**Structural basis of membrane disruption and cellular toxicity by α-synuclein oligomers**

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**Abstract**

Oligomeric species populated during the aggregation process of α-synuclein have been linked to neuronal impairment in Parkinson’s disease and related neurodegenerative disorders. By using solution and solid-state nuclear magnetic resonance techniques in conjunction with other structural methods, we identified the fundamental characteristics that enable toxic α-synuclein oligomers to perturb biological membranes and disrupt cellular function; these include a highly lipophilic element that promotes strong membrane interactions and a structured region that inserts into lipid bilayers and disrupts their integrity. In support of these conclusions, mutations that target the region that promotes strong membrane interactions by α-synuclein oligomers suppressed their toxicity in neuroblastoma cells and primary cortical neurons.