TETHERIN, AN INTERFERON-ALPHA INDUCED INHIBITOR OF RETROVIRUS RELEASE THAT IS ANTAGONIZED BY Vpu

Stuart J. D. Neil, Matthew McNatt, Nolwenn Jouvenet, David Perez-Caballero Maria Zhadina, Trinity Zang, Zerina Kratovac, Youngnam Lee, Theodora Hatziioannou and Paul D. Bieniasz

Howard Hughes Medical Institute, Aaron Diamond AIDS Research Center and Laboratory of Retrovirology, The Rockefeller University, New York, NY

The HIV-1 Vpu protein overcomes the action of an interferon-regulated antiviral restriction factor, termed tetherin, which causes the retention of virions on infected cell surfaces. Using comparative gene expression analysis and deductive constraints, we identified tetherin as a membrane protein with an unusual topology consisting of a N-terminal cytoplasmic tail, a transmembrane domain, an ectodomain predicted to form a coiled-coil, and anchored at the C-terminus by a putative GPI-linkage. Tetherin expression is necessary and sufficient to restrict the release of Vpu-defective HIV-1 from human cells. Tetherin induces dramatic accumulations of mature HIV-1 virions on the cell surfaces and, following endocytosis, in late endosomes.

To understand mechanisms by which tetherin might function, we examined its ability to inhibit the release of a variety of virions or virus like particles (VLPs) derived from retroviruses that share little sequence homology. Notably, tetherin appears capable of restricting the release of every retrovirus that we have tested. Additionally, tetherin inhibited the release of VLPs assembled by expression of the Ebola or Marburg virus matrix proteins, suggesting that its activity against enveloped viral particles might be very broad indeed and may simply involve crosslinking of lipid bilayers. Immunofluorescence and electron microscopy studies indicate that tetherin localizes to nascent tethered virions, consistent with the notion that it is directly involved in tethering, and is perhaps a component of the tethers that retain virions on cell surfaces.

We have cloned orthologs of tetherin from rhesus macaque, African green monkey and mouse. These non-human tetherins are inhibit HIV-1 release, but in contrast to the human protein, are not antagonized by Vpu. Determinants of Vpu sensitivity in tetherin reside in the transmembrane domain and these findings suggest that HIV-1 Vpu has specifically evolved to antagonize the human tetherin protein. Notably, Vpu abolishes tetherin's to localize with nascent virions, suggesting that Vpu functions by sequestering tetherin from sites of virus particle assembly.