Gene Amplification May Promote Cross-Species Transmission of Viruses

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Most new and emerging human infectious diseases are the result of cross-species pathogen transmissions from animals, including HIV/AIDS and avian influenza. The initial success of a virus after entering a new host cell depends on its ability to overcome cellular antiviral proteins known as host restriction factors. Viral antagonists to these host restriction factors are often species specific and only inhibit host restriction factors from closely related species. In order to productively infect cells from a new species, viruses must rapidly adapt to inhibit more resistant versions of these host restriction factors. In a recent paper published in *PLoS Pathogens*, Drs. Greg Brennan and Adam Geballe (Human Biology Division) and their collaborators model this process of viral adaptation and discover that genetic amplification of a weak viral antagonist is sufficient to improve virus replication in cells from multiple primate species.

The host restriction factor protein kinase R (PKR) blocks virus replication by shutting off cellular protein synthesis when it detects double-stranded RNA, a common byproduct of viral replication. Rhesus cytomegalovirus expresses a viral antagonist, RhTRS1, which can inhibit PKR from some African green monkey (AGM) cell lines, but not from human or rhesus macaque cells. To identify adaptations that may allow RhTRS1 to inhibit more resistant versions of PKR, the authors serially passaged a recombinant virus expressing RhTRS1 in an AGM cell line expressing an RhTRS1-resistant allele of PKR. After serial passage the authors found that the *rhtrs1* gene in this virus had duplicated, and this amplification was sufficient to fully rescue virus replication in these resistant AGM cells.

Rhtrs1 amplification also enabled virus replication in otherwise non-permissive cells from both humans and rhesus macaques. However, PKR was only partially antagonized in these cells, raising the possibility that further adaptation will be necessary to fully rescue virus replication in these cells. Importantly, the virus did not adapt when passaged directly in human cells, demonstrating that rhtrs1 amplification in AGM fibroblasts was a necessary intermediate step to increase the species tropism of this virus.

Gene duplication occurs in eukaryotes and prokaryotes, and recently this mechanism of adaptation has also been described in some viruses (Elde *et al*., 2012). DNA viruses tend to have a lower mutational rate than RNA viruses; therefore, gene amplification may be one mechanism for DNA viruses to rapidly adapt to new selective pressures. This study demonstrates that gene amplification of a weak viral antagonist may facilitate rapid adaptation to host restriction factors in divergent species, providing a "molecular foothold" to enable further species-specific adaptations necessary for efficient replication in new hosts. "After additional serial passage, we discovered two adaptive point mutations in virus genes outside of rhtrs1 that fully rescue virus replication in AGM cells. Going forward, we will determine how these unexpected mutations act to inhibit PKR," said Dr. Greg Brennan.

Brennan G, Kitzman JO, Rothenburg S, Shendure J, Geballe AP. 2014. Adaptive gene amplification as an intermediate step in the expansion of virus host range. *PLoS Pathogens*. Doi: 10.1371/journal.ppat.1004002

See also: Elde NC, Child SJ, Eickbush MT, Kitzman JO, Rogers KS, Shendure J, Geballe AP, Malik HS. 2012. Poxviruses deploy genomic accordions to adapt rapidly against host antiviral defenses. *Cell*. 150(4):831-41.

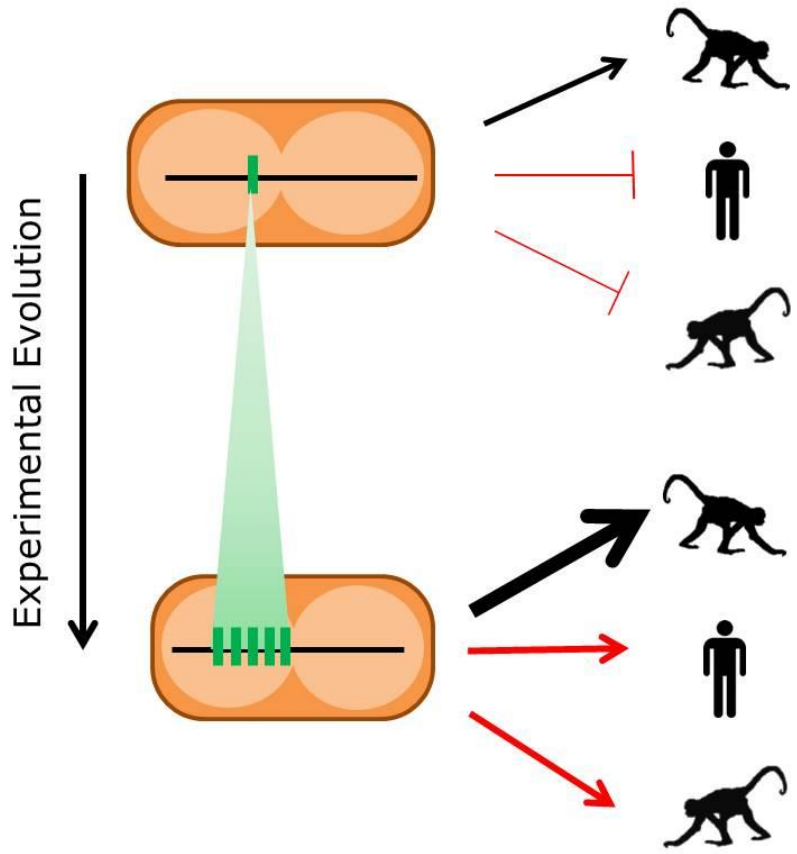

Image courtesy Dr. Greg Brennan

A recombinant virus expressing the weak viral antagonist RhTRS1 replicated modestly in African green monkey (AGM) cells but not at all in human or rhesus cells (top). Gene amplification of rhtrs1 evolved after serial passage in AGM cells, and this amplification improved virus replication in all three species (bottom).