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α-Synuclein (α-Syn) aggregation and amyloid formation is associated with Parkinson's disease (PD) pathogenesis. It was established that α-Syn aggregation occurs through nucleation dependent polymerization mechanism. Moreover, it is demonstrated that early nucleation event and soluble oligomer formed in early nucleation are responsible for dopaminergic neuronal cell death in PD. However, how highly soluble unstructured protein like α-Syn undergoes nucleation for amyloid aggregation is largely unknown. We recently demonstrated that α-Syn undergoes liquid-liquid phase separation (LLPS) (similar to oil droplet in water) in the cytoplasmic crowded milleu (*Ray et al Nature chemistry, 2020*). We also showed that after liquid droplet formation, high local concentration subsequently promotes liquid to solid phase transition of liquid droplet where amyloid fibrils nucleate from the solid-like droplet (*Ray et al Nature chemistry, 2020*). Not only the mechanism but we also established different domain responsible for liquid droplet formation and solid-like transition (*Ray et al. Nature chemistry, 2020*). Moreover, we showed how different environmental conditions like disease associated familial mutations, post translational modifications, acidic pH (lysosomic pH) can aggravate α-Syn LLPS and subsequent solid-like transition (*Sawner et al. Biochemistry, 2021, Mukherjee et al. Journal of Molecular Biology, 2022*). Our data strongly supports that small molecule and chaperones can target LLPS and can have high beneficial role in PD and other neurological disorders.

References:

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