Title:	AMYLOIDOGENIC INTRINSICALLY DISORDERED PROTEINS: CONFORMATIONAL PLASTICITY, MEMBRANE BINDING AND AGGREGATION
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Abstract:	Natively unfolded or intrinsically disordered proteins (IDPs) possess astonishing conformational plasticity that allows them to adopt a wide range of structures. My work involves the study of two amyloidogenic IDPs, namely □-synuclein and tau, aggregation of which are involved in Parkinson's and Alzheimer's diseases, respectively. □-synuclein adopts a helical structure upon binding to the membranes. However, the high-resolution structural and dynamical insights of the membrane bound □-synuclein remain elusive. We took the advantage of the fact that □-synuclein does not have any tryptophan and incorporated single Trp mutant along the polypeptide chain. These Trp mutants of the □- synuclein have been used as a crucial scout. The fluorescence anisotropy map illuminates the structural rigidification of various regions of the polypeptide chain mediated by membrane binding-induced folding. In order to obtain the depth-profile of different segments of α-synuclein from the membrane surface, we utilized a unique and reliable indicator, such as red-edge excitation shift (REES), which is utilized to monitor the dynamics of restricted water molecules at the membrane-water interface.1,2 The membrane-water interface comprises of ~ 15 Å thick water layers having strongly bound (restrained) water (also known as biological water) and has been hypothesized to play a pivotal role in a variety of crucial biomolecular processes. In order to achieve the distance profile between the membrane surface and the protein residues, we have used fluorescence resonance energy transfer (FRET) experiments between fluorescently labeled membrane and Trp locations of □-synuclein. Taking together all the results from these fluorescence readouts, we have proposed a model that elucidates the precise conformation of the □-synuclein protein on the negatively charged membrane. Additionally, we have also investigated the influence of □-synuclein in the amyloid aggregation of tau protein that is implicated in human neurodegenerative disorders.
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