How HIV Causes AIDS from the National Institute of Allergy and Infectious Diseases (NIAID)

An important focus of the National Institute of Allergy and Infectious Diseases (NIAID) is research devoted to the pathogenesis of human immunodeficiency virus (HIV) disease -- the complex mechanisms that result in the destruction of the immune system of an HIV-infected person. A detailed understanding of HIV and how it establishes infection and causes the acquired immunodeficiency syndrome (AIDS) is crucial to identifying and developing effective drugs and vaccines to fight HIV and AIDS. This fact sheet summarizes what scientists are learning about this process and provides a brief glossary of terms.

Overview

HIV disease is characterized by a gradual deterioration of immune function. Most notably, crucial immune cells called CD4+ T cells are disabled and killed during the typical course of infection. These cells, sometimes called "T-helper cells," play a central role in the immune response, signalling other cells in the immune system to perform their special functions. A healthy, uninfected person usually has 800 to 1,200 CD4+ T cells per cubic millimeter (mm^3) of blood. During HIV infection, the number of these cells in a person's blood progressively declines. When a person's CD4+ T cell count falls below $200/mm^3$, he or she becomes particularly vulnerable to the opportunistic infections and cancers that typify AIDS, the end stage of HIV disease. People with AIDS often suffer infections of the intestinal tract, lungs, brain, eyes and other organs, as well as debilitating weight loss, diarrhea, neurologic conditions and cancers such as Kaposi's sarcoma and lymphomas. Most scientists think that HIV causes AIDS by directly killing CD4+ T cells and by triggering other events that weaken a person's immune function. For example, the network of signalling molecules that normally regulates a person's immune response is disrupted during HIV disease, impairing a person's ability to fight other infections. The HIV-mediated destruction of the lymph nodes and related immunologic organs also plays a major role in causing the immunosuppression seen in people with AIDS.

Scope of the HIV Epidemic

Although HIV was first identified in 1983, studies of previously stored blood samples indicate that the virus entered the U.S. population sometime in the late 1970s. In the United States, 513,486 cases of people with AIDS had been reported to the Centers for Disease Control and Prevention (CDC) as of Dec. 31, 1995. Among these individuals, 319,849 had died by the end of 1995. AIDS is now the leading killer of people aged 25 to 44 in this country. Worldwide, an estimated 27.9 million people had become HIV-infected through mid-1996, and 7.7 million had developed AIDS, according to the World Health Organization (WHO). Various projections indicate that, by the year 2000, between 40 and 110 million people worldwide will be HIV-infected.

HIV is a Retrovirus

HIV belongs to a class of viruses called retroviruses, which have genes composed of ribonucleic acid (RNA) molecules. The genes of humans and most other organisms are made of a related molecule, deoxyribonucleic acid (DNA). Like all viruses, HIV can replicate only inside cells, commandeering the cell's machinery to reproduce. However, only HIV and other retroviruses, once inside a cell, use an enzyme called reverse transcriptase to convert their RNA into DNA, which can be incorporated into the host cell's genes.

Slow viruses

HIV belongs to a subgroup of retroviruses known as lentiviruses, or "slow" viruses. The course of infection with these viruses is characterized by a long interval between initial infection and the onset of serious symptoms. Other lentiviruses infect nonhuman species. For example, the feline immunodeficiency virus (FIV) infects cats and the simian immunodeficiency virus (SIV) infects monkeys and other nonhuman primates. Like HIV in humans, these animal viruses primarily infect immune system cells, often causing immunodeficiency and AIDS-like symptoms. Scientists use these and other viruses and their animal hosts as models of HIV disease.

The viral envelope

HIV has a diameter of 1/10,000 of a millimeter and is spherical in shape. The outer coat of the virus, known as the viral envelope, is composed of two layers of fatty molecules called lipids, taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded in the viral envelope are proteins from the host cell, as well as 72 copies (on average) of a complex HIV protein that protrudes from the envelope surface. This protein, known as Env, consists of a cap made of three or four molecules called glycoprotein (gp)120, and a stem consisting of three or four gp41 molecules that anchor the structure in the viral envelope. Much of the research to develop a vaccine against HIV has focused on these envelope proteins.

