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# HIV-1 antagonism of CD317/tetherin is species-specific and involves Vpu-mediated proteasomal degradation of the intrinsic immunity factor

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Mammals encode proteins that inhibit viral replication at the cellular level. In turn, certain viruses have evolved genes that can functionally counteract these intrinsic restrictions. Human CD317 (BST-2/tetherin) was recently identified as a restriction factor that blocks release of HIV-1 from the cell surface and can be overcome by HIV-1 Vpu. Here, we show that mouse and rat CD317 potently inhibit HIV-1, but are resistant to Vpu. To promote virus release, Vpu depletes cellular pools of human CD317, but not of the rodent orthologs, by accelerating its degradation via the 20S proteasome. Importantly, HIV-1 down-regulates surface-exposed CD317 and depletes endogenous pools of the restriction factor in infected human T-cells in a Vpu-dependent manner. Distinct mutants of CD317 indicate that also degradation-independent abilities of Vpu contribute to its ability to promote virus release. Interspecies-chimeras of CD317 reveal that the rodent-specific resistance and human-specific sensitivity to Vpu antagonism have a complex genetic basis involving all three major structural domains of the restriction factor. In rodent cells, knock-down of endogenous CD317 enhances HIV release and accelerates MLV spread, suggesting that CD317 contributes to the control of retroviral pathogenesis. Thus, HIV-1 Vpu suppresses the expression of the CD317 antiviral factor in infected human cells, and the species-specific resistance to Vpu antagonism may guide the advancement of small animal models of HIV infection.