Ancient Origins for the Simian Relatives of Modern HIV

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The HIV-1 pandemic began in the 20th century and currently infects 34 million people worldwide. Human and simian immunodeficiency viruses (HIVs and SIVs) belong to the '*Lentivirus*' genus of retroviruses (family Retroviridae), which also contains several other host-specific viruses infecting a variety of different mammalian species, ranging from cows to cats. Though it is clear that lentiviruses have existed for a very long time, the timeframe for the origin of the first primate lentiviruses has been controversial. Some attempts to date primate lentiviruses using the molecular clock approach applied to viral genes have estimated SIVs to have originated tens of thousands of years ago (Worobey *et al*., 2010). However, such an extremely recent entry of lentiviruses into primates is difficult to reconcile with the widespread occurrence of SIVs in many different primate species all over Africa, which generally appear to have already evolved tolerance to the viruses (Sharp *et al*., 2000).

Cyclical evolutionary arms races take place between host restriction factors – proteins that directly inhibit viral replication – and molecular countermeasures, or antagonists, encoded by the viruses. Establishing the evolutionary history of these arms races, and quantifying the pattern of selection on the molecular interface between a restriction factor and a viral antagonist, can inform the development of new antiviral therapies (Emerman & Malik, 2010). In a recent paper published in the journal *PLoS Pathogens*, Dr. Alex Compton and his graduate advisor, Dr. Michael Emerman (Human Biology Division), expand our understanding of the arms races that have taken place during the evolution of SIVs in primates. Their work also provides strong evidence for much more ancient origins of primate lentiviruses, on the order of several million years ago (MYA).

In their prior study, Compton *et al*. (2012) investigated the host restriction factor APOBEC3G (A3G) in four species of African green monkeys. A3G reduces the replication of lentiviruses by mutating viral DNA and inhibiting reverse transcription. Compton *et al*. (2012) also investigated the 'viral infectivity factor' (Vif) accessory protein encoded by the genomes of the SIVs that normally infect these monkeys. This protein targets A3G for proteasomal degradation. The authors found evidence that SIV infection has selected for Vif-resistant forms of A3G in African green monkeys by promoting adaptive changes in A3G at the Vif-binding site. This earlier result was a proof of principle that

mutations arising in A3G at the Vif binding interface could be used as markers for the presence of lentiviruses in primates.

In their more recent study, Drs. Compton and Emerman sought to clarify our understanding of the full evolutionary history of SIVs in primates by expanding their investigation to include 22 Old World primate species. Extremely rapid molecular evolution, which is true of SIV genes, can obscure the molecular clock-based approach for dating evolutionary events. Therefore, Compton and Emerman dated the history of lentiviruses in different primate lineages by detecting branches of the primate evolutionary tree that exhibit signatures of selection on A3G caused by Vif. They also assembled a collection of SIV isolates from a large number of primates, so that they could investigate the co-evolution of A3G and Vif across different time scales of primate evolution.

The authors found that, during the evolution of the Old World monkey subfamily, Cercopithecinae, the same A3G residues repeatedly underwent mutations, and that this occurred independently in several different cercopithecine lineages. Moreover, these recurrent mutations happened on the A3G surface that was already known to be targeted by Vif, reflecting events that the investigators dated to roughly 5-6 MYA. Using experimental infectivity assays, Drs. Compton and Emerman provided additional evidence that these ancient mutations were probably adaptive and allowed the populations harboring them to evade Vif-mediated SIV antagonism.

When the authors analyzed the other subfamily of Old World monkeys – the Colobinae – they discovered an unusual form of resistance to Vif that could not have been associated with the A3G residues found to confer SIV resistance among cercopithecine monkeys. Instead, all colobine monkeys exhibited a unique three amino acid insertion in the N-terminal region of A3G (see figure). This mutational event occurred approximately 12 MYA. Testing chimeric versions of A3G, the authors experimentally demonstrated that a novel A3G-Vif interface around this multi-residue insertion blocks Vif and confers resistance to some SIVs.

Drs. Compton and Emerman show us that primates and lentiviruses have coexisted and engaged in molecular arms races for several million years. Though HIV-1 has only appeared and devastated human populations in modern times, recurrent and unique patterns of virus-driven A3G co-evolution occurred about 5-6 MYA and 12 MYA, respectively. In addition to further exploring the evolutionary space of possibilities for how A3G and Vif interact functionally, the results of Compton and Emerman complement the recent paleovirological clues that ancient lentiviruses also infected prosimian primates some 4 MYA (*e.g.*, Gifford *et al*., 2008). This new finding that SIVs are ancient viruses in primates profoundly changes how we think about the adaptations of lentiviruses to their primate hosts. The exciting results of Compton and Emerman also clarify that SIVs are not at all new to

hominoids, the ape lineage containing humans and other primate species most closely related to the human species.

