A macaque model of HIV-1 infection

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Tips for understanding the paper:

Macaca mulatta is the rhesus macaque.

Macaca nemestrina is the pig-tailed macaque.

HIV-1 and -2, as well as SIV strains, are "lentiviruses." This is a category of retroviruses which cause "slow" diseases of the immune and nervous systems.

Strains of SIV are named according to the primate species they infect. For example:

- SIV_{mac} infects macaques
- SIV_{sm} infects sooty mangabeys
- SIV_{agm} infects African Green monkeys

TRIM5α is a small, cellular protein which functions in innate immunity against viruses. Such antiviral proteins are known as "viral restriction factors." TRIM5α recognizes sequence motifs in the viral capsid (of particular types of viruses) and prevents uncoating, thereby preventing infection of the cell. It was initially identified as a protein in rhesus macaque cells which blocks HIV-1 infection. Consequently, macaque cells are highly resistant to infection by HIV-1. Human TRIM5α is ineffective against HIV-1, although it can block infection by some other viruses.

APOBEC3 is another viral restriction factor. It is a cellular enzyme which causes hypermutation of the HIV provirus during reverse transcription. Specifically, APOBEC3 converts cytosines to uracils in the negative DNA strand as it is copied from the (+)RNA genome. The mutations render the provirus nonfunctional, and promote its degradation. Typically, APOBEC3 is incorporated into the virions during assembly and impacts the reverse transcription step in the next generation of viral progeny.

The **Vif protein** of HIV counteract APOBEC3 by promoting its degradation in the proteosome. Vif of different strains of HIV and SIV tends to work in a species-specific manner. For example, the Vif of SIV_{agm} counteracts APOBEC3 in African green monkeys but cannot neutralize the APBEC3 of humans or chimpanzees. HIV-1 Vif counteracts human APOBEC3, but cannot induce the degradation of APOBEC3 in African green monkeys or rhesus macaques.

Reading the **materials and methods** will help you understand the strains and how the experiments were done.

CA is the abbreviation for the sequence which encodes HIV capsid. It is located within the gag gene (which collectively encodes the capsid, matrix, and nucleocapsid proteins).

HIV-1 does not productively infect most non-human primate species. Therefore, a common animal model system is macaques infected with SIV or a chimeric SIV/HIV (SHIV).

SHIV has the following genetic make-up:

- HIV-1 vpu, tat, rev, env
- SIV gag, pol, vif, vpr, nef

stHIV-1$_{SCA+SV}$ is a chimeric virus. Most of the genes are from HIV-1, but it has an SIV$_{mac}$ capsid gene (SCA) and an SIV$_{mac}$ vif gene (SV). This was produced for a previous study of infection in rhesus macaques. It is resistant to rhesus macaque TRIM5α and APOBEC3.

Two new constructs were made for this study. They are entirely HIV-1 except for the **vif** gene. Note that although their **env** gene is from HIV-1, it is altered. It has been adapted by passage through macaques so that it leads to increased viral replication in this host.

- **stHIV-1$_{SV}$** is HIV-1, except for the vif gene, which is from SIV$_{mac}$.
- **stHIV-1$_{2v}$** is HIV-1, except for the vif gene, which is from HIV-2.

The Western blot in figure 3 indicates the presence (or absence) of HIV-1 proteins:

- gp120 surface protein (the outer protein of the envelope spike)
- p66 subunit of HIV reverse transcriptase
- p55 Gag polyprotein before cleavage into capsid, nucleocapsid, & matrix
- p24 capsid protein
- p17 matrix protein

Fig 5A

TZM cells are a HeLa cell line engineered to stably expresses high levels of CD4 and CCR5. They also harbor a luciferase reporter gene under the control of the HIV-1 LTR (promoter). The baseline activity of this promoter is low, unless one of the HIV-1 gene products, Tat protein, begins to accumulate. (Tat is a transcriptional activator which promotes HIV gene expression.) If the cells are infected with HIV-1, and virus replication ensues, the production of Tat will activate the reporter gene. Protocol can be found here mailto:http://www.hiv.lanl.gov/content/nab-reference-strains/html/Protocol-for-Neutralizing-Antibody-Assay-for-HIV-1-in-TZM-bl-Cells-December-2011.pdf

HIV-1 strains typically have a preference for using one specific coreceptor to access target cells. (This is determined by their env sequence, which evolves over the course of infection.) The strain which is initially acquired by a newly infected person will be an "R5 strain," which prefers to use CCR5 as its coreceptor. Over time, it will give rise to "X4 strains" within the body of the host. These prefer to use CXCR4 as the coreceptor. "Dual-tropic" viruses are able to use either coreceptor.