Abstract

AIDS, caused by the retroviruses human immunodeficiency virus type 1 and type 2 (HIV-1 and HIV-2), has reached pandemic proportions. Therefore, it is critical to understand how HIV causes AIDS so that appropriate therapies can be formulated. Primarily, HIV infects and kills CD4(+) T lymphocytes, which function as regulators and amplifiers of the immune response. In the absence of effective anti-retroviral therapy, the hallmark decrease in CD4(+) T lymphocytes during AIDS results in a weakened immune system, impairing the body's ability to fight infections or certain cancers such that death eventually ensues. The major mechanism for CD4(+) T cell depletion is programmed cell death (apoptosis), which can be induced by HIV through multiple pathways. Death of HIV-infected cells can result from the propensity of infected lymphocytes to form short-lived syncytia or from an increased susceptibility of the cells to death. However, the apoptotic cells appear to be primarily uninfected bystander cells and are eradicated by two different mechanisms: either a Fas-mediated mechanism during activation-induced cell death (AICD), or as a result of HIV proteins (Tat, gp120, Nef, Vpu) released from infected cells stimulating apoptosis in uninfected bystander cells. There is also evidence that as AIDS progresses cytokine dysregulation occurs, and the overproduction of type-2 cytokines (IL-4, IL-10) increases susceptibility to AICD whereas type-1 cytokines (IL-12, IFN-gamma) may be protective. Clearly there are multiple causes of CD4(+) T lymphocyte apoptosis in AIDS and therapies that block or decrease that death could have significant clinical benefit.