

**POSTER 45****STUDIES ON VPU-MEDIATED ANTAGONISM OF THE HOST RESTRICTION FACTOR CD317 (TETHERIN)**

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The HIV-1 accessory protein Vpu enhances virus particle release by counteracting host restriction factor(s) that retain budded virions on the cell surface of infected cells. Recently, two cellular proteins were reported to possess this virus-tethering activity. One is the interferon-induced transmembrane protein BST-2/CD317, also named tetherin; the other is the calcium modulating cyclophilin ligand (CAML). Vpu reportedly counteracts these restriction factors and enhances HIV-1 particle release. Further studies demonstrated that human tetherin is capable of blocking the release of not only HIV-1 particles but also the release of a variety of other enveloped viruses. Moreover, tetherin variants from mice, rhesus macaques (rh), and African green monkeys (agm) were able to inhibit HIV-1 particle release, but were resistant to antagonism by Vpu. We and others observed that tetherin but not CAML depletion in restrictive HeLa cells enhances Vpu-defective HIV-1 release, demonstrating that tetherin is the host restriction factor counteracted by Vpu. In the present study, we investigated the mechanism of action of Vpu antagonism. We show that the antagonism of Vpu is due to degradation of tetherin. This degradation is inhibited by the proteasome inhibitor MG132, suggesting that tetherin degradation induced by Vpu is proteasome-mediated. Ubiquitylation of tetherin is unlikely to play a role in its degradation as we observed that lysine mutants also undergo degradation by Vpu. Glycosylation of tetherin is also not required for degradation as both glycosylated and non-glycosylated forms of tetherin undergo degradation. Further, we observed that both tetherin and Vpu are associated with lipid rafts, suggesting that Vpu-mediated antagonism may take place in these membrane microdomains. The lack of antagonism of Vpu against mouse, rh, and agm tetherin corresponds to a lack of Vpu-mediated degradation, suggesting that the degradation of tetherin is required to overcome this host restriction for efficient HIV-1 release.