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The stalk domain of influenza pH1 HA tolerates substitutions that may confer decreased susceptibility to broadly neutralizing antibodies.

Content

The highly-conserved influenza hemagglutinin stalk domain is a favoured target for broadly neutralising antibodies (bnAbs), which are heralded as a new class of therapeutic biologics that would inhibit many different strains and subtypes of influenza A viruses. Based on structural and bioinformatics analyses of multiple bnAb-HA co-crystal structures, we rationally designed influenza virus libraries altered in pdm09 H1 HA stalk epitope residues. Our work revealed that this region can accommodate a greater sequence diversity than previously thought, challenging prevailing dogma that the stalk domain is intransient.

We recovered 27 virus mutants, some of which are observed in natural isolates at low frequency. Both in MDCK cells and also in a stringent primary human airway epithelial (HAE) cell culture system, the amino acid mutations in stalk residues often did not incur any fitness cost. Our in-silico residue mutational scanning predicted at least ten mutants from our rescued mutant pool that may reduce or abolish bnAb binding. To investigate this further, we tested binding and neutralization of the mutants by a panel of bnAbs. Although there were no large-effect (»10-fold) escape mutations, we found small-effect mutations that modestly decreased the neutralization of mutant virus by specific bnAbs. In summary, mutations which may confer escape from bnAbs are tolerated in the highly-conserved HA stalk, highlighting vulnerabilities in universal flu vaccines and viral therapeutics which need to be addressed.

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