Retrovirology

Poster presentation

P19-50. Simulation of an MPER peptide samples epitope conformations of two broadly neutralizing antibodies

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Background

The membrane proximal external region (MPER) of the HIV envelope protein gp41 is one of the most highly conserved regions of the HIV genome and is therefore an excellent candidate immunogen for eliciting broadly neutralizing antibodies (BNAbs). However, anti-MPER BNAbs are extremely rare and immunization with MPER peptides has, to date, failed to elicit them. It has been suggested that the lack of a BNAb response to the MPER immunogen may be due to the failure of the peptide to adopt the relevant binding conformation in solution.

Methods

We use replica exchange molecular dynamics to simulate the full-length MPER peptide (EQELLELDKWASLWNWF-NITNWLWYIK) in solution to investigate its conformational ensemble and determine whether relevant binding conformations of a BNAb epitope are populated and accessible.

Results

Our simulations show that the peptide inhabits a broad range of mostly helical conformations with the N-terminal half being most stable. In addition, backbone structures similar to that of the critical residues for the two most potent anti-MPER BNAbs, 2F5 and 4E10, are significantly populated, and these residues are found to be solvent accessible and available for BNAb recognition.

Conclusion

These results suggest that failure of the MPER peptide to elicit a BNAb response may not be due to conformational inaccessibility of relevant binding conformations, and that explicit stabilization may not be required. While it has been suggested that the relevant BNAb binding conformations may be present only in the context of the nearby lipid bilayer or as part of a fusion intermediate of gp41, our simulation results suggest that epitope conformations are accessible for interaction with BNAbs and therefore the rarity of BNAbs is likely due to other mechanisms such as B-cell tolerance.