**TRIM5 modulates penile mucosal acquisition of simian immunodeficiency virus in rhesus monkeys**

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**Introduction**

There is considerable variability in host susceptibility to HIV-1 infections, but the host genetic determinants of that variability are not well-understood. In addition to serving as a block for cross-species retroviral infection, TRIM5 has recently been shown to play a central role in limiting primate immunodeficiency virus replication. We sought to determine whether TRIM5 plays a role in the variable host susceptibility to SIV mucosal infections in rhesus monkeys. In addition, our secondary objective was to develop a simian immunodeficiency virus (SIV)/rhesus monkey penile infection model to study early HIV-1 mucosal pathogenesis in penile mucosa.

**Methods**

We hypothesized that TRIM5 alleles may play a role in modulating mucosal acquisition of SIV in Indian-origin rhesus monkeys. To test this hypothesis, we placed SIVsmE660 (4x 10^8 SIV RNA copies/ml) atraumatically into the prepuce pouch of rhesus monkeys that are either TRIM5 homozygous permissive, heterozygous permissive, or homozygous restrictive. Plasma SIV RNA levels were prospectively determined weekly using qRT-PCR. We then enumerated the number of transmitted/founder (T/F) viruses responsible for productive infection in infected monkeys using single genome amplification (SGA).

**Conclusion**

These data demonstrate that TRIM5 play a critical role in restricting mucosal transmission of SIV. This genetic factor can be exploited to create a more favorable environment for penile transmission of SIV in rhesus monkeys. In addition, the demonstration that a simplification of viral quasispecies occurred after SIV penile transmission lends credibility to the use of this nonhuman primate transmission model for HIV-1 pathogenesis, vaccine, and microbicide research.

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**Results**

**Figure 1.** Systemic infections following repeated penile exposures of rhesus monkeys to SIVsmE660. Rhesus monkeys (n=6/group) were exposed to SIVsmE660 via the penile mucosa for 12 weeks. The first exposure was on week 0 and the last exposure was on week 11. Monkeys were monitored for systemic infection weekly by assessing plasma SIV RNA levels. The lower limit of detection using qRT-PCR is 500 SIV RNA copies/ml. SIV RNA levels for the first 20 weeks following exposures in TRIM5 homozygous restrictive (A), heterozygous permissive (B), and homozygous permissive (C) monkeys. Monkeys that developed a positive plasma virus RNA level were not given further virus exposures. The numbers of monkeys that became infected in each group were statistically different as determined by 3x2 Fisher’s exact test (P=0.005).

**Figure 2.** Effect of TRIM5 genotype on the number of exposures to penile infection in Kaplan-Meier curves. The statistical comparison of the number of exposures between the three groups of monkeys with different TRIM5 genotypes was made using Log-rank test (P=0.017).

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**Figure 3.** Phylogenetic analyses of transmitted/founder (T/F) viruses and their progeny. Maximum-likelihood trees of env sequences from TRIM5 heterozygous permissive (A) and homozygous permissive (B) monkeys are shown at ramp-up and peak viremia along with SIVsmE660 inoculum sequences (black). Sequences from each monkey are displayed as similarly colored symbols. Square symbols represent sequences from monkeys in the heterozygous permissive group, while the circles denote sequences from monkeys in the homozygous permissive group. Env sequences at ramp-up viremia are denoted by open symbols, while sequences at peak viremia are represented by closed circles. Asterisks indicate monkeys that were infected with homogeneous T/F viruses. Bootstrap values are shown for nodes with at least 50% support. The scale bar indicates a distance of 1 nucleotide in the phylogram.