MAR11-2010-002273

Abstract for an Invited Paper
for the MAR11 Meeting of
the American Physical Society

Deconstruction of biophysical function in the HIV fusion peptide[1]

DENNIS BONG, The Ohio State University

We have synthesized a library of variants of the 23-residue fusion peptide domain found at the N-terminus of gp-41 glycoprotein of HIV. This sequence is critical for viral infectivity and is thought to be central in the membrane fusion of viral envelope with the host endosomal membrane. There has been extensive discussion in the literature regarding the mechanism by which this viral fusion sequence initiates membrane fusion, with importance placed on glycine-content, particular oligomeric states and secondary structure; both helical and sheet structures have been proposed to be the active fusogenic structure. Our library was designed to address the biophysical importance of secondary structure, peptide flexibility, glycine content and location as well as the nature of the membrane anchor. Each member of this library also bears a positively charged hexapeptide at the C-terminus for solubility and to facilitate binding to negatively charged membranes. We assayed each peptide for its ability to induce lipid-mixing and lysis in both large and giant unilamellar vesicles, and searched for correlations between aggregated peptides and heightened activity. We find that the information encoded in the viral fusion peptide required for may be greatly simplified: glycine is not required for fusion, aggregation is not correlated with activity, and any peptide within a window of hydrophobicity can be an effective fusion catalyst. Given the wide range of sequences which may be effective in catalyzing vesicle membrane fusion, it appears highly unlikely that a particular stably folded secondary structure is important for fusion. Rather, our data show that many flexible, linear, minimally hydrophobic peptides may achieve the biophysical function of fusion.

[1]This research was supported in part by an NSF-CAREER award to D.B.