Intraspecies contemporary evolution of bat antiviral effectors drives interindividual differences in host –virus interactions

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Résumé

The contemporary evolution of innate immunity is primarily driven by the combined pressures from modern viruses and environmental factors acting upon their hosts. This dynamic may result in inter-individual variability, occurring at the interface between innate immune genes and the viral genomes, which may ultimately manifest as functional differences (i.e., ability to restrict viral replication or escape viral antagonism) between individuals. Studying these dynamics can therefore provide crucial information on the genetic and molecular drivers of host immune diversity, especially in wildlife hosts such as bats, which naturally harbor high-profile zoonotic viruses. Here, we combined field sampling (n> 30 ind. / pop.), macro- (interspecies) and micro- (intraspecies) evolutionary analyses and *in vitro* functional assays to decipher the functional diversification of three broad antiviral effectors within four bat species, all known as natural hosts of various viruses. These effectors were chosen based on their potent antiviral activity against a wide range of RNA and DNA viruses, as well as their rapid evolution at the interspecies scale. We found important SNPs in all three effectors, including non-synonymous polymorphisms or insertions/deletions. Importantly, these changes mapped at coding sites evolving under significant positive selection, and known as targets of viral antagonists. In addition, variations were also witnessed by distinct species-specific isoforms across species and individuals, notably within two of the studied effectors. To assess the functional impacts and drivers of these variations, we tested the cellular function of

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one effector variants, as well as the sensitivity to viral antagonists from bat-borne viruses, including influenza, poxvirus and hepacivirus. We showed that the individual-specific variants encode functional proteins that differ in their ability to resist viral antagonists, thereby driving the specificity virus antagonist-host interactions. Altogether, these findings suggest that the observed genetic and functional changes may reflect adaptive selection driven by contemporary viral pressures, which may have important implications for virus circulation within bat populations.

Mots-Clés: bats, innate immunity, genetic conflicts, adaptive selection