Chimpanzee APOBEC3 proteins deter SIVs from any monkey business

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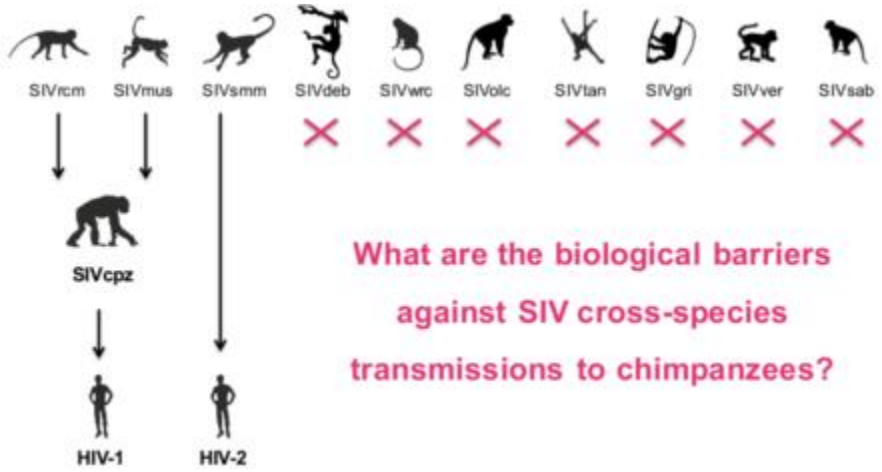

Illustration of the rationale behind the study of Drs. Michael Emerman, Lucie Etienne and colleagues.

Image provided by Dr. Lucie Etienne.

The current HIV-1 pandemic is a result of cross-species transmission of simian immunodeficiency viruses (SIVs) from chimpanzees to humans. Both SIV and HIV belong to family of viruses known as lentiviruses. To break the species barrier, a virus must adapt to a new suite of antiviral proteins collectively known as host restriction factors. While previous studies have documented the adaptation of lentiviruses from chimpanzees to humans, much less is known about the adaptive processes that enabled monkey SIVs to infect chimpanzees. Intriguingly, chimpanzees are infected by a single type of SIV (SIVcpz), despite being exposed to a wide variety of monkey SIVs through their predator-prey relationship hunting. A new Fred Hutch study from Dr. Michael Emerman's Laboratory (Basic Sciences and Human Biology Divisions), led by former post-doctoral fellow Dr. Lucie Etienne, now at the International Center for Infectiology Research in Lyon, asked why chimpanzees are resistant to infection by most SIVs, including ones present in their monkey prey. This work was recently published in *PLOS pathogens*.

The APOBEC3 family of host restriction factors potently blocks the lentiviral life cycle in the absence of the viral protein Vif. Vif is present in all primate lentiviruses and it inhibits APOBEC3 by targeting it for proteasomal degradation. Because adaptation of SIVcpz to chimpanzees involved the evolution of *vif* to counteract chimpanzee APOBEC3G, the authors hypothesized that APOBEC3G constituted a barrier to SIV infection. As a first step to test their hypothesis, they queried a panel of Vifs from ten

SIV lineages for their ability to antagonize chimpanzee APOBEC3G. Most SIV Vifs were incapable of inhibiting APOBEC3G in single-round infectivity assays. In addition, known cases of cross-species transmissions were shown to occur when the virus' Vif was capable of antagonizing APOBEC3G from their new host species. Next, the researchers tested the ability of the SIV Vif to counteract other APOBEC3 family members and found that most Vif proteins could antagonize APOBEC3F and APOBEC3H while only a few could counteract APOBEC3D and APOBEC3G. To determine whether these Vif-dependent restrictions also occurred in immune cells, the authors infected primary chimpanzee CD4+ T cells, the main target cells of HIV and SIV, with either no Vif or Vif from different SIV lineages. They demonstrated that *vif* was essential for replication in chimpanzee CD4+ T cells and that similar Vif-dependent restrictions were observed. Because APOBEC3 proteins mediate their function by inducing mutations in the viral genome, the investigators sequenced the *vif* DNA extracted from infected cells and found the characteristic G-to-A hypermutation in the absence of Vif, an effect that was counteracted by Vif from SIVcpz. Finally, the authors characterized the genetic variants of the *APOBEC3* genes in bonobos and in different subspecies of chimpanzees by analyzing sequencing data from the Great Ape Genome Project. While many polymorphisms were present, none appeared to affect either their antiviral activity or their Vif-sensitivity. Thus, although bonobos and western chimpanzees do not appear to have any current lentiviral infections, these studies imply that the ancestors of all current chimpanzee species may have been selected for resistance to SIV infections. Said Dr. Etienne "Overall, our study highlights that the evolution of the APOBEC3 antiviral gene family may directly participate in the protection of a species against viral cross-species transmissions. In the long-term, this may have impact for human health in mostly two ways: (a) it helps to better understand which viruses may be more prone to cross the species barrier to humans and (b) it characterizes how natural defense proteins may be strong barriers against heterologous viruses, which may ultimately help the design of novel antiviral strategies against pathogenic viruses".

Etienne L, Bibollet-Ruche F, Sudmant PH, Wu LI, Hahn BH, Emerman M 2015. The role of the antiviral APOBEC3 gene family in protecting chimpanzees against lentiviruses from monkeys. PLOS pathogens. 11(9):e1005149.

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