HIV-induced Cell Death : a Viral Strategy of Immune Evasion

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Viruses have evolved numerous mechanisms to evade the host immune system, and one of the strategies developed by HIV is to activate apoptotic programs in order to destroy immune effectors. Not only does the HIV genome encode for proapoptotic proteins, which kill both infected and uninfected lymphocytes, but it also creates a state of chronic immune activation responsible for the exacerbation of physiological mechanisms of clonal deletion.

HIV infects cells of the immune system and HIV-infection is characterized by the gradual loss of $CD4^+$ T cells and a progressive immune deficiency that leads to opportunistic infections, and ultimately death. Although our understanding of CD4 T cell homeostasis is still incomplete and controversial, a growing body of evidence points to HIV-driven lymphocyte apoptosis as an important contributor to the destruction of the immune system Because of persistent expression of viral particles, this infection results in high turnover rates of T cells, leading to increased T cell proliferation that is physiologically controlled by increased apoptosis. In addition, HIV has developed strategies to trigger the apoptotic machinery in both infected and non-infected cells, inducing the destruction of the effectors of the immune system. Death receptors, such as CD95, TNF-RI and –II or the TRAIL system, are activated in patients' T cells and are contributing to the destruction of HIV-specific CD4 T helper cells and cytotoxic T cells (CTL), required for the immune defense against HIV-infection. Syncytia arising from the fusion of cells expressing the HIV envelope protein with cells expressing the receptors CD4/CXCR4 undergo apoptosis through a mitochondrion-dependent pathway, contributing to the destruction of CD4 T cells. HIV-encoded proteins, such as gp120, Tat, Nef, Vpr, trigger apoptosis in both infected and bystander cells through several mechanisms, including the down-regulation of Bcl-2, the release of cytochrome-c, caspase activation, the up-regulation of death receptors and their ligands (CD95/CD95L, TNF-R/TNF) etc…

Exacerbated T cell apoptosis contributes to HIV disease evolution, and a positive correlation is found between the rate of apoptosis in CD4 T cells and their susceptibility to CD95-induced apoptosis. In addition, premature T cell apoptosis is not detected in non-pathogenic models of simian infections (SIV in African green monkeys, or HIV in chimpanzees) while it strongly occurs in the pathogenic models (SIV in macaques). New potent antiviral therapies (HAART) to HIV^+ persons leads rapidly to the suppression of HIV viral load in the blood and lymphoid organs and to a concomitant rise in the number of CD4 T cells. This restoration is attributable to decreased apoptosis due to the down-regulation of proapoptotic HIV proteins, the reduction of virus-driven immune activation, and probably the anti-apoptotic properties of some HIV drugs. Understanding the viral strategies involved in the destruction of HIV-specific effectors is particularly important since no currently available therapies can efficiently restore virus-specific immunity.

References:

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