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Poster presentation

P12-14. Design of hydrophilic, helical peptides that mimic the 4E10 epitope of HIV-1 gp41

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Background

The broadly neutralizing monoclonal antibody 4E10 binds a linear, alpha-helical epitope in the membrane-proximal external region (MPER) of HIV-1 gp41. The epitope, which lies immediately N-terminal of the single transmembrane segment of gp41, is partially inserted into the lipid bilayer. Efforts to design peptide immunogens containing the 4E10 epitope have been hampered by the hydrophobic nature of the sequence, and so far no neutralizing immune response could be elicited either with attached solubility tags, or with the peptide embedded in a lipophilic environment.

Methods

In an attempt to eliminate the requirement for lipids, we replaced the amino acids flanking the 4E10 core epitope by residues that 1) increase the overall hydrophilicity of the peptide, and 2) maintain the alpha-helical conformation. Using an in silico approach, we generated a series of 19-mer peptides, in which four variable positions were occupied by all permutations of six amino acids that fulfilled the two criteria mentioned above. These 1296 peptides were ranked according to their predicted hydrophilicity and alpha-helicity. A small set of "best bet" peptides was synthesized and analyzed for alpha-helicity by circular dichroism, and for binding to the 4E10 monoclonal antibody by surface plasmon resonance.

Results

One candidate peptide, P2.2, showed improved solubility in aqueous solution compared to a peptide corresponding to the parental 4E10 epitope, yet it maintained alpha-helicity. Moreover, the binding kinetics of P2.2 to the 4E10 monoclonal antibody were similar to the parental peptide. We are currently testing the immunogenicity of P2.2 conjugated to a carrier protein in a small animal model.

Conclusion

Our results demonstrate that variants of the 4E10 epitope with improved hydrophilicity have biophysical properties that are comparable to the wild-type sequence. This approach may be universally applicable to a large set of 4E10-derived peptides to identify a hydrophilic sequence that induces a broadly neutralizing antibody response.