MedicalXpress

Antiviral gene helps suppress jumping of AIDS viruses between host species

August 24 2010

The human AIDS viruses (HIV-1 and HIV-2) originated as viruses of apes and monkeys, respectively, yet little is known about whether or how these invaders adapted to the new genetic "environment" encountered in humans. One group of host genes, collectively known as restriction factors, is thought to influence the ability of such viruses to move between different primate species. A study conducted by Andrea Kirmaier and Welkin Johnson of Harvard Medical School, together with Dr. Vanessa Hirsch of the National Institutes of Health, provides direct evidence in apes and monkeys of a restriction factor gene called TRIM5 acting as a genetic barrier to cross-species transmission of a primate immunodeficiency virus related to HIV-2. The findings will publish next week in the online, open access journal *PLoS Biology*.

The primate immunodeficiency viruses include HIV-1 and HIV-2, as well as the numerous Simian Immunodeficiency Viruses (SIVs) found among African apes and monkeys. The distribution of SIVs among their natural hosts reflects a long history of viruses jumping between species, including the very recent invasions of humans by SIVs from chimpanzees, giving rise to HIV-1, and sooty mangabey monkeys, giving rise to HIV-2. SIV from sooty mangabeys also jumped into Asian rhesus monkeys where, like HIV-1 and HIV-2 in humans, it causes AIDS. Scientists believe that the movement of viral pathogens between hosts ultimately drove the evolution of certain genes, called restriction factors, as protection against such events. Expression of one such gene, TRIM5, renders cultured cells resistant to infection by retroviruses (including human retroviruses like HIV-1 and HIV-2) in the laboratory. The study

by Kirmaier and colleagues now confirms the ability of TRIM5 to suppress cross-species transmission of SIV in vivo.

In their study, Kirmaier and colleagues took advantage of the fact that rhesus macaques have several versions (or alleles) of TRIM5 in their gene pool. As a consequence, different macaques will harbor different versions of TRIM5, leading to the prediction that individual macaques will differ in their sensitivity to infection by viruses from other species. The investigators showed that SIVsm, a virus found naturally in sooty mangabeys, is inherently blocked by some but not all TRIM5 alleles found in rhesus monkeys.

Together with AIDS researchers at the NIH, the team next analyzed archived samples from a cohort of rhesus macaques that had been exposed to SIVsm. In so doing, they found a correlation between the combination of TRIM5 variants present in each individual rhesus monkey in the study, and whether that monkey had high or low levels of SIVsm virus growing in its blood. Importantly, the same TRIM5 alleles that blocked SIVsm infection in the laboratory were also present in those monkeys that had the lowest levels of SIVsm infection, and vice versa. This evidence in monkeys firmly establishes what was suspected from the prior cell culture studies; namely, that TRIM5 plays a role in suppressing replication of the virus in the new host. The researchers also identified a subset of the macaques that had started out with low levels of virus in the blood but eventually developed high levels of viral infection. In such cases, they found that viruses growing in the animals had specifically evolved to overcome the restrictive effects of the particular combination of TRIM5 alleles present in those animals.

This study directly demonstrates the potential for TRIM5 to act as a barrier to cross-species transmission of primate immunodeficiency viruses, a barrier that successful invaders must evolve to overcome. From a practical standpoint, variation in rhesus monkey versions of

genes like TRIM5 may be highly relevant to the central role these animals play as models for studying AIDS and AIDS vaccines. Although humans were not the focus of this study, the results raise the possibility that the outcome of human exposures to viruses from other primates may hinge on genetic variation in the human versions of genes like TRIM5.

More information: Kirmaier A, Wu F, Newman RM, Hall LR, Morgan JS, et al. (2010) TRIM5 Suppresses Cross-Species Transmission of a Primate Immunodeficiency Virus and Selects for Emergence of Resistant Variants in the New Species. PLoS Biol 8(8): e1000462. doi:10.1371/journal.pbio.1000462