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# Biophysics of α-Synuclein interaction with membranes

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## Abstract

**Introduction:** One of membrane proteins is the intrinsically disordered and amyloidogenic protein, α-synuclein (αS), which is involved in Parkinson's disease (PD) etiology. Although the exact function of αS is still unclear, substantial evidence now exists to suggest that αS interacts directly with lipids and membranes both physiologically as well as pathologically. The nature of the interaction of αS with biological and artificial membranes is complex and dependent on the phospholipid composition of the membranes, the size of the vesicles as well as the ratio of membrane lipids to protein.

**Methods:** Alpha synuclein protein, was considered for our study. Different methods such as fluorescence anisotropy, $^{19}F$ nuclear magnetic resonance, circular dichroism, atomic-force microscopy as well as dynamic light scattering were used to study the interaction between αS and lipid bilayer and vesicles that mimic the plasma and mitochondrial membranes.

**Results and discussion:** Lipid binding by αS can be associated with enhanced fibrillogenicity by promoting the formation of aggregates at the membrane surface. In the presence of lipid molecules and detergents, αS adopts an α-helical secondary structure and the aggregation rate of αS was found to increase several-fold. The protein binds to unilamellar phospholipid vesicles containing acidic phospholipids, but not to vesicles with a net neutral charge and this protein associates preferentially with vesicles of smaller diameter as opposed to larger vesicles. The middle of the N-terminal region of αS, which contains the KAKEGVVAAAE repeats, is involved in binding, probably via electrostatic interactions between the lysines and cardiolipin. Increasing the temperature increases the binding of wild-type, but not the A30P variant of αS.

**Conclusion:** The nature of αS binding to phospholipid membranes is intimately tied to the lipids physico-chemical properties. These results reveal the key role that membrane interactions can have in triggering conversion of αS from its soluble state to the aggregated state that is associated with neurodegeneration and to its associated disease states.

**Keywords:** α-Synuclein, Lipid vesicles, Model membranes, Parkinson's disease.

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