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Poster presentation

P04-39. Recognizing a dynamic HIV-1 target: a structural look at the interaction between bnAb 2F5 and varying gp41 MPER sequences

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Background

The quest to create an HIV-1 vaccine capable of eliciting broadly neutralizing antibodies (bnAbs) against Env has been challenging. Amongst others, one difficulty in creating a potent immunogen resides in the substantial overall sequence variability of HIV Env across different clades. One of the few conserved regions of Env is the membrane proximal external region (MPER) of gp41, a tryptophan-rich stretch spanning residues 660 to 683. To date, three bnAbs have had their primary epitope mapped to this region: 2F5, Z13 and 4E10.

Methods

In this study, we first extensively describe the variability of the gp41 MPER by performing a search of the Los Alamos National Laboratory HIV database and show variation at each position of the MPER. Subsequently, we evaluate the ability of the bnAb 2F5 to recognize varying sequences of the gp41 MPER at a molecular level. We report our attempts to co-crystallize 2F5 Fab' fragments with 28 different MPER peptides. In 16 cases, the resulting crystal structures show the various MPER peptides bound to the 2F5 Fab'.

Results

A variety of amino acid substitutions outside the ^{664}DKW^{666} core epitope are tolerated. However, changes at the ^{664}DKW^{666} motif itself are restricted to those residues that preserve the aspartate negative charge, the stacking arrangement between the beta-turn tryptophan and lysine, and the positive charge of the latter. We also characterize a possible molecular mechanism of 2F5 escape by sequence variability at position 667, when an alanine residue is replaced by amino acids with bulkier side chains, a substitution often found in HIV-1 clade C isolates.

Conclusion

From our results, we propose an expanded molecular model of epitope recognition by bnAb 2F5, which will help in guiding future attempts at designing small molecule MPER-like vaccines capable of eliciting 2F5-like bnAbs.