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A Tail of Tetherin: How Pandemic HIV-1 Conquered the World

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The study of successful versus failed zoonotic infections may provide important clues of how viral infection is naturally prevented. In this issue of *Cell Host & Microbe*, a collaborative group led by Frank Kirchhoff uncovers an important piece of the pandemic HIV-1 puzzle.

Phylogenetic analyses indicate that HIV-1 arose from a zoonotic infection from chimpanzees. Moreover, HIV-1 has been transmitted to humans on at least three separate occasions, and each of those zoonotic events has given rise to an independent group of HIV-1 sequences referred to as HIV-1 M (main), O (outlier), and N (non-M, non-O). Remarkably, the frequency of these viruses in the current human population is vastly different, with around 30 million people living with HIV-1 M group infection and about 10,000 with O group infection. Only a handful of N group infections have ever been described. Thus, O and N group viruses are not pandemic, and in the absence of HIV-1 M group infections, HIV/AIDS would be a rare tropical disease. It is obviously of great importance to understand the differences between the viruses that underlie their different frequencies. What are the features of pandemic HIV-1 that make it so much more successful? Now, Sauter and colleagues show that, although pandemic HIV-1 M group has successfully adapted its Vpu protein to antagonize the human antiviral restriction factor tetherin, the O group viruses have not. Could the ability to escape tetherin explain the different frequencies of pandemic and nonpandemic HIV-1 strains?

Mammalian cells encode interferon-inducible antiviral restriction factors as a means of protecting themselves from viral infection. The recently identified BST-2/CD317/HM1.24/tetherin (Neil et al., 2008; Van Damme et al., 2008) is an excellent example of one such protein that can restrict infectivity of retroviruses, filoviruses, and arena viruses. Tetherin has an N-terminal extracellular domain, a C-terminal GPI anchor, and a coiled coil in the middle that promotes dimerization (Figure 1). It is thus attached to the cell membrane at each end, and tetherin dimers are proposed to form a protein tether linking assembled virions to infected cells, leading to their endocytosis and degradation in lyzosomes (Neil et al., 2008; Van Damme et al., 2008). Two recent studies use electron microscopy and tetherin mutagenesis to show that it is probably tetherin itself that forms the tether between the virus and the cell membrane (Fitzpatrick et al., 2009; Perez-Caballero et al., 2009). Perez-Cabellero and colleagues elegantly demonstrate the simplicity of the tethering mechanism by generating an artificial tetherin with full activity by fusing a transmembrane region to a coiled coil with a GPI anchor at the C terminus. Although this artificial molecule had no sequence similarity to tetherin, tethered virions observed by electron microscopy appeared similar to those tethered by tetherin (Perez-Caballero et al., 2009). Fitzpatrick and colleagues use electron microscopy and antitetherin labeling to show that tetherin appears in the virion tethers and in the membrane of the few released virions that manage to escape (Fitzpatrick et al., 2009). These two studies favor different possibilities regarding the configuration of the tetherin dimers that constitute the tethers (Figure 1), but we predict that it will be difficult to rule out the possibility that tetherin can effectively tether in more than one configuration.

In order to replicate in cells that express tetherin, primate lentiviruses encode accessory proteins Vpu and Nef that specifically antagonize tetherin (Jia et al., 2009; Neil et al., 2008; Sauter et al., 2009; Zhang et al., 2009). It appears that a virus can have one or more tetherin antagonists, either Vpu or Nef, or even the envelope glycoprotein. Recent data demonstrate that the envelope glycoproteins from HIV-2 and Tantalus monkey SIV antagonize tetherin by sequestration in the Trans Golgi Network (TGN) (Gupta et al., 2009; Le Tortorec and Neil, 2009). It is not yet clear how Nef antagonizes tetherin, but HIV-1 Vpu leads to tetherin degradation. Importantly, tetherin shows evidence of positive (adaptive) selection (McNatt et al., 2009), presumably as a result of evolutionary pressure applied by antagonistic viral proteins that counteract its inhibition of viral replication. This has led to the species-specific tetherin sensitivity to viral countermeasures. For example, Tantalus monkey tetherin cannot be abrogated by HIV-1 Vpu due to variation in the tetherin transmembrane region (McNatt et al., 2009). Similarly, SIV Nefs are able to overcome simian tetherins, but not human tetherin, due to sequence variation in the cytoplasmic tail of tetherin (Jia et al., 2009; McNatt et al., 2009; Sauter et al., 2009; Zhang et al., 2009).

