On the Ancient Origins of HIV-1

September 16, 2013

GMR Deyter

The virus responsible for the global AIDS pandemic, HIV-1, originated from the cross-species transmission of a related virus, simian immunodeficiency virus (SIV) that came from chimpanzees within the last century. This virus, called SIVcpz, is itself the result of a much older cross-species transmission of two other SIVs from old world monkeys. A recent manuscript published by Michael Emerman's lab (Basic Sciences and Human Biology Divisions) with lead author Lucie Etienne showed that the adaptation of this HIV-like virus from old world monkeys to chimpanzees facilitated its subsequent transmission to humans.

Viral genomes encode proteins that antagonize host antiviral genes, called restriction factors, that try to inhibit viral infection. Many of the viral antagonists encoded in the SIV/HIV genome are involved in proteolytic processes, leading to the degradation of host restriction factors to promote infection. However, because of differences in the restriction factors between species, viruses need to evolve to recognize different forms of the restriction factors to establish infection in a new species.
The *vpx*gene is encoded by many SIVs to encode a protein that degrades the host antiviral protein SAMHD1, while the *vif* gene encodes a protein that degrades the host antiviral protein APOBEC3G. However, Vpx is not encoded by either SIVcpz nor HIV-1 although *vpx* was present in SIV precursors that generated SIVcpz. After ruling out other scenarios, the authors determined that the entire *vpx* gene was deleted during the generation of SIVcpz. Thus, the ability of SIVcpz (and subsequently HIV-1) to degrade SAMHD1 was lost.

The authors then set out to determine what could be responsible for the selection to lose what was thought to be a vital viral gene. Since the 5' end of *vpx* overlapped with the 3' end of *vif*, the deletion of *vpx* during the birth of SIVcpz caused *vif* to lose its normal stop codon. Instead, Vif translation terminates by using a stop codon in an alternative reading frame within the *vpr*gene, producing a novel Vif protein by a process called "over-printing" (see figure). The authors then showed that the novel Vif protein produced in SIVcpz increased the ability of the virus to overcome the chimpanzee version of APOBEC3G. Thus, the genomic reorganization leading to the birth of SIVcpz gave Vif species-specific activity. Lastly, Etienne *et al.* found that Vif from SIVcpz could efficiently degrade human APOBEC3G and that the passage of SIV through chimpanzees was crucial to allow SIV transmission to humans.

Altogether, this impressive body of work highlights key changes in SIV that helped it antagonize host restriction factors in chimpanzees. Once the hurdle to chimpanzee infection was overcome, important viral infectivity factors acquired additional activity, eventually becoming capable of infecting humans. The techniques used by the authors will undoubtedly uncover how other viruses that plague humans have evolved species-specific function.

Etienne L, Hahn BH, Sharp PM, Matsen FA, Emerman M. 2013. Gene loss and adaptation to hominids underlie the ancient origin of HIV-1. *Cell Host Microbe*. Jul 17;14(1):85-92.

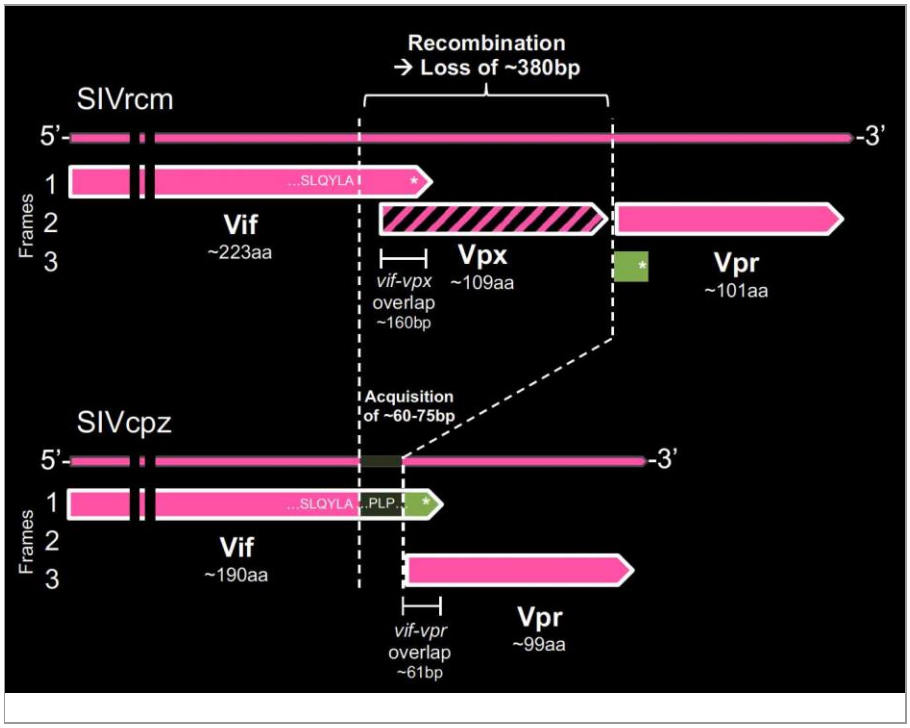

Image adapted from the manuscript

Diagram of changes in SIVrcm genome that had major consequences to the SIVcpz protein Vif. Large pink strands correspond to protein sequences related to SIVrcm, while the green box denotes sequences not expressed in SIVrcm but were part of an Vif ORF in SIVcpz. vpx gene deletion truncated the 3' end of Vif (due to vif-vpx overlap), removing a stop codon (asterisk) from vif. Translation of the SIVcpz Vif protein terminates using a stop codon found in the 5' region of vpr.