Biological Phase Transitions: Where Chemistry and Physics Meet Biology

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Cells contain membrane-enclosed organelles that compartmentalize cellular constituents and regulate biochemical processes. A growing body of exciting research now reveals that there is also an alternative mechanism of spatiotemporally-controlled intracellular compartmentalization and organization through biomolecular condensate formation via macromolecular phase separation of proteins and nucleic acids into noncanonical membraneless organelles with emergent material properties. These functional liquid-like biomolecular condensates can undergo aberrant irreversible phase transitions into gel-like or solid-like amyloid aggregates associated with a range of debilitating human diseases [1,2]. Our longstanding interest in prion biology led us to discover that the prion protein (PrP) (well-known for its association with mad cow disease and Creutzfeldt-Jakob disease) can undergo phase separation via weak, multivalent, transient intermolecular interactions between the N-terminal domain. An intriguing disease-associated amber stop codon mutation (Y145Stop) of PrP yields a C-terminally truncated intrinsically disordered fragment. We demonstrated that this fragment spontaneously phase-separates into highly dynamic liquid droplets under physiological conditions [3]. Upon aging, these liquid droplets undergo a liquid-to-solid phase transition into highly ordered, β-rich, amyloid-like aggregates that exhibit a characteristic autocatalytic self-templating behavior. 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. Our recent results also showed intriguing spatiotemporal modulations in complex coacervation of PrP with other neuronal intrinsically disordered proteins into heterotypic, multi-component, multiphasic, multilayered condensates in the presence of RNA [4,5]. I will also discuss our surface-enhanced Raman scattering (SERS), single-molecule FRET (Förster resonance energy transfer), and homoFRET studies that capture exquisite molecular details of in-vitro-reconstituted biomolecular condensates and cellular stress granules derived from neuronal RNA-binding proteins that are associated with Amyotrophic Lateral Sclerosis [6-8].

1. Mukhopadhyay *Nature Chemistry* (News & Views) (2021) 13, 1028-1030. **2.** Dogra et al. *J. Am. Chem. Soc.* (2019) 141, 20380-20389. **3.** Agarwal et al. *Proc. Natl. Acad. Sci.* (2021) 118, 45, e2100968118. **4.** Agarwal et al. *Nature Communications* (2022) 13, 1154. **5.** Rai et al. *Proc. Natl. Acad. Sci.* (2023) 120, e2216338120. **6.** Avni et al. *Nature Communications* (2022) 13, 4378. **7.** Joshi et al. *Nature Communications* (2023) 14, 7331. **8.** Joshi et al. *bioRxiv* (2024).