So how do the various HIV-1 and chimpanzee SIV (SIVcpz) strains compare in their ability to antagonize tetherin? Sauter and colleagues show that, like a variety of SIVs, SIVcpz uses Nef to antagonize tetherin. As we now know from several studies, HIV-1 uses its Vpu protein (McNatt et al., 2009; Neil et al., 2008). This suggests that SIVcpz-derived HIV-1 has had to adapt its Vpu in order to effectively transmit to humans. However, adaptation to use Vpu to antagonize tetherin has not been achieved by the significantly less prevalent HIV-1 O group viruses. Adaptation was required due to sequence variation between the various tetherin proteins. Importantly, the

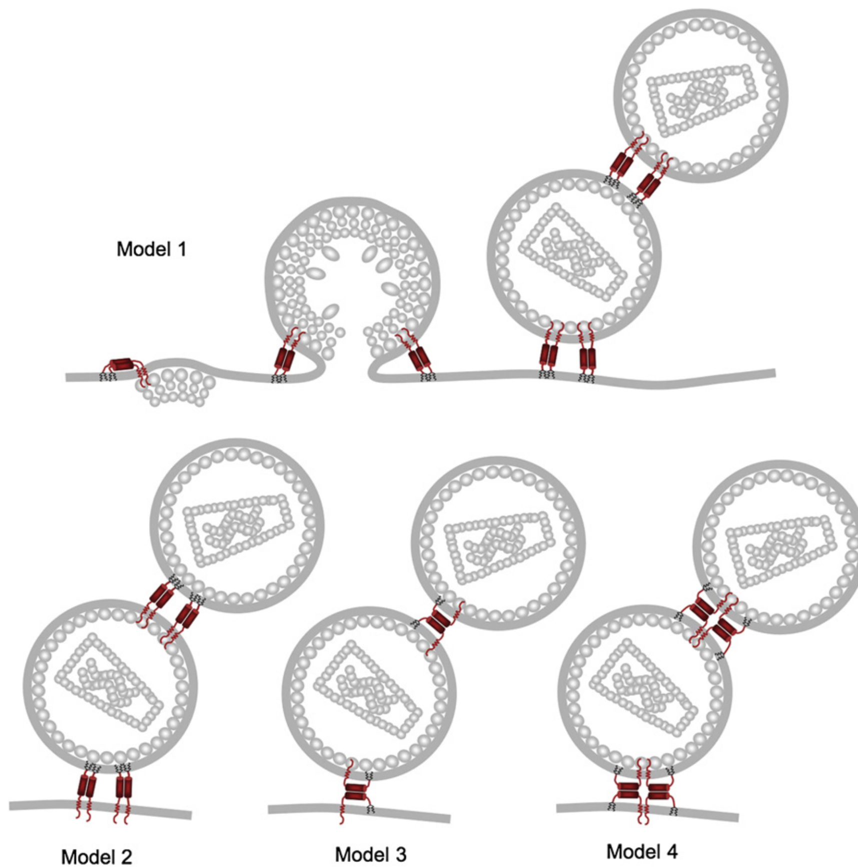

Figure 1. Models for Tetherin's Antiretroviral Tethering Activity
Tetherin restricts retroviral release by tethering newly formed virions to the cell surface. The protease-sensitive tether probably consists solely of dimeric tetherin protein. Shown are models for the various tetherin protein configurations. Currently, Perez-Caballero et al. (2009) and Fitzpatrick et al. (2009) favor different models, but we expect that it will be difficult to rule out the existence of more than one of these examples. The figure is reprinted from Perez-Caballero et al. (2009).

human tetherin protein uniquely has a 4 amino acid deletion in its cytoplasmic tail that makes it insensitive to Nef from a variety of SIVs, including SIVcpz (Sauter et al., 2009; Zhang et al., 2009). Replacing these amino acids makes human tetherin almost fully sensitive to antagonism by SIVcpz Nef and moderately sensitive to O group Nefs (Sauter et al., 2009). We suggest that the tetherin tail deletion was selected by previous encounters with viral antagonists, perhaps even Nef/Vpu-like molecules from long-lost infections. The high level of relatedness between humans and chimpanzees has led us to believe that the species barriers to zoonotic viral infection between chimpanzees and humans are rather low. This is the first example of an adaptation made by HIV-1 to improve replication in humans or human-human transmission. The difference in prevalence between M and O suggests that this adaptation has been critical for the establishment of the human pandemic. The chimp-human species barrier may be low, but tetherin seems to have made an important contribution by virtue of the loss of 4 amino acids in its cytoplasmic tail.

What of N group virus' ability to antagonize tetherin? N group infections are extremely rare; fewer than 20 have ever been described. Sauter and colleagues tested Vpu from three N group viruses and found that one of them antagonized tetherin quite well, whereas the other two did so but rather poorly. It is hard to conclude that N group Vpus can generally antagonize tetherin from these observations, but certainly, N group Vpus are better at this than are O group Vpus. On the other hand, the N group Vpus were unable to downregulate cell surface expression of the T cell receptor CD4. This is thought to be a critical Vpu function that is essential for preventing superinfection and facilitating infectious viral release. These observations suggest that N group viruses may have other problems or at least have alternate, perhaps less effective, strategies for manipulating their new human host.

