

# Toggle Switch: Interactions Between Vpx/Vpr And SAMHD1 In Lentiviruses

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HIV-1, responsible for the current AIDS pandemic, is a type of virus called a lentivirus. There are many lentiviruses besides HIV which infect at least 40 different primate species. These viruses are called simian immunodeficiency viruses, SIV. Lentiviruses can be grouped into eight different major lineages. While all SIVs encode Vpr, the paralog Vpx protein evolved relatively recently and is encoded by only two of the eight primate lentivirus lineages. Both Vpx and Vpr bind the host restriction factor SAMHD1, an antiviral protein that depletes cellular dNTP pools to inhibit reverse transcription, and target it for proteasomal degradation in order to enhance viral infectivity. However, there are conflicting reports as to which region of the SAMHD1 protein is most important for interactions with Vpx derived from different lentiviruses (Lim *et al.*, 2012 and Laguette *et al.*, 2012). In a recent report published in *PLoS Pathogens*, Drs. Oliver Fregoso and Michael Emerman (Human Biology and Basic Sciences) and their collaborators resolve this apparent discrepancy, demonstrating that the interaction between Vpx/Vpr and SAMHD1 is surprisingly plastic, toggling back and forth between the N-terminus and the C-terminus during the evolutionary adaptation of lentiviruses to their primate hosts.

Phylogenetically, extant Vpx genes cluster into two distinct clades. Therefore, the authors hypothesized that Vpx from these different clades may recognize SAMHD1 through different mechanisms. Through a series of SAMHD1 truncations and chimeras they demonstrated that one Vpx clade, which includes the human lentivirus HIV-2, required interactions with the SAMHD1 C-terminus, while the second Vpx clade which includes viruses that infect mangabey monkeys required interactions with the SAMHD1 N-terminus. However, despite the difference in the mechanism of recognition, both Vpx lineages degrade SAMHD1 through a conserved interaction with the same ubiquitin ligase complex.

Because Vpx evolved from an ancient duplication of Vpr (Lim *et al.*, 2012); the authors could look at the evolutionary history of viral interactions with SAMHD1 by determining how Vpr from diverse SIVs recognize SAMHD1. While they found that Vpr from some SIV lineages required interactions with the SAMHD1 C-terminus, similar to the requirements for HIV-2 Vpx, they discovered that Vpr from

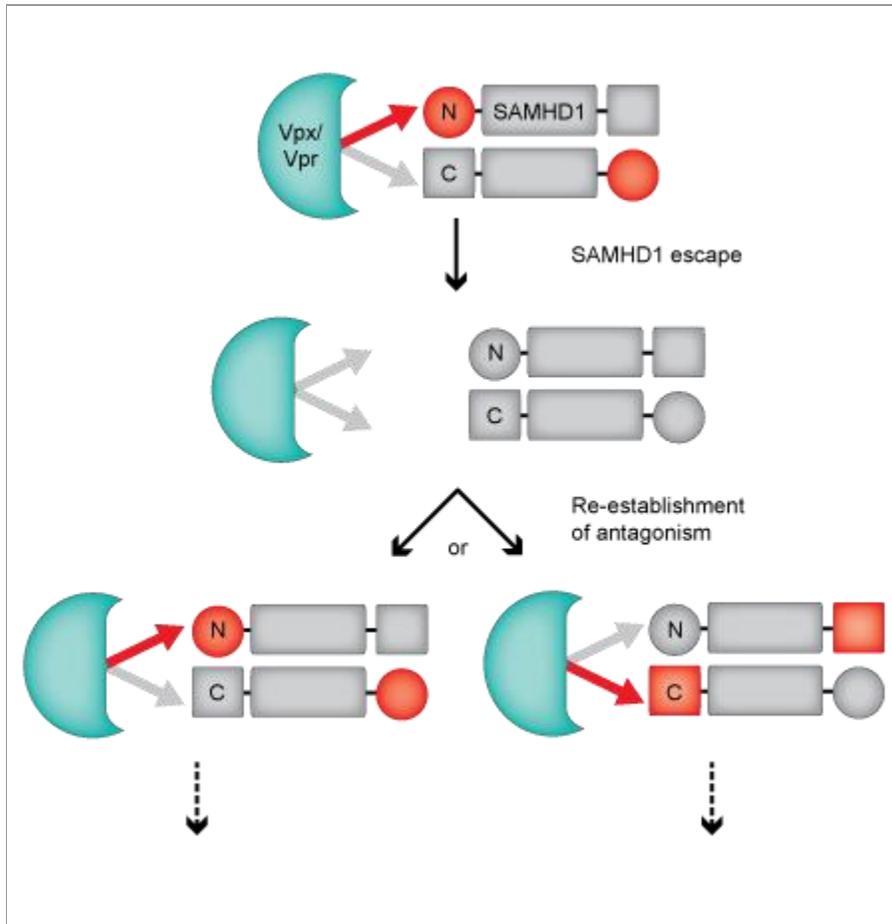
De Brazza's monkey SIV could at least weakly recognize SAMHD1 truncated at either or both N- and C-termini, suggesting this Vpr may have multiple interaction sites with SAMHD1. The authors note that SAMHD1 forms a head-to-tail tetramer and suggest a model in which Vpx/Vpr can interact with both ends of SAMHD1 simultaneously. This model elegantly explains how Vpx/Vpr recognize such different portions of SAMHD1, allowing the viral protein to toggle recognition sites without substantially changing the overall binding pattern between these proteins (see figure).

While the overall interaction pattern between Vpx/Vpr and SAMHD1 is complex, in general the interaction site is conserved within a given virus clade. This pattern suggests that the interaction site has toggled between the N-terminus and C-terminus over evolutionary time. Such dynamic adaptation to maintain the Vpx/Vpr interaction with SAMHD1 shows that the degradation of SAMHD1 has been a selective advantage for primate lentiviruses. "Our plan is to modulate the ability of lentiviruses to degrade SAMHD1 in vivo to understand more about the biology of this important restriction factor, as well as the role it has played in shaping lentiviral evolution," said Dr. Fregoso.

[Fregoso OI, Ahn J, Wang C, Mehrens J, Skowronski J, Emerman M](#). 2013. Evolutionary toggling of Vpx/Vpr specificity results in divergent recognition of the restriction factor SAMHD1. *PLoS Pathog*. doi: 10.1371/journal.ppat.1003496.

See also: [Lim ES, Fregoso OI, McCoy CO, Matsen FA, Malik HS, Emerman M](#). 2012. The ability of primate lentiviruses to degrade the monocyte restriction factor SAMHD1 preceded the birth of the viral accessory protein Vpx. *Cell Host Microbe*. 2:194-204.

See also: [Laguette N, Rahm N, Sobhian B, Chable-Bessia C, Münch J, Snoeck J, Sauter D, Switzer WM, Heneine W, Kirchhoff F, Delsuc F, Telenti A, Benkirane M](#). 2012. Evolutionary and functional analyses of the interaction between the myeloid restriction factor SAMHD1 and the lentiviral Vpx protein. *Cell Host Microbe*. 2:205-17.



*Image from the manuscript published in the open access journal PLoS Pathogens.*

Model of Vpx/Vpr toggling between SAMHD1 restriction sites. Vpx/Vpr binds to SAMHD1 contacting both the N- and C-termini. Escape mutations in SAMHD1 are counteracted by compensatory mutations in Vpx/Vpr that may recognize either end of SAMHD1.