Intrinsically Disordered Proteins share a common molecular mechanism in membranes damages: the lipid-chaperone hypothesis.

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Researchers over the past thirty years have highlighted the role played by a class of small proteins that form pathogenic amyloid aggregates in vivo include the amyloid Aβ peptide (Alzheimer's disease), α-synuclein (Parkinson's disease), and IAPP, (type 2 diabetes). These proteins called also intrinsically disordered proteins (IDPs) are present as highly dynamic ensembles characterized by significantly variable atom positions over time. An increasing number of reports linking the toxicity of amyloid proteins with their membrane rupture integrity, but there is a lack of molecular detail on how IDPs transfer from the aqueous environment to the bilayer. Three major membrane damage models have been proposed: a) generation of stable transmembrane protein pores (oligomer hypothesis); b) membrane destabilization via a "carpet model" or c) removal of lipid components from the bilayer by a detergent-like mechanism (amyloid hypothesis) and the inflammation/oxidative stress hypothesis. Whether these three models are mutually exclusive or if and how they cooperate in triggering membrane damage remains unknown. Biophysical studies have addressed this issue by using Large Unilamellar Vesicles (LUVs) as the simplest lipid assembly mimicking the cell membrane. Chemical equilibrium between monodispersed lipids and their self-assemblies (LUVs) is always established and is characterized by a critical micellar concentration (CMC). Recently, some of us have developed a phenomenological model simulating the transfer kinetics of a lipid-protein complex from water to the bilayer-lipid-phase. According to this model, water-soluble lipid-protein complexes may insert into the membrane wall provided the hydrophobicity of the lipid-protein complexes is higher than that of the bare protein. Experiments on hIAPP supported this hypothesis, demonstrating the key role played by free lipids in driving membrane poration mechanisms and fibril formation. Here, we tested the generality of lipid-assisted amyloid penetration into the membrane by other amyloidogenic proteins including Aβ peptide and α-synuclein. Besides, we study rat-amylin and β-synuclein, non-amyloidogenic proteins as control. Molecular Dynamics simulations, Fluorescence, circular dichroism, isothermal calorimetry, and 2D NMR measurements were carried out to support this model. From our data and literature reports, we do a new hypothesis, called ***lipid-chaperon hypothesis***, able to explain toxicity/membrane damage of IDPs.