Does the relative success or failure of these host virus interactions have an impact on disease? This is hard to say, but there is little evidence that they do. O and M group infections appear to lead to similarly high frequencies of clinical AIDS, high plasma viral loads, and similar frequencies of mother-to-child transmissions. Furthermore, rhesus macaque SIV with a human Nef gene, which is apparently unable to antagonize rhesus tetherin, can cause disease in rhesus macaques, although it is less pathogenic. Thus, the ability to antagonize tetherin may be more important for transmission than pathogenesis. However, more work is required, and we propose that the continued comparison of the molecular details of host virus interactions between common and rare types of HIV and their hosts will reveal important information.

The central message from Sauter's important study is that SIVcpz-derived HIV-1 has switched from using Nef to using Vpu to counteract tetherin during zoonosis from chimpanzees to humans. It appears that this change may have made a significant contribution to its ability to spread through the human population. Importantly, primate lentiviruses distantly related to HIV-1, such as SIVgsn, SIVmus, and SIVmon, also use Vpu to antagonize tetherin, suggesting that primate lentiviruses have switched which proteins they use to antagonize tetherin on several occasions. We are reminded of the plasticity of lentiviral protein function and the power of selective pressure. The Red Queen hypothesis suggests an ongoing evolutionary conflict between hosts and their pathogens, and in this case, we have a vivid example of how tetherin and primate lentiviruses have swapped the advantage throughout their evolution. Currently, HIV-1 M group appears to have the lead.

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Cell PRESS

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Jenner's Irony: Cowpox Taps into T Cell Evasion

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CPXV12 is the first poxvirus gene product demonstrated to inhibit the transporter associated with antigen processing (TAP). This cowpox virus function acts in concert with a second gene product, CPXV203, to efficiently suppress MHC class I antigen presentation and enhance in vivo virulence.

2010 marks the 30th anniversary of the global eradication of smallpox, a remarkable achievement that began on May 14th, 1796, when Edward Jenner (Figure 1) inoculated James Phipps with live cowpox virus from the hand of a milkmaid, Sarah Nelmes, and subsequently showed the boy to be immune to smallpox. This experiment not only laid the foundation for the global eradication of smallpox, but also established vaccination (Latin *vacca*, for cow) as a means of generating a protective immune response. The protective immunity elicited by orthopoxviruses is thought to involve both humoral and cellular components of the adaptive immune system (Dasgupta et al., 2007). Two papers in this issue of *Cell Host & Microbe* now identify a second cowpox virus (CPXV) gene product that downregulates major histocompatibility complex class I (MHC class I) molecules and confounds the adaptive cellular immune response (Alzhanova et al., 2009; Byun et al., 2009).

Downregulation of MHC class I was first identified in adenovirus (E3-19K) and is now recognized as a major immune strategy for many viruses, including HIV (Hansen and Bouvier, 2009). Decreased cell surface MHC class I expression will prevent specific viral peptides from being presented to cytotoxic T lymphocytes (CTLs) and therefore promote immune evasion. In recent years, the field has been dominated by studies on herpesviruses. An impressive array of herpesviral gene products target multiple stages in the MHC class I antigen presentation pathway, including peptide generation by proteasomes, TAP-mediated transport of peptides into the ER, and the retention or ER-associated degradation of newly synthesized MHC class I heavy chain. Once formed, the heterotrimeric complex of MHC class I heavy chain, β2-microglobulin, and peptide traffics to the cell surface, but may yet be arrested in the secretory pathway or removed from the cell surface by ubiquitination and endocytosis.

Interest is now growing in the capacity of poxviruses to actively evade the cellular immune response (Guerin et al., 2002; Campbell et al., 2007; Hammarlund et al., 2008). The research group headed by Klaus Früh first demonstrated that CPXV inhibits MHC class I trafficking, while Wayne Yokoyama's laboratory identified the CPXV203 gene product as responsible for ER retention of newly synthesized MHC class I. However, when CPXV203 was deleted from the virus, it was clear that CPXV encoded a second MHC class I evasion function capable of acting independently. Both groups now identify this second function to be encoded by CPXV12 and, in complementary studies, go on to investigate its mechanism of action and role in evading CD8+ cytotoxic T cells (Figure 1).

The two groups came to CPXV12 from opposite directions. Yokoyama's group performed a series of iterative deletions in the CPXV genome to ultimately map the gene by loss-of-function in the virus (Byun et al., 2009), whereas Früh's group interrogated a panel of potential candidates in transient gain-of-function assays (Alzhanova et al., 2009). In the prototype BR strain, CPXV12 encodes a 69 amino acid (8.5 kDa) type II membrane protein that localizes to the ER. In vitro expression studies using microsomal extracts are consistent with the protein consisting of an N-terminal membrane-spanning region with the C terminus extruding into the lumen of the ER (Alzhanova et al., 2009). To get a handle on CPXV12, the protein was expressed with an epitope tag and