A Deep Dive into Biomolecular Condensates formed via Liquid-Liquid Phase Separation of Intrinsically Disordered Proteins

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Liquid-liquid phase separation (LLPS) of intrinsically disordered proteins/regions (IDPs/IDRs) into intracellular biomolecular condensates is involved in critical cellular functions. However, aberrant phase transitions are associated with debilitating neurodegenerative diseases. We discovered that the prion protein (PrP) can undergo LLPS via weak, multivalent, transient intermolecular interactions between the N-terminal IDR that resembles a yeast prion-like domain comprising five glycine-rich octapeptide repeats and a hydrophobic segment. An intriguing disease-associated amber stop codon mutation (Y145Stop) of PrP yields a C-terminally truncated intrinsically disordered fragment that is associated with Gerstmann-Sträussler-Scheinker syndrome and familial cerebral amyloid angiopathy. We demonstrated that Y145Stop spontaneously phase-separates into highly dynamic liquid droplets under physiological conditions (1). Our bioinformatic, spectroscopic, microscopic, and mutational studies coupled with single-droplet vibrational Raman spectroscopy revealed highly dynamic internal organization within condensates and illuminated the critical molecular drivers of LLPS of Y145Stop. Upon aging, these highly dynamic liquid droplets undergo a liquid-to-solid phase transition into highly ordered, beta-rich, amyloid aggregates that exhibit a characteristic autocatalytic self-templating behavior. Therefore, LLPS-mediated amyloid formation can potentially represent a noncanonical phase transition pathway to self-replicating prions. The propensity for the aberrant phase transition is much lower for the full-length PrP indicating an evolutionarily conserved role of the folded C-terminal domain (1,2). Our recent results also showed intriguing spatiotemporal modulations in complex coacervation of PrP with other neuronal IDPs into heterotypic, multi-component, multi-phasic, multi-layered condensates in the presence of RNA. These multi-component condensates can act as reaction crucibles to catalyze the amyloid conversion of these functional assemblies into pathological aggregates associated with overlapping neuropathological features (3). I will describe our work on the characterization of biomolecular condensates using ultrasensitive surface-enhanced Raman scattering (4). I will also discuss our recent findings on the contribution of Ramachandran dihedral dynamics in controlling the internal friction of IDPs that govern their phase behavior (5).

References

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