Hooked on HIV

HIV-1 expresses an accessory protein called Vpu that is required for the efficient release of viral particles from certain human cells and subsequent dissemination of infection. Without this protein, the virus remains trapped on the host cell surface, which indicates the presence of an antiviral host protein that prevents HIV-1 from leaving infected cells. Reporting in *Nature*, Paul Bieniasz and colleagues show that the human cell-surface-associated molecule CD317, which they rename tetherin, is the host protein that tethers HIV-1 to the infected cell surface.

Following viral replication and assembly at the host cell surface, HIV-1 virions escape infected cells by budding off from the cell membrane in a process that requires Vpu. Earlier work had established that the retention of HIV-1 particles on the cell surface is induced by the immune effector interferon- α (IFN- α), and that Vpu can counteract the inhibitory effect of IFN- α on HIV-1 release. Exploiting this understanding of the antiviral-factor biology, the authors searched for an IFN- α -induced, cell-surface-located human protein that is expressed in cells in which Vpu is essential for retroviral particle release. Using these constraints and gene-expression analyses, CD317, a membrane protein of previously unknown function, was identified as the putative tetherin. This protein was expressed only by cells that required the viral protein Vpu for HIV-1 escape, and depletion of tetherin in these cells abolished the requirement for Vpu. The authors

Image showing HIV-1 particles (photographed using an electron microscope) that have become trapped at the surface of infected cells through the action of a newly discovered host defence molecule called tetherin. Image kindly provided by Stuart Neil and Paul Bieniasz, Aaron Diamond AIDS Research Center, New York, USA.

were also able to demonstrate that tetherin mediated the retention of virion particles on cell surfaces and, following endocytosis, in tetherin-positive compartments. This finding suggests that the tetherin interaction with HIV-1 virions promotes viral uptake, and subsequent degradation, by the endocytotic machinery of the infected cell.

Together, these results suggest that a major function of the HIV-1 Vpu protein is to facilitate virus dissemination by preventing tetherin-induced viral-particle retention on the surface of infected cells. Interestingly, a number of independent findings are suggestive of a broader antiviral role for tetherin, including the ability of Vpu to promote the cellular release of a wide range of retroviruses and Ebola virus, and the observation that tetherin protein levels are decreased by the expression of the K5 protein from Kaposi's sarcoma-associated

herpesvirus, an entirely unrelated virus. Future work will focus on determining the range of viruses that are susceptible to the antiviral effects of tetherin, as well as unravelling the molecular basis of tetherin antiviral activity and how this action is counteracted by the HIV-1 Vpu protein.

Ultimately, the identification of a previously unknown strategy that is used by organisms to protect themselves against certain viruses could lead to the development of a new generation of antiviral therapeutic options.

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ORIGINAL RESEARCH PAPER Neil, S. J. D., Zang, T. & Bieniasz, P. D. Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. *Nature* **451**, 425–430 (2008)

FURTHER READING Neil, S. J. D. et al. An interferon- α -induced tethering mechanism inhibits HIV-1 and Ebola virus particle release but is counteracted by the HIV-1 Vpu protein. *Cell Host Microbe* **2**, 193–203 (2007)