The viral core

Within the envelope of a mature HIV particle is a bullet-shaped core or capsid, made of 2000 copies of another viral protein, p24. The capsid surrounds two single strands of HIV RNA, each of which has a copy of the virus's nine genes. Three of these, gag, pol and env, contain information needed to make structural proteins for new virus particles. The env gene, for example, codes for a protein called gp160 that is broken down by a viral enzyme to form gp120 and gp41, the components of Env. Three regulatory genes, tat, rev and nef, and three auxiliary genes, vif, vpr and vpu, contain information necessary for the production of proteins that control the ability of HIV to infect a cell, produce new copies of virus or cause disease. The protein encoded by nef, for instance, appears necessary for the virus to replicate efficiently, and the vpu-encoded protein influences the release of new virus particles from infected cells. The ends of each strand of HIV RNA contain an RNA sequence called the long terminal repeat (LTR). Regions in the LTR act as switches to control production of new viruses and can be triggered by proteins from either HIV or the host cell. The core of HIV also includes a protein called p7, the HIV nucleocapsid protein; and three enzymes that carry out later steps in the virus's life cycle: reverse transcriptase, integrase and protease. Another HIV protein called p17, or the HIV matrix protein, lies between the viral core and the viral envelope.

Life Cycle of HIV

Entry of HIV into cells

Infection typically begins when an HIV particle, which contains two copies of the HIV RNA, encounters a cell with a surface molecule called cluster designation 4 (CD4). Cells with this molecule are known as CD4 positive (CD4+) cells. One or more of the virus's gp120 molecules binds tightly to CD4 molecule(s) on the cell's surface. The membranes of the virus and the cell fuse, a process that probably involves both gp41 and a second "fusion cofactor" molecule on the cell surface. Recent research by NIAID intramural and extramural researchers has identified two fusion cofactors for different types of HIV strains. Following fusion, the virus's RNA, proteins and enzymes are released into the cell. Although CD4+ T cells appear to be HIV's main target, other immune system cells with CD4 molecules on their surfaces are infected as well. Among these are long-lived cells called monocytes and macrophages, which apparently can harbor large quantities of the virus without being killed, thus acting as reservoirs of HIV. Scientists suspect that HIV also may infect cells without CD4 on their surfaces, using other docking molecules. For example, cells of the central nervous system may be infected via a receptor known as galactosyl ceramide. The role of HIV fusion cofactors in this process is currently under intense investigation. Cell-to-cell spread of HIV also can occur through the CD4-mediated fusion of an infected cell with an uninfected cell.

Reverse transcription

In the cytoplasm of the cell, HIV reverse transcriptase converts viral RNA into DNA, the nucleic acid form in which the cell carries its genes. Six of the

nine antiviral drugs approved in the United States for the treatment of people with HIV infection -- AZT, ddC, ddI, d4T, 3TC and nevirapine -- work by interfering with this stage of the viral life cycle.

Integration

The newly made HIV DNA moves to the cell's nucleus, where it is spliced into the host's DNA with the help of HIV integrase. Once incorporated into the cell's genes, HIV DNA is called a "provirus." Billions of cells in an HIV-infected person may contain HIV DNA.

Transcription

For a provirus to produce new viruses, RNA copies must be made that can be read by the host cell's protein-making machinery. These copies are called messenger RNA (mRNA), and production of mRNA is called transcription, a process that involves the host cell's own enzymes. Viral genes in concert with the cellular machinery control this process: the tat gene, for example, encodes a protein that accelerates transcription. Cytokines, proteins involved in the normal regulation of the immune response, also may initiate transcription. Molecules such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-6, secreted in elevated levels by the cells of HIV-infected people, may help to activate HIV proviruses. Other infections, by organisms such as Mycobacterium tuberculosis, may also initiate transcription.

Translation

After HIV mRNA is processed in the cell's nucleus, it is transported to the cytoplasm. HIV proteins are critical to this process: for example, a protein encoded by the rev gene allows mRNA encoding HIV structural proteins to be transferred from the nucleus to the cytoplasm. Without the rev protein, structural proteins are not made. In the cytoplasm, the virus co-opts the cell's protein-making machinery -- including structures called ribosomes -- to make long chains of viral proteins and enzymes, using HIV mRNA as a template. This process is called translation.

Assembly and budding

Newly made HIV core proteins, enzymes and RNA gather just inside the cell's membrane, while the viral envelope proteins aggregate within the membrane. An immature viral particle forms and pinches off from the cell, acquiring an envelope that includes both cellular and HIV proteins from the cell membrane. During this part of the viral life cycle, the core of the virus is immature and the virus is not yet infectious. The long chains of proteins and enzymes that make up the immature viral core are now cleaved into smaller pieces by a viral enzyme called protease. This step results in infectious viral particles. Drugs called protease inhibitors interfere with this step of the viral life cycle. Three such drugs -- saquinavir, ritonavir and indinavir -- have been approved for marketing in the United States.

