HIV infects memory and activated T cells but is inefficient at productively infecting naive (unactivated) T cells. Naive T cells contain an active form of an enzyme that introduces mutations in the HIV genome. This enzyme has been given the rather cumbersome name APOBEC3G (for apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G). It is a cytidine deaminase that introduces cytosine-to-uracil mutations in the viral DNA that is produced by reverse transcription. These mutations inhibit further DNA replication by mechanisms that are not fully defined. Activation of T cells converts cellular APOBEC3G into an inactive, high-molecular-mass complex, which explains why the virus can replicate in previously activated (e.g., memory) T cells and T-cell lines. HIV has also evolved to counteract this cellular defense mechanism; the viral protein Vif binds to APOBEC3G and promotes its degradation by cellular proteases.

Completion of the viral life cycle in latently infected cells occurs only after cell activation, and in the case of most CD4+ T cells virus activation results in cell lysis. Activation of T cells by antigens or cytokines upregulates several transcription factors, including NF-κB, which stimulate transcription of genes encoding cytokines such as IL-2 and its receptor. In resting T cells, NF-κB is held inactive in the cytoplasm in a complex with the IκB (inhibitor of κB) protein. Stimulation of cells by antigen or cytokines activates cytoplasmic kinases that phosphorylate IκB and target it for enzymatic degradation, thus releasing NF-κB and allowing it to translocate to the nucleus. In the nucleus, NF-κB binds to sequences within the promoter regions of several genes, including those of cytokines that are expressed in activated T cells. The long-terminal-repeat sequences that flank the HIV genome also contain NF-κB–binding sites that can be triggered by the same transcription factors. Imagine now a latently infected CD4+ cell that encounters an environmental antigen. Induction of NF-κB in such a cell (a physiologic response) activates the transcription of HIV proviral DNA (a pathologic outcome) and leads ultimately to the production of virions and to cell lysis. Furthermore, TNF and other cytokines produced by activated macrophages also stimulate NF-κB activity and thus lead to production of HIV RNA. Thus, it seems that HIV thrives when the host T cells and macrophages are physiologically activated, an act that can be best described as "subversion from within." Such activation in vivo may result from antigenic stimulation by HIV itself or by other infecting microorganisms. HIV-infected people are at increased risk for recurrent exposure to other infections, which lead to increased lymphocyte activation and production of proinflammatory cytokines. These, in turn, stimulate more HIV production, loss of additional CD4+ T cells, and more infection. Thus, it is easy to visualize how in individuals with AIDS a vicious cycle may be set up that culminates in inexorable destruction of the immune system.

Mechanism of T-Cell Depletion in HIV Infection

Loss of CD4+ T cells is mainly because of infection of the cells and the direct cytopathic effects of the replicating virus. In infected individuals, approximately 100 billion new viral particles are produced every day, and 1 to 2 billion CD4+ T cells die each day. Because the frequency of infected cells in the circulation is very low, for many years it was suspected that the immunodeficiency is out of proportion to the level of infection and cannot be attributed to death of infected cells. In fact, many infected cells may be in mucosal and other peripheral lymphoid organs, and death of these cells is a major cause of the relentless, and eventually profound, cell loss. Also, up to a point the immune system can replace the dying T cells, and hence the rate of T cell loss may appear deceptively low, but as the disease progresses, renewal of CD4+ T cells cannot keep up with their loss. Possible mechanisms by which the virus directly kills infected cells include increased plasma membrane permeability associated with budding of virus particles from the infected cells, and virus replication interfering with protein synthesis.

In addition to direct killing of cells by the virus, other mechanisms may contribute to the loss of T cells. These include:

- Chronic activation of uninfected cells, responding to HIV itself or to infections that are common in individuals with AIDS, leads to apoptosis of these cells by the process of *activation-induced cell death*. Thus, the numbers of CD4+ T cells that die may be considerably more than the numbers of infected cells. The molecular mechanism of this type of cell death is not known.
- Non-cytopathic (abortive) HIV infection activates the inflammasome pathway and leads to a form of cell death that has been called *pyroptosis* (Chapter 2). During this process, inflammatory cytokines and cellular contents are released, thus potentiating recruitment of new cells and increasing the numbers of cells that can be infected. This form of cell death may play an important role in spread of the infection.
- HIV infects cells in lymphoid organs (spleen, lymph nodes, tonsils) and may cause progressive destruction of the architecture and cellular composition of lymphoid tissues.
- Loss of immature precursors of CD4+ T cells can also occur, either by direct infection of thymic progenitor cells or by infection of accessory cells that secrete cytokines essential for CD4+ T-cell maturation.
- Fusion of infected and uninfected cells with formation of syncytia (giant cells) can occur. In tissue culture the gp120 expressed on productively infected cells binds to CD4 molecules on uninfected T cells, followed by cell fusion. Fused cells usually die within a few hours. This property of syncytia formation is generally confined to the T-tropic X4 type of HIV-1. For this reason, this type is often referred to as syncytia-inducing (SI) virus, in contrast to the R5 virus.
- Although marked reduction in CD4+ T cells, a hallmark of AIDS, can account for most of the immunodeficiency late in the course of HIV infection, there is evidence of qualitative defects in T cells even in asymptomatic HIV-infected persons. Reported defects include a reduction in antigen-induced T-cell proliferation, a decrease in T_H1-type responses relative to the T_H2 type, defects in intracellular signaling, and many more. The loss of T_H1 responses results in profound deficiency in cell-mediated immunity, leading to increased susceptibility to infections by viruses and other intracellular microbes. There is also a selective loss of the memory subset of CD4+ helper T cells early in the course of disease, which explains poor recall responses to previously encountered antigens.