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Poster presentation

P19-23. Putative prefusion mechanism of HIV-1 Env revealed by ligand-induced quaternary alterations in o-gp140 trimers

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Background

The human immunodeficiency virus envelope spike is the key mediator of membrane fusion with the host cell and is a promising research target for vaccine development. The surface spike gp120 and the transmembrane protein gp41 result from cleavage of immature cytosolic gp160 and are expressed as trimers. Conformational rearrangement upon binding of gp120 to host CD4 receptors and chemokine coreceptors mediates membrane fusion, exposes the fusion peptide of gp41 and enables viral genome insertion.

Methods

This project aims to elucidate the quaternary arrangement of the soluble Env construct gp140 in both its unbound and CD4-bound states by single particle reconstruction, which generates 3D density maps from cryoelectron microscopy images. The CD4-bound conformation was elicited by conjugation of gp140 with a synthetic CD4-mimicking minipeptide. We used a predicted structure of the missing, disordered N-terminus of the SIV gp120 X-ray coordinates.

Results

Our observations suggest a mechanism of prefusion peptide exposure for subsequent membrane fusion. First, an outward density shift of gp120 upon CD4 binding diminishes gp120-gp41 interactions to facilitate fusion peptide exposure, while rotation of individual gp120 subunits allows optimal exposure of the elicited coreceptor epitope. CD4-binding-induced trimer flattening is observed in the binary complex, juxtaposing the fusion peptide with the host membrane. Density attributed to gp41 bundle decreases considerably in length, suggesting that the gp41 conformational change to a prefusion intermediate occurs at this point. Rigid-body docking of gp120 and gp41 coordinates into the two density maps resulted in close fitting. The gp120 modelled in the density map has the missing N- and C-termini and V1/V2 loops, filling the currently void density, oriented towards gp41 at the threefold axis.

Conclusion

Structural insights gleaned from these studies should greatly aid development of neutralizing antibodies against exposed conformational epitopes. Additionally, precise dimensions of epitope locations presented here can aid rational design of synthetic multivalent compounds.