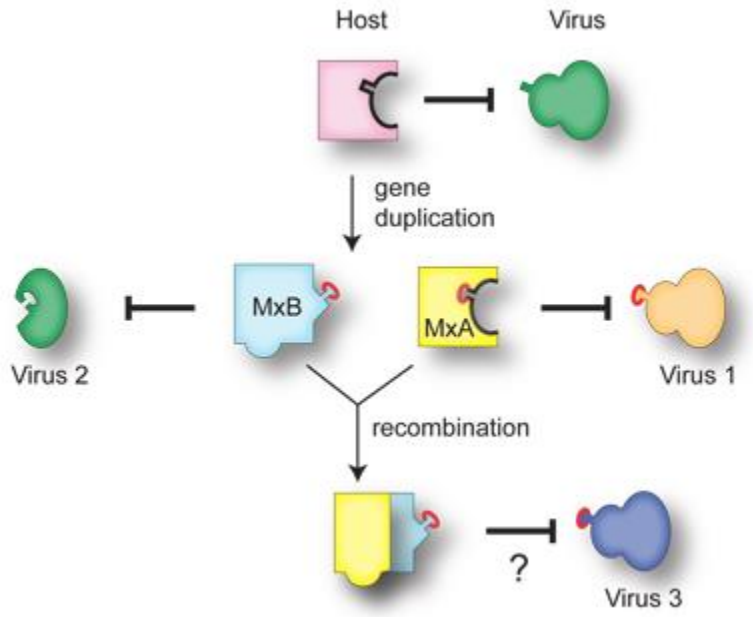
Evolution records a Mx tape for anti-viral immunity

January 17, 2016

L Koch



Model of the evolution of the antiviral Mx proteins.

Graphic provided by Dr. Harmit Malik.

Antiviral genes often evolve rapidly, undergoing positive selection such that the protein they encode can better combat new variants of a virus, as it is evolving to better infect the host. The myxovirus resistance (*Mx*) genes encode interferon-inducible GTPases that confer immunity to the cells that express them. Most mammals have two *Mx* genes; MxA has broad antiviral activity and MxB was recently shown to specifically inhibit HIV-1 replication as well as similar lentiviruses. Patrick Mitchell, formerly a graduate student in Harmit Malik's and Michael Emerman's Labs (Basic Sciences Division), and staff scientist Janet Young (Malik Lab) set out to uncover whether primate MxB has evolved to combat lentiviral infection and whether or not the selective pressures on MxA and MxB have been similar. "The Malik and Emerman labs have pioneered approaches to tease out genomic signatures of these host-virus conflicts," said Patrick. "Such signatures have the potential to help us understand, at a molecular level, how these interactions have played out in the past, which in turn provides clues to explain our susceptibility to modern day pathogens," he continued. Their investigation was recently published in PLOS Pathogens.

After analyzing the sequences of *MxB* from twenty-one species of hominoids, Old World monkeys, and New World monkeys, the scientists found two regions that showed strong evidence of positive selection. These regions had more non-synonymous changes (changes in their DNA sequence that lead to a change in the amino acid sequence of the protein) than synonymous changes (changes of the DNA sequence that do not lead to amino acid changes) than expected by chance. This supports the idea that MxB is engaging with viruses in a molecular " arms race" . However, neither of these two regions of MxB correspond to a region of MxA that is undergoing positive selection. This data, along with the observation from other groups that MxA and MxB localize to different parts of the cell, argues that MxA and MxB are evolving to defend the cell against different types of pathogenic challenges.

Several recent studies have shown that primate MxB can restrict lentiviral replication and have identified specific amino acid residues required for that function. Nonetheless, Patrick and Janet found no overlap between the residues they identified as evolving under positive selection and the residues previously shown to be important for the specificity of the anti-lentiviral activity. Moreover, Old World monkeys are the natural reservoir of primate lentiviruses (and are the ancestral source of HIV-1) so if lentiviruses had driven the selection of MxB, one would expect to find differences in MxB selection in Old World monkeys versus other primates. In fact, the scientists found the same several residues to be undergoing positive selection within each group of primates, suggesting instead that these residues confer a broader immunity to viruses throughout primates.

Antiviral genes are commonly duplicated or lost over evolutionary history, like a genetic accordion. This allows cells to diversify and tailor their response to ever-evolving viral antagonists. Thus, the observation that there are only two *Mx* genes in primate genomes seems at odds with this trend. To comprehensively characterize *Mx* gene evolutionary history, Patrick and Janet performed a phylogenetic analysis of *Mx* paralogs from at least one species from all sequenced mammalian orders. Interestingly, their tree has ancestral *MxA* and *MxB* genes in the common ancestor of all mammals. However, they found several clades that have lost *MxB* and were unable to identify either MxA or MxB genes in marsupials. Looking even further in depth at conserved regions of *MxA* and *MxB*, they found evidence for extensive recombination between the two across evolutionary time. Their data highlights the complexity of antiviral gene evolution and the need for accounting for recombination in evolutionary analyses.

Overall, their work "provides a "molecular map" of positions on MxB that have been recurrently altered throughout evolution, which we hope the community can use to reveal new roles of MxB in host immunity," said Patrick.

Mitchell PS, Young JM, Emerman M, Malik HS. 2015. "Evolutionary analyses suggest a function of MxB immunity proteins beyond lentivirus restriction." *PLOS Pathogens*. 11(12):e1005304. doi:10.1371/journal.ppat.1005304.

This research was supported by the National Science Foundation, the National Institutes of Health, and Howard Hughes Medical Institute.