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Murder on the HIV Express



DESPITE MORE THAN 20 YEARS of study, the mechanism by which HIV so effectively depletes CD4 T cells in untreated, infected subjects remains a mystery. It is precisely this progressive elimination of CD4 T cells that leads to AIDS. Understanding the underlying killing pathway might provide new approaches for preserving CD4 T cells in HIV-infected individuals.

Dr. Gilad Doitsh in my laboratory launched an exciting series of studies designed to explore how HIV depletes CD4 T cells in a biologically relevant tissue, human tonsil. These studies revealed that tonsil CD4 T cells are readily killed in the presence of HIV, but the dying cells are not productively infected with HIV. Rather, the dying CD4 T cells are abortively infected with the virus, reflecting arrest of the viral life cycle during the reverse transcription step. The accumulation of incomplete reverse transcripts is “sensed” within the cell, triggering caspase-3 activation and apoptosis. This killing requires the budding of HIV virions from the productively infected cell plus close cell-cell contact, implying that a host factor on the surface of cells may be required as well. Thus, a few productively infected cells in lymphoid tissue appear to be capable of mounting a murderous form of abortive viral infection involving many surrounding CD4 T cells that leads to their demise and the progressive loss of CD4 T cells.

Key future directions are to define the nature of the cellular sensor that trig-

gers apoptosis and the host cell factor that appears to be uniquely produced in lymphoid tissue.

RECENT PUBLICATIONS

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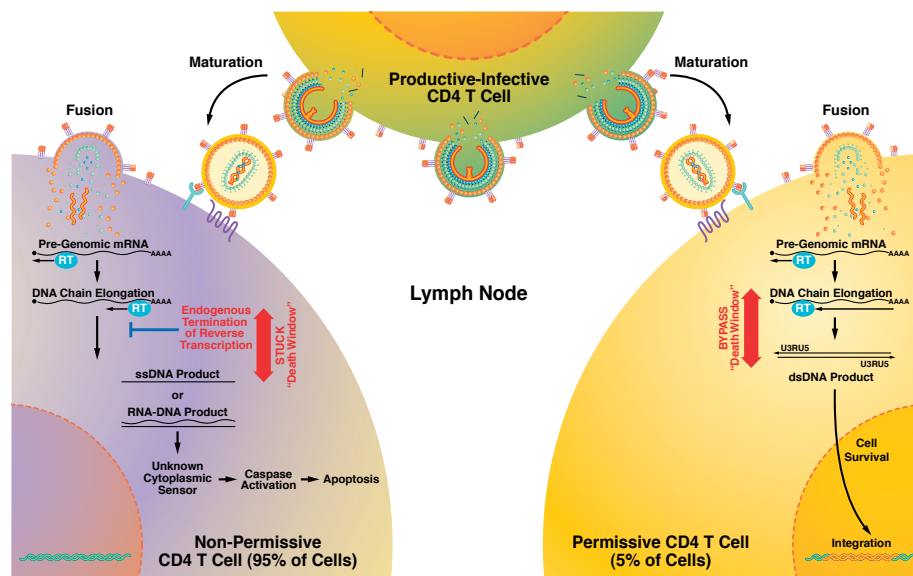
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Overview of HIV-induced CD4 T-cell killing showing how the fusion and entry of virions to quiescent nonpermissive CD4 T cells results in an arrest of reverse transcription, sensing of these cytoplasmic nucleic acids, and triggering of caspase-3-dependent apoptosis. These cytopathic events occurring as a result of abortive HIV infection appear to play an important role in CD4 T-cell depletion.