Title:	Structural and Dynamical Insights into the Membrane-Bound α-Synuclein
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Abstract:	Membrane-induced disorder-to-helix transition of α-synuclein, a presynaptic protein, has been implicated in a number of important neuronal functions as well as in the etiology of Parkinson's disease. In order to obtain structural insights of membrane-bound α-synuclein at the residue-specific resolution, we took advantage of the fact that the protein is devoid of tryptophan and incorporated single tryptophan at various residue positions along the sequence. These tryptophans were used as site-specific markers to characterize the structural and dynamical aspects of α-synuclein on the negatively charged small unilamellar lipid vesicles. An array of site-specific fluorescence readouts, such as the spectral-shift, quenching efficiency and anisotropy, allowed us to discern various features of the conformational rearrangements occurring at different locations of α-synuclein on the lipid membrane. In order to define the spatial localization of various regions of the protein near the membrane surface, we utilized a unique and sensitive indicator, namely, red-edge excitation shift (REES), which originates when a fluorophore is located in a highly ordered micro-environment. The extent of REES observed at different residue positions allowed us to directly identify the residues that are localized at the membrane-water interface comprising a thin (~ 15 Å) layer of motionally restrained water molecules and enabled us to construct a dynamic hydration map of the protein. The combination of site-specific fluorescence readouts allowed us to unravel the intriguing molecular details of α-synuclein on the lipid membrane in a direct model-free fashion. Additionally, the combination of methodologies described here are capable of distinguishing subtle but important structural alterations of α-synuclein bound to different negatively charged lipids with varied head-group chemistry. We believe that the structural modulations of α-synuclein on the membrane could potentially be related to its physiological functions as well as to the onset of Parkinson's diseases.
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