Course of HIV Infection

Among patients enrolled in large epidemiologic studies in western countries, the median time from infection with HIV to the development of AIDS-related symptoms has been approximately 10 years. However, researchers have observed a wide variation in disease progression. Approximately 10 percent of HIV-infected people in these studies have progressed to AIDS within the first two to three years following infection, while 5 to 10 percent of individuals in the studies have stable CD4+ T cell counts and no symptoms even after 12 or more years. Factors such as age or genetic differences among individuals, the level of virulence of an individual strain of virus, and co-infection with other microbes may influence the rate and severity of disease progression.

Viral burden predicts disease progression

Recent studies show that people with high levels of HIV in their bloodstream are more likely to develop new AIDS-related symptoms or to die than individuals with lower levels of virus. New anti-HIV drug combinations that reduce a person's "viral burden" to very low levels may delay the progression of HIV disease, but it remains to be seen if these drugs will have a prolonged benefit. Other drugs that fight the infections associated with AIDS have improved and prolonged the lives of HIV-infected people by preventing or treating conditions such as Pneumocystis carinii pneumonia.

Transmission of HIV

Among adults, HIV is spread most commonly during sexual intercourse with an infected partner. During sex, the virus can enter the body through the mucosal linings of the vagina, vulva, penis, rectum or, very rarely, via the mouth. The likelihood of transmission is increased by factors that may damage these linings, especially other sexually transmitted diseases that cause ulcers or inflammation. Research suggests that immune system cells called dendritic cells, which reside in the mucosa, may begin the infection process after sexual exposure by binding to and carrying the virus from the site of infection to the lymph nodes where other immune system cells become infected. HIV also can be transmitted by contact with infected blood, most often by the sharing of drug needles or syringes contaminated with minute quantities of blood containing the virus. The risk of acquiring HIV from blood transfusions is now extremely small in the United States, as all blood products in this country are screened routinely for evidence of the virus. Almost all HIV-infected children acquire the virus from their mothers before or during birth. In the United States, approximately 25 percent of pregnant HIV-infected women not receiving antiretroviral therapy have passed on the virus to their babies. NIAID-sponsored researchers have shown that a specific regimen of the drug zidovudine (AZT) can reduce the risk of transmission of HIV from mother to baby by two-thirds. The virus also may be transmitted from a nursing HIV-infected mother to her infant.

Early Events in HIV Infection

Once it enters the body, HIV infects a large number of CD4+ cells and replicates rapidly. During this acute or primary phase of infection, the blood contains many viral particles that spread throughout the body, seeding various organs, particularly the lymphoid organs. Lymphoid organs include the lymph nodes, spleen, tonsils and adenoids. During the acute phase of infection, the number of CD4+ T cells in the bloodstream decreases by 20 to 40 percent. Scientists do not yet know whether these cells are killed by HIV or if they leave the blood and go to the lymphoid organs in preparation to mount an immune response. Two to four weeks after exposure to the virus, up to 70 percent of HIV-infected persons suffer flu-like symptoms related to the acute infection. The patient's immune system fights back with killer T cells (CD8+ T cells) and B-cell-produced antibodies, which dramatically reduce HIV levels. A patient's CD4+ T cell count may rebound to 80 to 90 percent of its original level. A person then may remain free of HIV-related symptoms for years despite continuous replication of HIV in the lymphoid organs seeded during the acute phase of infection. One reason HIV is unique is that despite the body's aggressive immune responses, which are sufficient to clear most viral infections, some HIV invariably escapes. One explanation is that the immune system's best soldiers in the fight against HIV -- certain subsets of killer T cells -- multiply rapidly following initial HIV infection and kill many HIV-infected cells, but then appear to exhaust themselves and disappear, allowing HIV to escape and continue replication. Additionally, in the few weeks that they are detectable, these specific cells appear to accumulate in the bloodstream rather than in the lymph nodes, where most HIV is sequestered.

HIV is Active in the Lymph Nodes

Although HIV-infected individuals often exhibit an extended period of clinical latency with little evidence of disease, the virus is never truly latent. NIAID researchers have shown that even early in disease, HIV actively replicates within the lymph nodes and related organs, where large amounts of virus become trapped in networks of specialized cells with long, tentacle-like extensions. These cells are called follicular dendritic cells (FDCs). FDCs are located in hot spots of immune activity called germinal centers. They act like flypaper, trapping invading pathogens (including HIV) and holding them until B cells come along to initiate an immune response. Close on the heels of B cells are CD4+ T cells, which rush into the germinal centers to help B cells fight the invaders. CD4+ T cells, the primary targets of HIV, probably become infected in large numbers as they encounter HIV trapped on FDCs. Research suggests that HIV trapped on FDCs remains infectious, even when coated with antibodies. Once infected, CD4+ T cells may leave the germinal center and infect other CD4+ cells that congregate in the region of the lymph node surrounding the germinal center. Over a period of years, even when little virus is readily detectable in the blood, significant amounts of virus accumulate in the germinal centers, both within infected cells and bound to FDCs. In and around the germinal centers, numerous CD4+ T cells are probably activated by the increased production of cytokines such as TNF-alpha and IL-6, possibly secreted by B cells.

