Tetherin Antagonism by Vpu Protects HIV-Infected Cells From ADCC
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Background: HIV-1 Vpu facilitates virus replication by downmodulating at least three different cellular proteins: Tetherin (BST-2 or CD317), a restriction factor that interferes with the detachment of nascent virions from infected cells, CD4, the primary receptor for virus entry, and NTB-A, a co-stimulatory molecule required for natural killer (NK) cell activation. While the mechanisms of these Vpu activities have been studied in detail, their role in immune evasion is not well understood.

Methodology: Using an assay recently developed in our laboratory to measure the ability of antibodies to direct the killing of HIV-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC), we compared the effects of IFNα-treatment, mutations that differentially affect functional activities of Vpu, and RNAi-knockdown of tetherin, CD4 and NTB-A, on the susceptibility of HIV-infected cells to Env-specific antibodies.

Results: Treatment with increasing concentrations of IFNα resulted in a dose-dependent increase in the susceptibility of HIV-infected cells to ADCC, which corresponded to a dose-dependent increase in cell-surface expression of tetherin, but not NTB-A or CD4. Mutations in Vpu that specifically impair tetherin antagonism, without affecting CD4- or NTB-A-downmodulation, increased the susceptibility of HIV-infected cells to ADCC. Conversely, RNAi-knockdown of tetherin, but not NTB-A or CD4, decreased the susceptibility of virus-infected cells to ADCC.

Conclusions: Our results reveal that Vpu protects HIV-infected cells from ADCC as a function of its ability to counteract restriction by tetherin. These observations suggest that by preventing the accumulation of nascent virions on the cell surface, the anti-tetherin activity of Vpu reduces the exposure of HIV-infected cells to antibodies that might otherwise result in their elimination by antibody-dependent immune responses. By serving as link between innate and adaptive immunity, the antiviral activity of tetherin may be augmented by virus-specific antibodies, and hence much greater than previously appreciated based solely on its ability to inhibit virus replication in cell culture assays.