History of Primate-SIV Conflict Drives Adaptive Diversification of A3G

March 19, 2012

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The major route to the emergence of new viral pathogens occurs when viruses jump from their original hosts to new host species, which is usually followed by intense rounds of virus-host adaptation. Over the past century, several viruses with pathogenic properties have entered the human population, including human immunodeficiency virus type 1 (HIV-1), severe acute respiratory syndrome coronavirus (SARS-CoV) and several assortments of influenza A. For example, HIV-1 and HIV-2 arose from a number of cross-species transmissions of simian immunodeficiency viruses (SIVs), which naturally infect nonhuman primates in Africa. Studies of the co-evolution of host defenses and their viral antagonists are critical to understanding the origins of new pathogenic viruses, as well as the susceptibilities of our innate antiviral defenses to these novel threats.

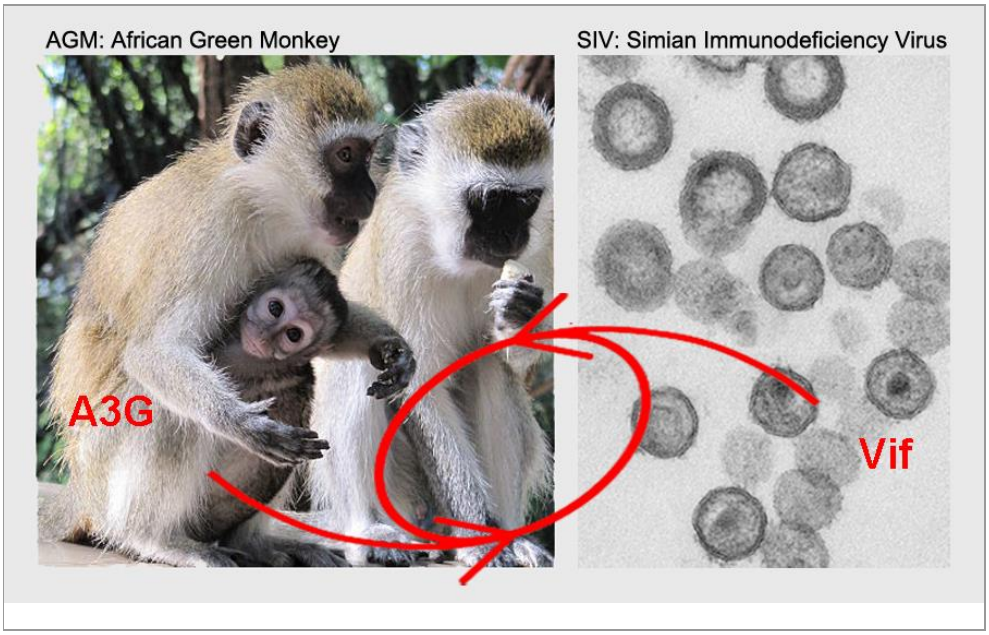
Host restriction factors impose species-specific barriers to viral replication. One such factor, the cytidine deaminase APOBEC3G (A3G), inhibits HIV-1 and related lentiviruses by mutating viral nucleic acids. Viral countermeasures include 'viral infectivity factor' (Vif), which triggers the ubiquitination and proteasomal degradation of A3G. In a recent study, principal investigator Dr. Michael Emerman (Human Biology Division), his graduate student, Alex Compton, and an outside collaborator at the NIH examined the co-evolutionary dynamics of the A3G-Vif interaction in four African green monkey (AGM) species. Next to humans, AGMs are the most abundant primates in Africa. Natural variation in SIV infections among AGMs offers a unique opportunity to study how the evolution of lentiviruses and the evolution of host antiviral genes influence one another.

Compton *et al.* surveyed the degree of A3G genetic diversity in AGMs and found 28 single nucleotide polymorphisms (SNPs) that each cause an amino acid replacement, but only a single 'synonymous' SNP that results in no change to the protein. Two of the amino acid-altering polymorphisms affect a motif critical to the interaction between Vif and A3G. The authors used infectivity assays to show that amino acid substitutions in A3G in two AGM species (grivet and sabaeus monkeys) confer resistance to Vif proteins from several SIV strains not normally infecting grivet or sabaeus hosts. SIV lineages that do naturally infect these two AGM species have co-evolved to overcome their novel A3G polymorphisms. To gain insights into the timeframe of viral adaptation to host switching, Emerman's team then investigated samples collected from a prior

experimental evolution study, in which sabaeus monkeys were infected with a vervet strain of SIV and monitored for almost 2 years. The researchers found that the Vif proteins of the viruses rapidly evolved specificity of antagonism with respect to the A3G genotypes of the sabaeus monkey hosts, implicating Vif as a key factor underlying retroviral adaptation.

The findings presented in this new paper by Compton *et al*. provide important evidence that SIV infection has selected for Vif-resistant forms of A3G in AGMs, even though SIV infection currently appears to be generally asymptomatic and nonpathogenic in African green monkeys. In addition to shedding light on processes of virus-host adaptation in general, Compton and co-authors provide valuable evolutionary context for the development of new HIV therapies that target Vif.

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.



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Compton et al. (2012) report on a counter-evolutionary 'arms race' between A3G (produced by African green monkeys and other primates) and Vif, which is encoded by human and simian immunodeficiency viruses (HIV and SIVs). The authors investigated A3G-Vif interactions using SIV strains collected from four African green monkey species, known commonly as the vervet (above), sabaeus, tantalus and grivet monkeys (Chlorocebus spp.).