

Invited speaker presentation

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Antagonizing the effects of Bst-2/tetherin: multiple ways to accomplish a common goal

Klaus Strebel

Address: Viral Biochemistry Section, LMM, NIAID, NIH; Bldg. 4/310, 4 Center Drive MSC 0460, Bethesda, MD 20892-0460, USA
from *Frontiers of Retrovirology: Complex retroviruses, retroelements and their hosts*
Montpellier, France. 21-23 September 2009

Published: 24 September 2009

Retrovirology 2009, **6**(Suppl 2):110 doi:10.1186/1742-4690-6-S2-110

This abstract is available from: <http://www.retrovirology.com/content/6/S2/110>

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The HIV-1 Vpu protein has long been known to enhance the release of virions from infected cells and to induce proteasomal degradation of the CD4 receptor. While the mechanism of CD4 degradation has been reasonably well explored, our mechanistic understanding of how Vpu facilitates virus release has remained vague. A breakthrough came with the recent identification of Bst-2 (also referred to as CD317 or tetherin). Bst-2 is a host factor whose expression is associated with the inhibition of HIV-1 virus release. Interestingly, Vpu is not the only viral accessory protein with the ability to overcome the inhibitory effect of Bst-2. Indeed, some HIV-2 isolates, although lacking a *vpu* gene, have been known to encode a Vpu-like activity in their Env glycoprotein and were now shown to antagonize Bst-2. Very recently, several SIV Nef isolates have also been associated with enhanced virus release through inhibition of Bst-2 function. Thus, there appear to be at least three retroviral proteins targeting Bst-2. Interestingly, these are the same three viral proteins that can target CD4. We have started a functional analysis to understand at what level HIV-1 Vpu and HIV-2 Env proteins interfere with Bst-2 function to determine if the mechanisms for targeting CD4 and Bst-2 are the same or not. Consistent with published reports we find that Vpu can induce surface down modulation of Bst-2 and cause degradation of Bst-2. However, Vpu can also facilitate virus release in the absence of detectable Bst-2 surface down modulation and degradation and in that respect resembles the HIV-2 Env protein. Possible mechanisms of Bst-2 inhibition by HIV-1 Vpu and HIV-2 Env will be discussed.