

THE EVOLUTIONARY DYNAMICS OF APOBEC3 FUNCTION

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The APOBEC3 family of cytidine deaminases (APOBEC3A-H) restricts various retroviruses and retroelements by causing G-to-A hypermutation in the viral genome and other mechanisms. As a result, some viruses have evolved strategies to counteract APOBEC3 antiviral activities. For example, HIV-1 encodes the viral Vif protein that targets APOBEC3 for degradation. The “genetic conflict” between these host defense genes and viral evasion has likely driven the strong signature of adaptive evolution that we observe in primate APOBEC3 genes.

The most divergent member of this family of genes, APOBEC3H, is encoded at the distal end of the locus. We have found that APOBEC3H is polymorphic in humans. Among the four major haplotypes of APOBEC3H, only one haplotype, called haplotype II, that is found mostly in African populations, is stably expressed and active against HIV-1 and non-LTR retroelements. The other haplotypes can make mRNA, but their proteins are unstable. An evolutionary analysis shows that the instability phenotype of APOBEC3H occurred twice independently in recent human evolution. This suggests that there may be a cost associated with expression of the modern human form of APOBEC3H. Moreover, when we reconstructed the ancestral version of APOBEC3H, we find that it has even more activity than any of the extant versions of this gene. We hypothesize that APOBEC3H alleles have evolved to become more resistant to a Vif-like protein in an ancient pathogen but these same changes also compromised modern APOBEC3H antiretroelement activity.