Modeling HIV Evolution from SIV Using a Humanized Mouse Model

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Objective

The objective of this study is to identify the genomic changes required for various SIVs to successfully undergo cross-species transmission events to become HIVs using a humanized mouse model.

Origin of HIV

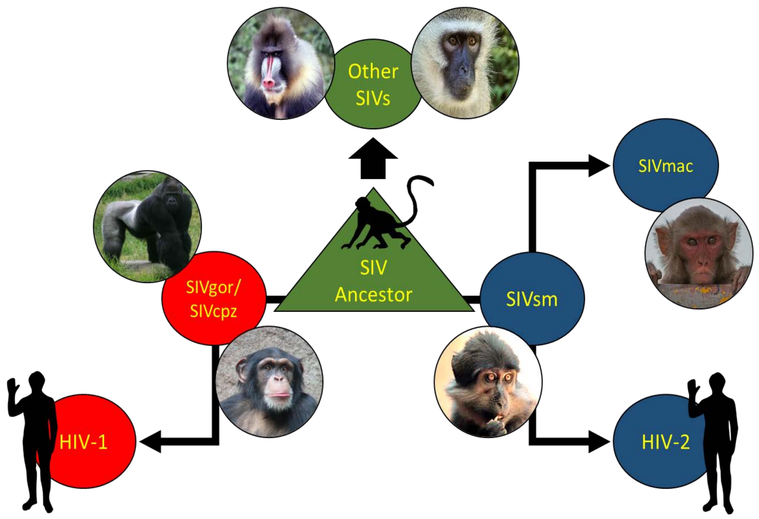

Figure 1: Theoretical origin of HIV. A number of non-human primates have respective SIVs. HIV-1 and HIV-2 are theorized to have crossed over from gorilla/chimpanzee and sooty mangabey strains of SIV, respectively (SIVgor/SIVcpz; SIVsm). Rhesus Macaques gave rise to SIVmac after being exposed to SIVsm in captivity.

Generation of Humanized Mice

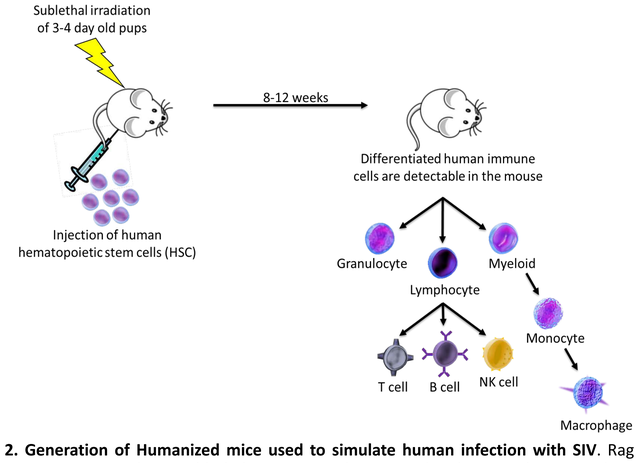

Figure 2. Generation of Humanized mice used to simulate human infection with SIV. Rag knockout mice pups are exposed to sublethal ionizing radiation and subsequently injected with CD34$^+$ hematopoietic stem cells (HSC). HSCs give rise to a complete complement of fully differentiated human immune cells

Serial Passaging Methodology

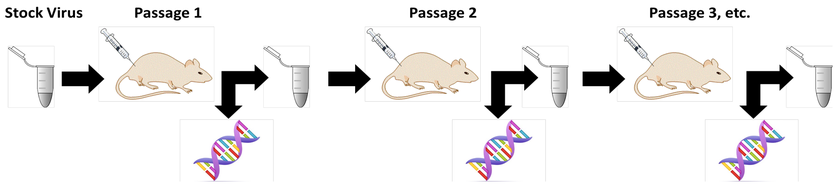

Figure 3. Serial passaging methodology to replicate conditions giving rise to HIV from SIV. Different SIV strains were injected into hu-HSC mice, allowed to replicate for 6 months, purified and sequenced via Next-generation sequencing (NGS). Virus was then propagated and injected into the next generation of mice. Serial passaging is repeated until adaptation occurs.

