

HIV-1 RESTRICTION BY A CYCLOPHILIN-RELATED FACTOR IN HUMAN CELLS

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We have isolated HeLa cell subclones that have increased resistance to HIV-1 and designated them HeLa.HR cells. These cells resisted infection by various HIV-1, but not Mo-MLV or SIV, vectors pseudotyped with VSV-G. Real-time PCR analysis revealed that the block in HeLa.HR cells occurs prior to or during the initiation of HIV-1 reverse transcription. The presence of an early block and difference between HIV-1 and SIV susceptibility prompted us to examine whether HIV-1 with CA substitutions could evade the restriction. Notably, HIV-1 isolates with CA substitutions that preclude the interaction of host cell cyclophilin A (CypA) were not impaired in their ability to infect HeLa.HR cells. Consistent with this observation, treatment of cells with cyclosporine A (CsA), a competitive inhibitor of CypA, also rescued HIV-1 infectivity. Furthermore, depletion of cellular CypA by RNA interference made HeLa.HR cells permissive to wild-type HIV-1 infection, providing additional evidence that the CypA interaction with HIV-1 CA underlies this restriction. Although restoration of CypA expression in HeLa.HR CypA-knockdown cells impaired HIV-1 infection, this restriction was only partial relative to unmodified HeLa.HR cells. Moreover, we observed that an shRNA targeting a subset of CypA pseudogenes rescued HIV-1 infection without reducing endogenous CypA expression in HeLa.HR cells. Infection of HIV-1 with the CA mutation A92E, a virus that is sensitive to cellular CypA levels, was not enhanced by the expression of this shRNA. Collectively, these data suggest the presence of a CsA-sensitive, CypA-related restriction to HIV-1 in human cells.