

Poster presentation

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P12-04. Topology of the C-terminal tail of HIV-1 gp41: Differential exposure of the Kennedy epitope on cell and viral membranes

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Background

The HIV-1 envelope (Env) transmembrane protein, gp41, is typically considered a type I membrane protein with an extracellular N-terminus, a single membrane spanning domain, and a C-terminus forming a ~150 residue intracytoplasmic tail. However, published studies have indicated an alternative or dynamic topology for portions of the C-terminal tail (CTT) that results in exposure of specific CTT segments on the membrane surface.

Methods

To distinguish between these alternative CTT models, we evaluated the accessibility of a reference CTT sequence, the "Kennedy epitope" (KE), in viral and cellular membranes to map CTT topology relative to the lipid bilayer. Specifically, KE accessibility in cell-associated Env was defined by reactivity of native or VSV-G epitope-tagged KE to specific monoclonal antibodies (MAbs), measured by FACS of intact cells. In parallel, KE exposure in virion-associated Env was characterized by MAb binding to intact virions as measured in immunoprecipitation or surface plasmon resonance (SPR/Biacore) assays.

Results

Results of FACS analyses of live cell-associated Env indicated significant reactivity of the KE with MAbs to native or VSV-G epitope-tagged KE. Additionally, no antibody reactivity was observed in cells expressing Env with the VSV-G epitope substituted into the LLP2 segment. In contrast to cellular Env, KE in the context of virions failed to react with MAbs directed to the native KE sequence, as measured both by immunoprecipitation and Biacore

assays. However, MAbs specific for the gp41 MPER segment bound virions in both assays.

Conclusion

Taken together, the results of these accessibility assays indicate that the KE sequences of gp41 are accessible to antibody binding in cell surface-expressed Env, but not accessible to antibody binding in virion-associated Env. These observations suggest that the CTT may assume distinct topologies (reflected in KE exposure) that depend on the membrane environment (viral/cellular) and that parts of the CTT may be (transiently) exposed on the membrane surface.