VIRAL PATHOGENESIS

Vpu puts the brakes on ADCC

Vpu counteracts ADCC by a mechanism that is dependent on the antagonism of tetherin

The restriction factor tetherin, which is induced by type I interferon (IFN), has an established role in preventing the release and spread of enveloped viruses by physically ‘tethering’ viral particles to the host cell surface. However, HIV-1 viral protein U (Vpu) blocks restriction and aids pathogenesis by promoting the degradation of tetherin. Two new studies now reveal that Vpu antagonism of tetherin has a second functional role, by enabling HIV-1 infected cells to evade elimination by antibody-dependent cell-mediated cytotoxicity (ADCC).

In the absence of Vpu, the antiviral activity of tetherin results in the accumulation of HIV-1 virions on the surface of infected cells, which suggests that such cells might be more easily recognized by antibodies and, therefore, be more

susceptible to ADCC. Indeed, Arias *et al.* found that, compared with cells infected with wild-type virus, cells infected with HIV-1 Δvpu showed a fivefold increase in surface expression of the viral envelope glycoprotein Env and were ~60-fold more susceptible to ADCC. Importantly, the increase in Env availability correlated with a tenfold increase in surface expression of tetherin. Furthermore, IFN α treatment of HIV-1 Δvpu -infected cells resulted in a dose-dependent increase in both the surface expression of tetherin and ADCC. Thus, in the absence of Vpu, the IFN α -dependent increase in tetherin expression results in the accumulation of tethered virions on the cell surface and enhanced susceptibility to ADCC.

The authors then went on to show that mutations in Vpu (A14L and A18H), which abrogate the ability of Vpu to antagonize tetherin, result in increased ADCC. By contrast, RNAi knockdown of tetherin reduced susceptibility to ADCC. Collectively, these data show that Vpu counteracts ADCC by a mechanism that is dependent on the antagonism of tetherin.

In an independent study, Alvarez *et al.* also show that increased surface expression of tetherin in HIV-1 Δvpu -infected cells correlates with increased antibody binding and ADCC. During viral infection, ADCC by natural killer (NK) cells is mainly mediated by signalling through the Fc γ RIIIa receptor, which causes the release of lytic granules

into antibody-opsonized target cells. The authors found that, compared with infection with wild-type virus, HIV-1 Δvpu infection resulted in a 70% increase in Fc γ RIIIa stimulation and a fourfold increase in NK cell degranulation, which, together with high surface expression of tetherin, increased susceptibility to ADCC. Furthermore, cells infected with virus containing the Vpu mutation A14L showed higher levels of antibody binding and a twofold increase in Fc γ RIIIa induction compared with cells that were infected with wild-type virus. Finally, high surface expression of tetherin was also shown to correlate with increased binding of patient antibodies to infected lymphocytes and the induction of Fc γ RIIIa receptor signalling.

These two studies show that ADCC is a central adaptive immune response to HIV-1 infection, which is augmented by surface expression of tetherin. However, HIV-1 has evolved a counter-strategy, in which Vpu antagonism of tetherin provides a mechanism to evade antibody recognition and ADCC-mediated clearance of infected cells.

Christina Tobin Kåhrström

ORIGINAL RESEARCH PAPERS Arias, J. F. *et al.* Tetherin antagonism by Vpu protects HIV-infected cells from antibody-dependent cell-mediated cytotoxicity. *Proc. Natl Acad. Sci. USA* <http://dx.doi.org/10.1073/pnas.1321507111> (2014) | Alvarez, R. A. *et al.* HIV-1 Vpu antagonism of tetherin inhibits antibody-dependent cellular cytotoxic responses by natural killer cells. *J. Virol.* <http://dx.doi.org/10.1128/JVI.00449-14> (2014) **FURTHER READING** Martin-Serrano, J. & Neil, S. J. D. Host factors involved in retroviral budding and release. *Nature Rev. Microbiol.* **9**, 519–531 (2011)

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