



भारतीय प्रौद्योगिकी संस्थान मुंबई

पबई, मुंबई - 400 076, भारत

Indian Institute of Technology Bombay

Powai, Mumbai - 400 076, India

दूरभाष/Phone : (+91-22) 2572 2545

फैक्स/Fax : (+91-22) 2572 3480

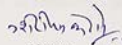
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α -Synuclein (α -Syn) aggregation and amyloid formation are associated with Parkinson's disease (PD) pathogenesis. It was established that α -Syn aggregation occurs through a nucleation-dependent polymerization mechanism. Moreover, it is demonstrated that early nucleation events and soluble oligomers formed in early nucleation are responsible for dopaminergic neuronal cell death in PD. However, how highly soluble unstructured proteins like α -Syn undergo nucleation for amyloid aggregation is largely unknown. We recently demonstrated that α -Syn undergoes liquid-liquid phase separation (LLPS) (similar to oil droplets in water) in the cytoplasmic crowded milieu (Ray et al. *Nature Chemistry*, 2020). We also showed that after liquid droplet formation, high local concentration promotes liquid to solid phase transition of liquid droplets where amyloid fibrils nucleate from the solid-like droplet (Ray et al. *Nature chemistry*, 2020). Not only the mechanism but also established different domains 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, and acidic pH (lysosome pH) can aggravate α -Syn LLPS and subsequent solid-like transition (Sawner et al. *Biochemistry*, 2021). Our data strongly supports that small molecules and chaperones can target LLPS and have a highly beneficial role in PD and other neurological disorders. Previously, it was known that LLPS mainly occurs through non-specific weak interactions by intrinsically disordered proteins (IDP)/or domains. We hypothesize that globular proteins can also phase-separate and propose that proteins/polypeptides, irrespective of their sequence and structure, can phase-separate in a crowded milieu. This changes the notion in the field that cells might be actively promoting or inhibiting phase separation for cellular fitness (Paudyal et al., *Nature Communication*, 2023)

References:

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2. Paudyal et al., Intermolecular interactions underlie protein/peptide phase separation irrespective of sequence and structure at crowded milieu. *Nature Communication*. 2023.
3. Sawner AS, Ray S, Yadav P, Mukherjee S, Panigrahi R, Poudyal M, et al. Modulating α -Synuclein Liquid-Liquid Phase Separation. *Biochemistry*. 2021;60(48):3676–96.



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(IIT Bombay)