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Tetherin restricts direct cell-cell viral transfer and transmission of HIV-1

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Background

Tetherin (BST-2/CD317/HM1.24) is an interferon-inducible factor of the innate immune system, recently shown to exert antiviral activity against HIV-1 and other enveloped viruses by tethering nascent viral particles to the cell surface, thereby inhibiting viral release. In HIV-1 infection, the viral protein U (Vpu) counteracts this antiviral action by down-modulating tetherin from the cell surface. Viral transmission between T cells can occur via cell-free transmission or the more efficient direct cell-cell route through virological synapses. Virological synapses are associated with lipid raft-rich microdomains in the membrane. Tetherin is known to localize to these microdomains and is capable of modulating actin architecture, which is crucial for viral entry, assembly and budding.

Methods

We established a flow cytometry-based co-culture assay to distinguish viral transfer from viral transmission and investigated the impact of tetherin on cell-cell spread of HIV-1. Sup-T1 cells inducible for tetherin expression were used to examine the impact of effector and target cell tetherin expression on virus transfer and transmission.

Results

We show that tetherin, in addition to inhibiting viral release, also inhibits direct cell-cell virus transfer and transmission. Viral Vpu promotes viral transmission from tetherin-expressing cells by down-modulating tetherin from the effector cell surface, outweighing its possible cost of fitness in cell-cell transmission. Further, we have shown that tetherin on the target cell promotes viral transfer and transmission in a manner that favours Vpu-deficient virus.

Conclusions

The results suggest a role for tetherin in cell-cell contacts, specifically at virological synapses. Our data further contribute to the body of knowledge that the targeting of Vpu could be a valuable strategy aimed at blocking HIV replication.

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