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Adaptive evolution of the virus resistance gene *Apobec* in the genus *Mus*

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Background

APOBEC3 (A3) is a cytidine deaminase gene with antiviral activity. It was originally discovered as a human cell factor that inhibits the replication of *vif*-defective HIV-1. A3 can be packaged in virions and subsequently blocks infection by causing G to A hypermutation following reverse transcription. Humans carry a tandem array of 7 hA3 genes most of which have antiviral activity, whereas the mouse has only a single copy. Several observations indicate that mA3 functions in anti-viral defense: mA3 inhibits infection by several viruses including HIV-1, mA3 knockout mice are more susceptible to MMTV infection and tumorigenesis, and mA3 restricts Friend MLV and virus-induced disease and may encode the resistance factor *Rfv3* (recovery from Friend virus 3). In Friend virus sensitive and resistant mice, mA3 differs in expression level, splicing, and protein sequence.

Materials and methods

We sequenced mA3 genes from 21 inbred strains and wild mouse species representative of the major taxonomic groups of *Mus*. The sequences were used to construct a phylogeny, and a free-ratio model was used to calculate branch-specific ratios of nonsynonymous to synonymous substitutions. Likelihood ratio tests using different neutral and selection models were used to test for positive selection and to identify codon positions subject to positive selection.

Results

We found evidence for strong positive selection of mA3 in *Mus* and identified 7 codons with very high posterior probabilities (>0.99) of having evolved under positive selection. Six of these codons are in two clusters in the N-terminal enzymatically active CDA (catalytically active deaminase domain) of mA3, and both clusters include codons that are polymorphic in the prototype *Rfv3* resistant and susceptible mouse strains [1]. Codons at comparable positions in the active CDA of hA3G are critical for deaminase activity. Sequence comparisons of virus resistant and susceptible mice also identified the presence of an inserted sequence associated with mA3 that may contribute to alternative splicing and/or expression differences. We describe the limited distribution of the Friend virus restricting mA3 variant in inbred and wild mice.

Conclusion

Phylogenetic analysis suggests that mA3 has had an antiviral role throughout *Mus* evolution. We identified specific codons that may define sites of virus interaction as well as an inserted sequence that might be responsible for altered expression in virus resistant mice.

References

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