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Microfluidic methods for α-synuclein - lipid interactions

Content

We propose to expand on current approaches for the study of the initial steps in Parkinson's Disease (PD) progression in a systematic manner, in order to explore fundamental mechanisms of self-association processes and protein aggregation in the context of lipid membranes, which represents one of the central themes in current neurodegenerative conditions studies. Low molecular weight oligomers of protein α-synuclein (αSyn) have recently been found to be the main neurotoxic agents in PD. αSyn-lipid co-aggregates are found in PD-associated Lewy bodies, indicating that membranes play a key role in αSyn-associated toxicity in PD, yet the specific mechanism governing the interaction between αSyn oligomers and lipid membranes is still not fully elucidated. We propose a set of biophysical microfluidic methods to study binding of both monomers and oligomers towards model Small and Large Unilamellar Vesicles (SUVs and LUVs). Through in solution measurements of sizes of molecular complexes, we determine binding affinities and find that oligomers have generally higher affinity towards negatively charged lipid bilayers in comparison to monomers. Distinct mechanism of monomers binding towards DOPS LUVs was also found, suggesting membrane aggregation events induced by monomeric αSyn. In addition, we measure the electrophoretic mobilities to obtain zeta-potential values of protein/lipid complexes and show that α-synuclein bound to negatively charged vesicles effectively reduces the overall charge of the complex. Further understanding of α-Syn interactions with lipid surfaces is brought by the employment of microdroplets as distinct compartments for following of the aggregation of protein. Using arrays of droplets provides and alternative to bulk experiments and allows for quiescent conditions, long-term observation of aggregating protein exposed to various surfaces, including lipid membranes.

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