,^{75,77-79} even during states of apparent immunologic quiescence, may serve to sustain a constant level of viral expression, particularly in the lymph nodes (see below), throughout the prolonged course of infection.

ROLE OF THE LYMPHOID ORGANS IN HIV INFECTION

A number of recent studies have focused on the role of the lymphoid organs in the pathogenesis of HIV infection.^{13,89-95} These organs may represent the major anatomical sites for the establishment as well as the short- and long-term propagation of HIV infection.^{13,93} Although most studies necessarily focus on HIV infection of peripheral-blood mononuclear cells, the lymphocytes that are in the peripheral blood at any given time represent only about 2 percent of the total lymphocyte pool, most of which is in the lymphoid organs.⁹⁶ Hence, in certain pathologic processes involving lymphoid cells, the peripheral blood may not accurately reflect the status of disease. Furthermore, specific immune responses are generated predominantly in the lymphoid organs⁹⁷ rather than in the peripheral blood.

The presence of HIV has been demonstrated in lymphoid organs by *in situ* hybridization^{95,98} and the polymerase chain reaction (PCR),^{93,94} but that does not mean that lymphoid organs are the preferential anatomical sites of HIV infection. A study using standard PCR to detect HIV DNA and reverse transcriptase PCR to detect HIV RNA found 5 to 10 times more HIV-infected cells⁹³ and higher concentrations of both regulatory and structural mRNAs¹³ in the lymphoid organs (lymph nodes, adenoids, and tonsils)

of a group of patients than in their peripheral blood. This viral burden in lymphoid organs is greater throughout the period of clinical latency.¹³ In this regard, the assumptions that the body burden of HIV is very low and that HIV is latent during the long period of clinical latency, which are based on studies of peripheral blood, may not be correct.

The role of lymphoid organs as reservoirs of HIV infection has been confirmed by *in situ* hybridization^{95,98} and electron microscopy.^{89,99} In early and intermediate disease, HIV particles in complex with antibodies and complement accumulate in lymph nodes, where they are trapped within the network of follicular dendritic cells in the germinal centers.^{89,95,98-101} Follicular dendritic cells function during the normal immune response to trap antigens in the environment of the germinal center and to allow the presentation of antigen to competent immune cells.^{102,103} This is an efficient natural means of initiating and propagating an appropriate immune response to antigenic challenge, be it microbial or environmental. At the early stage of HIV infection, only a few isolated cells in the lymph nodes have been found to be infected with HIV, predominantly CD4 T lymphocytes and rarely follicular dendritic cells, either in or outside the germinal centers.^{95,98} In the advanced stages of infection, free viral particles are no longer detected in the lymphoid organs; HIV is detectable only in cells⁹⁵ (and Pantaleo G: unpublished data). The progression of disease is temporally associated with the degeneration of the network of follicular dendritic cells and the loss of the ability of lymphoid organs to trap HIV particles, thus contributing to increased viremia (see below).

These observations have allowed the development of a hypothesis describing the role of lymphoid organs in the immunopathogenic mechanisms that propagate HIV infection (Fig. 5). After HIV enters through the circulation or mucosa, it is carried, like other invading microbes, to the regional lymph nodes. Primary infection results in an intense viremia that leads to the seeding of multiple lymph nodes, which causes detectable or subclinical lymphadenopathy,¹⁰⁻¹² and the initiation of an HIV-specific immune response. Associated with this process is the nodal accumulation of CD4 T cells, either by *in situ* proliferation or migration to the lymph nodes. These cells are activated¹⁰⁴ and can provide help for HIV-specific B-cell responses in the germinal centers.¹⁰⁵ This antigen-driven migration and concentration of CD4 T cells in the lymph nodes may contribute to the abrupt decline in the level of circulating CD4 T cells characteristic of the acute HIV syndrome.^{10-12,106} Furthermore, the activated state of these cells facilitates their infection by the virus trapped in the lymph node, as well as the subsequent replication of virus within the cells. In this regard, a substantial proportion of CD4 T cells (25 to 50 percent) are activated in the lymph nodes of patients with HIV infection, as compared with a small percent-

