Effective reconstitution of HIV-1 gp41 transmembrane-domain derived peptides displaying the neutralizing MPER epitope on the surface of lipid bilayers

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The envelope glycoprotein (Env) gp41 subunit plays a pivotal role in HIV-1 entry by promoting the merger of the host cell and virus membranes. Although recently reported structural data help to elucidate the mechanistic basis of gp41 ectodomain functioning during the process, much less is known on the organization and functional roles of the following membrane-proximal external region (MPER) and the transmembrane domain (TMD). However, it is known that the MPER-TMD connecting segment harbors a conserved sequence targeted by the broadly neutralizing antibodies 4E10 and 10E8 pointing out to an active role of these region in the fusion process. Here, based on previous examination of a series of C-terminal-truncation mutants (Yue et al. (2009) J. Virol. 83, 11588), we report attempts to reconstitute the MPER-TMD segment in lipid bilayers with a phospholipid to cholesterol molar ratio similar to that of the viral membrane. We have used two different peptides to represent the MPER-TMD segment, namely, MPER-TMD1 and MPER-TMD2, spanning Env gp41 residues 671-700 and 671-709, respectively, which would act as platforms to expose the 4E10/10E8 MPER epitopes at membrane surfaces. Infrared spectroscopy (IR) measurements demonstrated the efficient reconstitution of the MPER-TMD1 sequence as a predominant a-helix in membranes while MPER-TMD2 retained a significant fraction of unfolded-aggregated structures. Moreover, as evidenced from antigenicity and immunogenicity assays, and supported by Molecular Dynamics Simulations, MPER-TMD1 bearing vesicles, but not MPER-TMD2 bearing ones, effectively exposed the MPER C-terminal stretch, harboring the 4E10/10E8 MPER epitopes, on the surface of cholesterol-enriched membranes. These findings provide new clues for the design and development of peptide-liposome vaccines targeting the MPER vulnerability site on Env.