Plasma Viral Loads

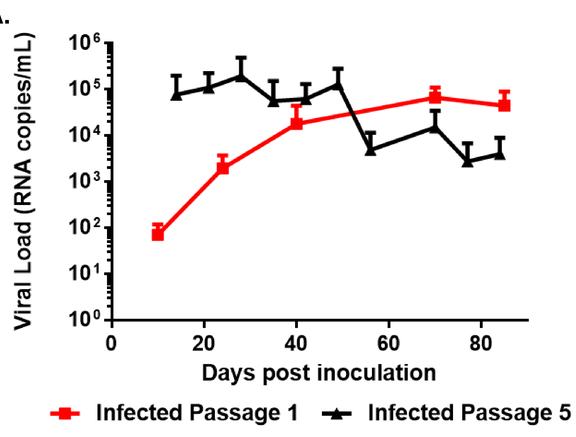

Figure 4. Plasma Viral Loads and CD4$^+$ T cell levels of SIVsm and SIVcpz strains. A) Plasma Viral loads in SIVsmE041 peaked sooner in passage 5 than in passage 1, followed by a gradual decline.

CD4 T-cell Decline in SIVsm Infection

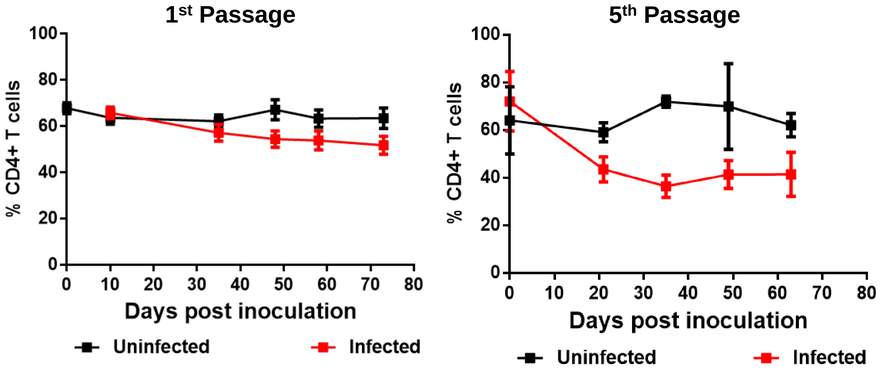

Figure 5. CD4 T-cell levels in the 1st and 5th generations of SIVsm infection. T-cell decline was significantly more pronounced in 5th passage relative to the 1st passage

Variants of Increasing Frequency

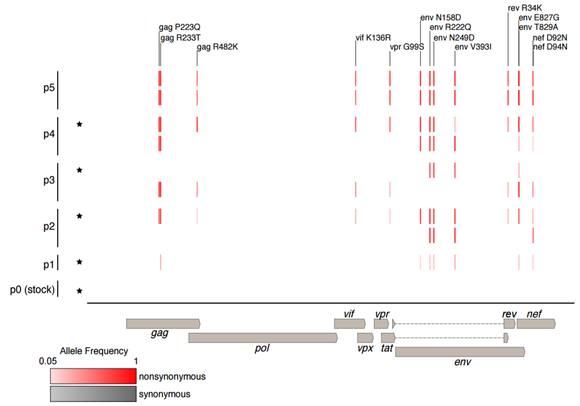

Figure 6. Single Nucleotide Variants that displayed increasing frequency between passage 1 and passage 5. Several mutations were found in each gene that arose immediately and persisted across each passage, indicating that they may be responsible for viral adaptation.

Conclusions

- SIVsm and SIVcpz strains can successfully infect humanized mice and produce detectable viral loads
- Certain regions of the SIVsm genome are undergoing greater frequencies of mutations than others
- Some mutations arise immediately and are maintained across multiple generations in SIVsm

Future Directions

- Functional assays are still necessary to determine the exact nature of the observed mutations.
- The SIVcpz viral strains are still in the first generation, and will require several passages before any concrete claims can be made about viral adaptation.

Acknowledgements

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