INNATE IMMUNITY

TRIM5 α : the tie that binds

Cross-species transmission of simian immunodeficiency virus (SIV) has resulted in the spread of the virus among monkey species and has given rise to HIV-1 and HIV-2 in humans. However, before becoming established in a new species, retroviruses must overcome any immune barriers to cross-species transmission. Kirmaier and colleagues, writing in *PLoS Biology*, now show that tripartite motif protein 5 α (TRIM5 α), a part of the host intrinsic immune system, can prevent cross-species transmission of SIV.

TRIM5 α is a cytosolic protein that recognizes retroviral particles and blocks retroviral replication. The protein contains three signature motifs and a carboxy-terminal B30.2(SPRY) domain that recognizes viruses; polymorphisms in this domain determine the specificity of the protein towards different retroviruses. The growth of SIV in cell culture is restricted by TRIM5 α through recognition of the viral capsid protein, and changes in the capsid protein can circumvent this restriction.

The authors tested whether TRIM5 α plays a part in preventing

natural cross-species transmission using retrospective analysis of animal colonies combined with *in vitro* studies. In a colony of rhesus macaques, they detected three TRIM5 alleles that vary in the B30.2(SPRY) domain: TRIM5^{TFP}, TRIM5^Q and TRIM5^{CypA}. Each of the encoded proteins could restrict the growth of only a subset of the four SIV strains tested, which were derived from different monkey species and had variations in the capsid-encoding gene. The sensitivity of this subset of viruses to particular TRIM5 alleles was dependent on the viral capsid sequence.

To determine whether TRIM5 α forms an important barrier to cross-species transmission in a natural setting, the authors investigated the spread of sooty mangabey SIV strains (SIV_{SMG}) in two rhesus macaque colonies. In one colony, rhesus macaques were either TRIM5^{TFP}/TRIM5^{TFP} or TRIM5^{TFP}/TRIM5^{CypA}. None of the animals had a high viral burden after the initial infection, mirroring the restriction of SIV_{SMG} by these TRIM5 alleles in *in vitro* culture. In one animal, high viral loads were detected after

1 year, and sequencing revealed a point mutation in the capsid gene of the circulating virus. In the second colony of rhesus macaques, in which all three TRIM5 alleles were present as homozygotes and heterozygotes, the pattern of viral growth also reflected the *in vitro* restriction of the viral strain. Again, the viral load in several animals became high despite the presence of alleles that restrict SIV_{SMG} *in vitro*, and in these cases the capsid gene had also acquired mutations to avoid recognition by TRIM5 α .

Therefore, the restriction of retroviral growth by TRIM5 α that is seen *in vitro* also acts as an important barrier to the spread of retroviruses in natural settings. Furthermore, it forms a selective force for the emergence of mutated viruses, and so a better understanding of TRIM5 α and its interaction with retroviruses will allow better prediction of future zoonoses.

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ORIGINAL RESEARCH PAPER Kirmaier, A. et al. TRIM5 suppresses cross-species transmission of a primate immunodeficiency virus and selects for emergence of resistant variants in the new species. *PLoS Biol.* **8**, e1000462 (2010)