Title:	Energy migration captures membrane-induced oligomerization of the prion protein
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Abstract:	Excitation energy migration via homo-Förster resonance energy transfer (homo-FRET) can serve as an intermolecular proximity ruler within complex biomolecular assemblies. Here we present a unique case to demonstrate that energy migration can be a novel and sensitive readout to capture the membrane-mediated misfolding and oligomerization of the human prion protein (PrP), which is known to undergo an aberrant conformational conversion from an α-helical form into a self-propagating aggregated β-rich state causing deadly transmissible neurodegenerative diseases. Using site-specific energy migration studies by monitoring steady-state and time-resolved fluorescence anisotropy of fluorescently-tagged PrP, we elucidate the molecular details of lipid membrane-induced oligomers. We show that the intrinsically disordered N-terminal segment is critical for lipid-induced conformational sequestration of PrP into higher-order, β-rich oligomeric species that exhibit membrane permeabilization. Our results revealed that the N-terminal regions constitute the central core of the oligomeric architecture, whereas the distal C-terminal ends participate in peripheral association with the lipid membrane. Our study will find applications in the sensitive detection and in the structural characterization of membrane-induced protein misfolding and aggregation in a variety of deadly amyloid diseases.
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