Prevention of Intrinsically Disordered Protein Aggregation with Solvent Tuning: Unraveling the Role of Water in Condensate Aging

In cells protein aggregation is facilitated by compartmentalization, in which intrinsically disordered proteins are sequestered into membrane-less biomolecular condensates. Condensates are liquid-like in nature and undergo aging to a fibril solid state, implying that the water solvent participates in regulating protein assembly. Coupling of water molecules to protein surfaces creates an interfacial population of water with distinct properties, hydration water. **Hydration water directs the structure and function of proteins, but how it regulates emergent properties of biomolecular condensates, such as aging, is still poorly understood.**

Using Terahertz (THz) spectroscopy, we were recently able to demonstrate for the first time the correlation between IDP hydration water and bimolecular condensate formation. Condensates composed of the IDP FUS (Fused in sarcoma) show spectral features (Fig. 1) corresponding to a loss of water solvating hydrophobic groups and increased tetrahedral coordination of water molecules remaining in the liquid-like droplet. **Two concerted molecular driving forces for biomolecular condensates were revealed: entropically favorable release of less favorable hydration water (protein-water interactions), and the enthalpically favorable cation-π interaction (protein-protein interaction).** This laid the foundation for understanding solvation in biomolecular condensates and emphasizes the necessity of establishing the connection between hydration water properties and IDP properties within biomolecular condensates.

This PhD project aims to determine the fundamental correlation between solvent and protein dynamics in condensates. We will probe solvent properties in biomolecular condensates to reveal how they affect the aging process, how hydration water promotes protein aggregation, and how solvent conditions impact condensate aging.

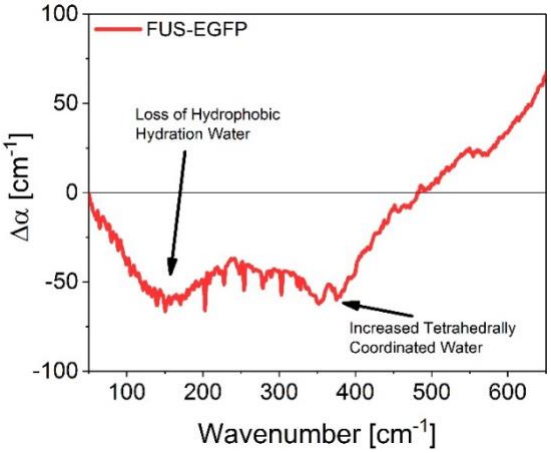

Fig. 1. Entropic release of hydration water drives biomolecular condensate formation*. Terahertz difference spectra of FUS-EGFP condensates. Two distinct negative spectral features are observed.*

References

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