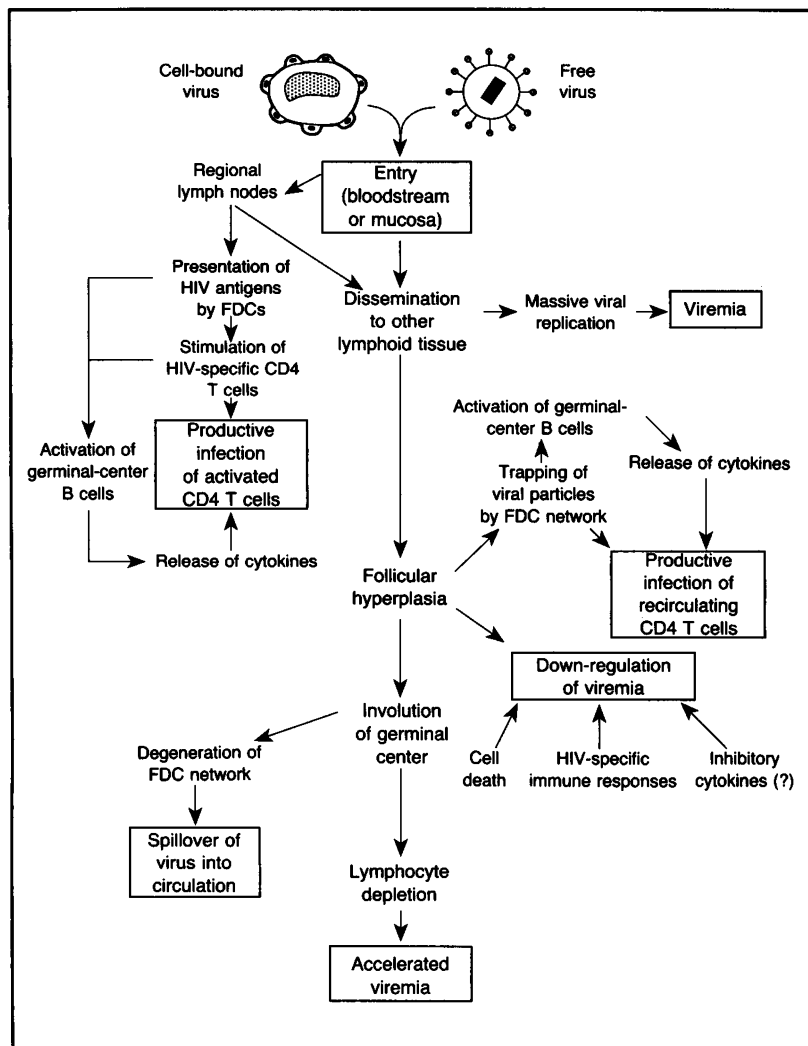


Figure 5. The Complex, Multifaceted Roles of the Lymphoid Organs in the Pathogenesis of HIV Disease.

FDC denotes follicular dendritic cell.

age (5 to 10 percent) in the blood (Pantaleo G: unpublished data). Cytokines such as $\text{TNF-}\alpha$ that are released by activated germinal-center B cells may contribute to the induction of viral replication.¹⁰⁷ Thus, the microenvironment of the lymphoid organs is ideal for the initial establishment and propagation of HIV infection.

Down-regulation of viral replication in peripheral-blood mononuclear cells (Graziosi C: unpublished data) and a decrease in plasma viremia and p24 antigenemia^{11,12} generally signal the transition from the acute to the latent phase of HIV infection. However, HIV is concentrated in lymphoid organs and actively replicates during clinical latency.^{13,93} The dichotomy between the absence of HIV in the peripheral blood and its presence in lymphoid organs is probably related to histopathologic alterations such as follicular hyperplasia and the expansion of the network of fol-

licular dendritic cells,^{91,92,95,98,99,101} which may alter the circulatory kinetics of CD4 T cells, including those infected with HIV. Furthermore, HIV-infected cells may be unable to enter the circulation. The trapping of virus in lymph nodes (whether extracellularly or in T cells that cannot recirculate), the emergence of HIV-specific immunity, and the death of the initial pool of infected cells may explain the clearance of HIV particles and HIV-infected cells in the circulation during the prolonged period of clinical latency.

As the late stages of HIV disease evolve, the architecture of the lymph nodes is disrupted and the network of follicular dendritic cells dissolves, removing the trapping mechanisms for HIV virions, although HIV-infected CD4 T cells can still be identified⁹⁵ (and Pantaleo G: unpublished data). HIV is thus free to recirculate, a finding that has been interpreted as a reflection of a massive increase in the total viral burden in late-stage disease. However, rather than a true increase in viral burden, these high levels of viremia in late-stage disease may reflect at least in part the recirculation of HIV particles removed from the constraints of lymph-node entrapment.

CONCLUSIONS

The immunopathogenic mechanisms of HIV infection are complex and not well understood. Although the clinical course is characterized by a prolonged period of latency after primary infection, HIV replication continues at high levels in the lymphoid organs during this period. Initial seeding of the lymphoid organs probably occurs during the period of viremia soon after primary infection and is often accompanied by an acute HIV syndrome. These early events probably play a critical part in determining the subsequent course of HIV disease. Peripheral-blood measurements do not accurately reflect the total-body burden of HIV infection; the lymphoid organs are the major reservoirs of virus and sites of viral replication. The mechanisms whereby individual CD4 cells are depleted are not entirely clear, and although HIV itself has a direct or indirect role in the cytopathic process, other mechanisms, such as apoptosis, inappropriate cell signaling, immune-mediated mechanisms, and superantigen stimulation, are being ac-

tively studied. Recognition of the critical nature of the events early in the course of infection as well as the role of the lymphoid organs in the evolution of HIV disease has important implications not only for a better understanding of the immunopathogenic mechanisms of HIV infection, but also in the design of therapy.

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