SAMHD1 Antagonism is Conserved in Non-Human Lentiviruses

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The current HIV-1 pandemic is due to a series of cross-species transmission events of related primate lentiviruses (SIV): first from Old World monkeys to chimpanzees, and then from chimpanzees to humans. During this process of adaptation the virus that ultimately became HIV-1 lost the ability to inhibit the antiviral activity of the host protein SAMHD1; however, it can still replicate efficiently (Etienne *et al*., 2013). This observation raises the possibility that SAMHD1 inhibition may not be an important determinant of viral fitness in vivo. Graduate student Chelsea J. Spragg (Molecular and Cellular Biology Program) and Dr. Michael Emerman (Divisions of Basic Sciences and Human Biology) tested this hypothesis in a recent study published in the *Proceedings of the National Academy of Sciences (U.S.A.)* and report evolutionary and phenotypic evidence for ongoing conflict between SAMHD1 and the viral antagonist Vpr in African green monkeys (AGM). This study demonstrates that SAMHD1 evasion is important for the viral lifecycle, and suggests that HIV-1 may have evolved different strategies to minimize the impact of SAMHD1.

There are four genetically and phenotypically distinct species of AGMs in sub-Saharan Africa. Although these monkeys diverged from each other relatively recently (~3 million years ago), each species is infected with its own distinct SIV variant. One barrier to lentiviral infection is mediated by the host protein SAMHD1, which depletes free nucleotide pools in the cell after infection and thereby prevents reverse transcription. The viral protein Vpr antagonizes SAMHD1 in all four of these SIV_{AGM} variants by targeting it for degradation. Consistent with ongoing genetic conflict driving rapid evolution between SAMHD1 and Vpr, Spragg and Emerman identified seven distinct SAMHD1 haplotypes (a set of single nucleotide polymorphisms) in AGMs. No haplotype was fixed in any AGM species, although each species had a different major haplotype and one or more minor haplotypes of SAMHD1. Spragg and Emerman demonstrated that the widespread amino acid differences, or polymorphism, in AGM SAMHD1 had a functional impact during infection. Four of the seven SAMHD1 variants were resistant to degradation by different subsets of Vpr. However, Vpr from a given virus was always able to degrade the predominant SAMHD1 haplotype from its natural AGM host. Thus, these viruses have adapted to antagonize their native host SAMHD1, even when the

variant is resistant to a closely related virus. This means these viruses are selected to maintain the ability to antagonize host SAMHD1, and it therefore must be a determinant of viral fitness in vivo.

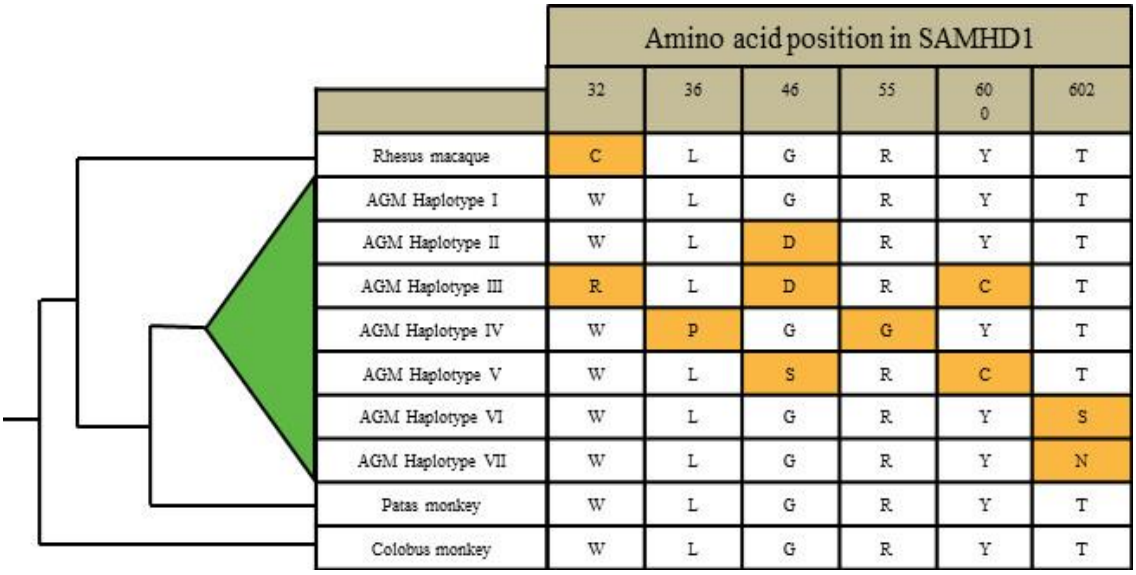
Interestingly, the amino acid differences in AGM SAMHD1 that are responsible for resistance to Vpr are clustered at both ends of the protein. Similar to Vpx-mediated degradation of SAMHD1 (Fregoso *et al*., 2013), the susceptibility of SAMHD1 to different Vpr variants was mediated by amino acid differences at either the N- or C-termini of the host protein. This pattern of amino acid differences between AGM haplotypes raises the possibility that there is ongoing genetic conflict driving these changes. The evolution of such different interacting faces on such a short evolutionary time scale provides strong evidence that the conflict between SAMHD1 and Vpr is ongoing among many species of SIV infected monkeys.

"This study indicates that antagonism of SAMHD1 must provide a fitness advantage to the virus, despite the absence of this capability in HIV-1," said Chelsea J. Spragg. The antiviral activity of SAMHD1 is cell type specific, blocking viral replication in myeloid cells and resting CD4+ lymphocytes. Therefore, the authors suggest, SAMHD1 effects on HIV-1 may be limited to the early stages of infection in myeloid cells, and this pressure may be relieved during later stages of infection when HIV-1 infects primarily infects cycling CD4+ lymphocytes.

Spragg, C.J. and Emerman, M. 2013. Antagonism of SAMHD1 is actively maintained in natural infections of Simian Immunodeficiency Virus. *Proc. Natl. Acad. Sci. USA*: 21136-21141.

See also: Etienne, L., Hahn, B.H., Sharp, P.M., Matsen, F.A., and Emerman, M. 2013. Gene loss and adaptation to hominids underlie the ancient origin of HIV-1. *Cell Host Microbe*: 85-92.

See also: Fregoso, O.I., Ahn, J., Wang, C., Mehrens, J., Skowronski, J., and 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.



	Amino acid position in SAMHD1					
	32	36	46	55	600	602
Rhesus macaque	C	L	G	R	Y	T
AGM Haplotype I	W	L	G	R	Y	T
AGM Haplotype II	W	L	D	R	Y	T
AGM Haplotype III	R	L	D	R	C	T
AGM Haplotype IV	W	P	G	G	Y	T
AGM Haplotype V	W	L	S	R	C	T
AGM Haplotype VI	W	L	G	R	Y	S
AGM Haplotype VII	W	L	G	R	Y	N
Patas monkey	W	L	G	R	Y	T
Colobus monkey	W	L	G	R	Y	T

Image courtesy Chelsea J. Spragg.

Phylogenetic tree of primate SAMHD1. African green monkey haplotypes are highlighted by a green triangle, and non-consensus amino acid positions are highlighted in orange.