Retrovirology

Oral presentation

Kinetic Factors Control Efficiencies of Cell Entry by HIV-1

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In order to understand HIV-1 inactivation by entry inhibitors and neutralizing antibodies, we quantitatively examined the factors that limit viral entry into cultured cells. Previous results suggested that only a minute proportion of HIV-1 virions (c.a., 10^{-3}–10^{-4}) are infectious and that the remainder are defective. Experiments will be described showing that this is incorrect and that newly made HIV-1 virions are almost completely infectious. Following their attachment onto cells that contain CD4 and appropriate coreceptors, a race ensues between successful viral entry by membrane fusion and a competing process(es) of viral inactivation. Many entry inhibitors reduce virus titers kinetically, simply by slowing the pathway for membrane fusion and thereby enhancing the efficiency of spontaneous inactivation. In contrast, neutralizing monoclonal antibodies appear to cause a true viral inactivation by a non-kinetic mechanism. The membrane fusion pathway requires assembly of a reversible complex containing multiple coreceptors, which lowers the activation energy barrier for a slow rate-limiting conformational change in the gp41 envelope subunits. Evidence will be described showing how this slow entry step is affected by mutations in coreceptors and by compensating adaptive mutations in HIV-1 envelope glycoproteins. This kinetically determining step of entry is critically influenced by the gp120 V3 loop and and by a gp120 N-linked oligosaccharide. In addition to its proposed role in association with coreceptors, our results suggest that the gp120 V3 loop has a major kinetic influence on the slow step in entry. We propose that this may explain why viral adaptations in cell cultures including resistances to entry inhibitors frequently involve changes in the V3 loop.