Activation allows uninfected cells to be more easily infected and increases replication of HIV in already infected cells.
While greater quantities of certain cytokines such as TNF-alpha and IL-6 are secreted during HIV infection, others with key roles in the regulation of normal immune function may be secreted in decreased amounts. For example, CD4+ T cells may lose their capacity to produce interleukin 2 (IL-2), a cytokine that enhances the growth of other T cells and helps to stimulate other cells' response to invaders. Infected cells also have low levels of receptors for IL-2, which may reduce their ability to respond to signals from other cells.

Breakdown of FDC networks

Ultimately, accumulated HIV overwhelms the FDC networks. As these networks break down, their trapping capacity is impaired, and large quantities of virus enter the bloodstream. Although it remains unclear why FDCs die and the FDC networks dissolve, some scientists think that this process may be as important in HIV pathogenesis as the loss of CD4+ T cells. The destruction of the lymph node structure seen late in HIV disease may preclude a successful immune response against not only HIV but other pathogens as well. This devastation heralds the onset of the opportunistic infections and cancers that characterize AIDS.

Role of CD8+ T Cells

CD8+ T cells are important in the immune response to HIV during the acute infection and the clinically latent stage of disease. These cells attack and kill infected cells that are producing virus. CD8+ T cells also appear to secrete soluble factors that suppress HIV replication. Three of these molecules -- RANTES, MIP-1alpha and MIP-1beta -- apparently block HIV replication by occupying receptors necessary for the entry of certain strains of HIV into their target cells. Researchers have hypothesized that an abundance of RANTES, MIP-1alpha or MIP-1beta, or a relative lack of receptors for these molecules, may help explain why some individuals have not become infected with HIV, despite repeated exposure to the virus. CD8+ T cells probably also secrete other soluble factors -- as yet unidentified -- that suppress HIV replication.

Rapid Replication and Mutation of HIV

HIV replicates rapidly; several billion new virus particles may be produced every day. In addition, the HIV reverse transcriptase enzyme makes many mistakes while making DNA copies from HIV RNA. As a consequence, many variants of HIV develop in an individual, some of which may escape destruction by antibodies or killer T cells. Additionally, HIV can recombine with itself to produce a wide range of variants or strains. During the course of HIV disease, viral strains emerge in an infected individual that differ widely in their ability to infect and kill different cell types, as well as in their rate of replication. Scientists are investigating why strains of HIV from patients with advanced disease appear to be more virulent and infect more cell types than strains obtained earlier from the same individual.

Theories of Immune System Cell Loss in HIV Infection

Researchers around the world are studying how HIV destroys or disables CD4+ T cells, and many think that a number of mechanisms may occur simultaneously in an HIV-infected individual. Recent data suggest that billions of CD4+ T cells may be destroyed every day, eventually overwhelming the immune system's regenerative capacity.

Direct cell killing

Infected CD4+ T cells may be killed directly when large amounts of virus are produced and bud off from the cell surface, disrupting the cell membrane, or when viral proteins and nucleic acids collect inside the cell, interfering with cellular machinery.

Syncytia formation

Infected cells also may fuse with nearby uninfected cells, forming balloon-like giant cells called syncytia. In test-tube experiments at NIAID and elsewhere, these giant cells have been associated with the death of uninfected cells. The presence of so-called syncytia-inducing variants of HIV has been correlated with rapid disease progression in HIV-infected individuals.

Apoptosis

Infected CD4+ T cells may be killed when cellular regulation is distorted by HIV proteins, probably leading to their suicide by a process known as programmed cell death or apoptosis. Recent reports indicate that apoptosis occurs to a greater extent in HIV-infected individuals, both in the bloodstream and lymph nodes. Uninfected cells also may undergo apoptosis. Normally, when CD4+ T cells mature in the thymus gland, a small proportion of these cells are unable to distinguish self from non-self. Because these cells would otherwise attack the body's own tissues, they receive a biochemical signal from other cells that results in apoptosis. Investigators have shown in cell cultures that gp120 alone or bound to gp120 antibodies sends a similar but inappropriate signal to CD4+ T cells causing them to die even if not infected by HIV.

