Combinatorial mutagenesis of rapidly evolving residues yields super-restrictor antiviral proteins

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Antagonistic interactions drive host-virus evolutionary arms races, which often manifest as recurrent amino acid changes (i.e., positive selection) at their protein-protein interaction interfaces. Here, we investigated whether combinatorial mutagenesis of positions under positive selection in a host antiviral protein could enhance its restrictive properties. We tested approximately 700 variants of human MxA, generated by combinatorial mutagenesis, for their ability to restrict Thogotovirus (THOV). We identified MxA super-restrictors with increased binding to the THOV nucleoprotein (NP) target protein and 10-fold higher anti-THOV restriction relative to wild-type human MxA, the most potent naturally occurring anti-THOV restrictor identified. Our findings reveal a means to elicit super-restrictor antiviral proteins by leveraging signatures of positive selection. Although some MxA super-restrictors of THOV were impaired in their restriction of H5N1 influenza A virus (IAV), other super-restrictor variants increased THOV restriction without impairment of IAV restriction. Thus, broadly acting antiviral proteins such as MxA mitigate breadth-versus-specificity trade-offs that could otherwise constrain their adaptive landscape.