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Poster presentation

P05-09. 4e10 epitope-scaffolds mimic the antibody-bound epitope conformation and block neutralization by sera from rare HIV+ individuals

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Background

A protective vaccine against HIV will likely require elicitation of potent broadly neutralizing antibodies as well as cellular immunity. mAb 4e10 has the greatest breadth of the known neutralizing monoclonal antibodies, but 4e10-like antibodies are rarely elicited in natural infection. The crystal structure of the 4e10 antibody-epitope complex was solved previously. To develop immunogens that elicit 4e10-like antibodies, we employed computational methods to design "4e10 epitope-scaffolds" – protein scaffolds that present and stabilize the 4e10-bound conformation of the epitope.

Methods

Within the Rosetta protein modeling platform we developed methods that (1) identified protein scaffolds with structural similarity to the 4e10 epitope and suitable for 4e10 binding without steric clash; and (2) transplanted epitope side-chains to scaffolds and optimized the scaffold-antibody interaction. Epitope-scaffolds were designed automatically and then subjected to human-guided refinement.

Results

More than twenty epitope-scaffolds were expressed and purified. Most of the epitope-scaffolds bound to 4e10 with 10- to 1000-fold higher affinity than the cognate peptide, as assessed by surface plasmon resonance. Crystal structures of multiple epitope-scaffolds were determined, both unbound (six structures) and bound (two structures) to the 4e10 antibody. Multiple bound and unbound structures revealed near perfect mimicry of the 4e10 epitope conformation. All the epitope-scaffolds tested blocked broadly-neutralizing activity in serum from an HIV-1 chronically-infected individual who developed 4E10-like NAbs; one scaffold mutated to kill the epitope did not block this activity, indicating that the block was specific to the epitope.

Conclusion

We successfully transferred the 4e10 epitope to non-HIV protein scaffolds. The scaffolds are useful as candidate immunogens and as reagents to characterize cross-reactive neutralizing specificities in HIV+ sera. The immunogen design methods are general and can be applied to other epitopes with other conformations.

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