Innocent bystanders

Uninfected cells may die in an innocent bystander scenario: HIV particles may bind to the cell surface, giving them the appearance of an infected cell and marking them for destruction by killer T cells. Killer T cells also may mistakenly destroy uninfected CD4+ T cells that have consumed HIV particles and that display HIV fragments on their surfaces. Alternatively, because HIV envelope proteins bear some resemblance to certain molecules that may appear on CD4+ T cells, the body's immune responses may mistakenly damage such cells as well.

Anergy

Researchers have shown in cell cultures that CD4+ T cells can be turned off by a signal from HIV that leaves them unable to respond to further immune stimulation. This inactivated state is known as anergy.

Superantigens

Other investigators have proposed that a molecule known as a superantigen, either made by HIV or an unrelated agent, may stimulate massive quantities of CD4+ T cells at once, rendering them highly susceptible to HIV infection and subsequent cell death.

Damage to Precursor Cells

Studies suggest that HIV also destroys precursor cells that mature to have special immune functions, as well as the parts of the bone marrow and the thymus needed for the development of such cells. These organs probably lose the ability to regenerate, further compounding the suppression of the immune system.

Central Nervous System Damage

Although monocytes and macrophages can be infected by HIV, they appear to be relatively resistant to killing. However, these cells travel throughout the body and carry HIV to various organs, especially the lungs and brain. People infected with HIV often experience abnormalities in the central nervous system. Neurologic manifestations of HIV disease, seen in 40 to 50 percent of HIV-infected people, are the subject of many research projects. Investigators have hypothesized that an accumulation of HIV in brain and nerve cells, or the inappropriate release of cytokines or toxic byproducts by these cells, may be to blame.

Role of Immune Activation in HIV Disease

During a normal immune response, many components of the immune system are mobilized to fight an invader. CD4+ T cells, for instance, may quickly proliferate and increase their cytokine secretion, thereby signalling other cells to perform their special functions. Scavenger cells called macrophages may double in size and develop numerous organelles, including lysosomes that contain digestive enzymes used to process ingested pathogens. Once the immune system clears the foreign antigen, it returns to a relative state of quiescence. During HIV infection, however, the immune system may be chronically activated, with negative consequences. As noted above, HIV replication and spread are much more efficient in activated CD4+ cells. Chronic immune system activation during HIV disease may also result in a massive stimulation of a person's B cells, impairing the ability of these cells to make antibodies against other pathogens. Chronic immune activation also can result in apoptosis, and an increased production

of cytokines that may not only increase HIV replication but also have other deleterious effects. Increased levels of TNF-alpha, for example, may be at least partly responsible for the severe weight loss or wasting syndrome seen in many HIV-infected individuals. The persistence of HIV and HIV replication probably plays an important role in the chronic state of immune activation seen in HIV-infected people. In addition, researchers have shown that infections with other organisms activate immune system cells and increase production of the virus in HIV-infected people. Chronic immune activation due to persistent infections, or the cumulative effects of multiple episodes of immune activation and bursts of virus production, likely contribute to the progression of HIV disease.

NIAID Research on the Pathogenesis of AIDS

NIAID-supported scientists conduct HIV pathogenesis research in laboratories on the campus of the National Institutes of Health (NIH) in Bethesda, Md., at the Institute's Rocky Mountain Laboratories in Hamilton, Mont., and at universities and medical centers in the United States and abroad. An NIAID-supported collaborative center of the World Health Organization, known as the NIH AIDS Research and Reference Reagent Program, provides AIDS-related research materials free to qualified researchers around the world. In addition, the Institute convenes groups of investigators and advisory committees to exchange scientific information, clarify research priorities and bring research needs and opportunities to the attention of the scientific community. The NIAID HIV/AIDS Research Agenda and fact sheets on NIAID HIV/AIDS vaccine research, clinical trials for AIDS therapies and vaccines, and AIDS-related opportunistic infections are available from the NIAID Office of Communications. To receive free copies, call (301) 496-5717, Monday through Friday, 8:30 a.m. to 5:00 p.m. Eastern Time. These materials also are available via the NIAID home page on the Internet at http://www.niaid.nih.gov/
NIAID, a component of the National Institutes of Health, supports research on AIDS, tuberculosis and other infectious diseases, as well as allergies and immunology. NIH is an agency of the U.S. Public Health Service, U.S. Department of Health and Human Services.

This information is designed to support, not replace, the relationship that exists between you and your doctor.

HOME