Analysis of human immunodeficiency virus cytopathicity by using a new method for quantitating viral dynamics in cell culture

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Human immunodeficiency virus (HIV) causes complex metabolic changes in infected CD4(+) T cells that lead to cell cycle arrest and cell death by necrosis. To study the viral functions responsible for deleterious effects on the host cell, we quantitated the course of HIV type 1 infection in tissue cultures by using flow cytometry for a virally encoded marker protein, heat-stable antigen (HSA). We found that HSA appeared on the surface of the target cells in two phases: passive acquisition due to association and fusion of virions with target cells, followed by active protein expression from transcription of the integrated provirus. The latter event was necessary for decreased target cell viability. We developed a general mathematical model of viral dynamics in vitro in terms of three effective time-dependent rates: those of cell proliferation, infection, and death. Using this model we show that the predominant contribution to the depletion of viable target cells results from direct cell death rather than cell cycle blockade. This allows us to derive accurate bounds on the time-dependent death rates of infected cells. We infer that the death rate of HIV-infected cells is 80 times greater than that of uninfected cells and that the elimination of the vpr protein reduces the death rate by half. Our approach provides a general method for estimating time-dependent death rates that can be applied to study the dynamics of other viruses.
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