Compton AA, Emerman M. 2013. Convergence and divergence in the evolution of the APOBEC3G-Vif interaction reveal ancient origins of simian immunodeficiency viruses. *PLoS Pathog*. 9:e1003135.

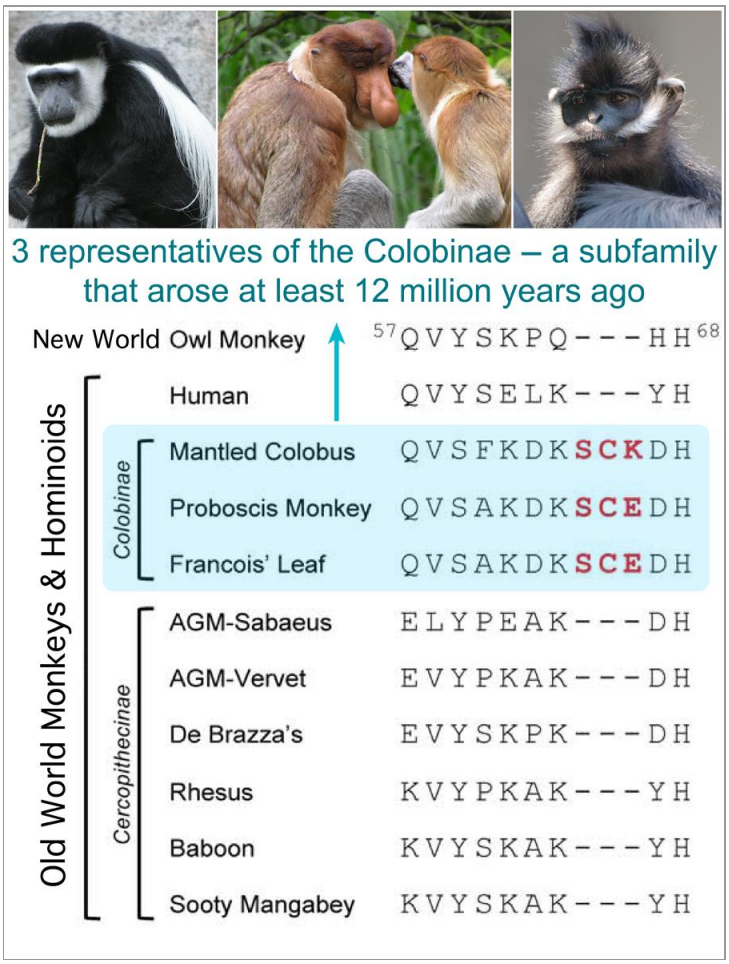
Also see: Compton AA, Hirsch VM, Emerman M. 2012. The host restriction factor APOBEC3G and retroviral Vif protein coevolve due to ongoing genetic conflict. *Cell Host Microbe* 11:91-98.

Emerman M, Malik HS. 2010. Paleovirology–modern consequences of ancient viruses. *PLoS Biol*. 8:e1000301.

Gifford RJ, Katzourakis A, Tristem M, Pybus OG, Winters M, Shafer RW. 2008. A transitional endogenous lentivirus from the genome of a basal primate and implications for lentivirus evolution. *Proc. Natl. Acad. Sci. USA.* 105:20362-20367.

Sharp PM, Bailes E, Gao F, Beer BE, Hirsch VM, Hahn BH. 2000. Origins and evolution of AIDS viruses: estimating the time-scale.*Biochem. Soc. Trans.* 28:275-82.

Worobey M, Telfer P, Souquière S, Hunter M, Coleman CA, Metzger MJ, Reed P, Makuwa M, Hearn G, Honarvar S, Roques P, Apetrei C, Kazanji M, Marx PA. 2010. Island biogeography reveals the deep history of SIV. *Science* 329:1487.



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Alignment of amino acids making up part of the A3G protein (bottom) from eleven primate species reveals a three-residue insertion unique to the Colobinae, a subfamily of Old World monkeys that arose at least twelve million years ago. Photos at the top show the three sequenced colobine monkeys, which represent the three major lineages composing this subfamily: the mantled colobus monkey or mantled guereza (Colobus guereza; placed in the 'African group'; left), the proboscis monkey or bekantan (Nasalis larvatus; in the 'odd-nosed group'; middle), and the Francois' leaf monkey or François' langur (Trachypithecus francoisi; 'langur group'; right).