Retrovirology

Poster presentation

P05-06. Masking of MPER epitopes through self-associations

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Background

Potently-neutralizing, anti-MPER humoral responses are uncommon in AIDS patients, though some anti-MPER antibodies, like 4E10, are broadly cross-reactive and protective in combination passive immunizations. The difficulty in raising these specificities may be the result of steric occlusion of this region on virions and/or 'masking' of the epitopes by some means; understanding these mechanisms, and the mechanisms by which anti-MPER antibodies neutralize, are critical in the selection and design of vaccine immunogens targeting this region.

Methods

The Stamatatos CAVD consortium has used computational methods to design isolated epitope-scaffold proteins that effectively present the 4E10 epitope, as defined by binding to 4E10 with tight affinities (determined using surface plasmon resonance) and conservation of epitope structure (using macromolecular crystallography).

Results

Many of the 4E10-based epitope-scaffold proteins show multimerization in solution by a variety of biophysical techniques, with the 4E10 epitope itself buried at the multimer interface. We conclude that many of these proteins are in rapid monomer/multimer equilibration in solution since 4E10 can bind tightly to many of these species. Burial of the epitope, however, may affect presentation during immunization and formulation for immunization may affect the equilibrium.

Conclusion

We are exploring the possibility that 4E10 epitope self-association may also explain 'masking' in context of the virion, using epitope-scaffold proteins as surrogates for Env protein in studies of the effects of resistance mutations in this region. These studies reveal another potential mechanism of epitope masking, where conserved, sensitive surfaces on the Env MPER are hidden through self-associations and only transiently exposed to the immune system, either though rapid dynamic equilibria or induced conformational changes.

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