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Molecular mechanisms underlying phase separation in functional compartmentalization and disease

Biomolecular condensates coordinate a variety of important functions in cells including stress responses, RNA metabolism and membrane receptor clustering. Here, I will focus on discussing our work on two systems: the RNA-binding protein hnRNPA1 that associates with stress granules and mutations in which drive familial forms of neurodegenerative diseases; and the tumor suppressor SPOP, a substrate adaptor of a ubiquitin ligase which targets substrates in biomolecular condensates and mutations in which lead to a variety of solid tumors. I will use our work on these systems to address the following questions:

(1) Which interactions mediate LLPS and can we device protocols to identify them in an unbiased manner?

(2) If we know the interaction strengths of adhesive elements in proteins, can we develop models to predict their full phase behavior?

(3) Is phase separation required for function or can smaller complexes mediate function? Our results are transferable to other phase-separating proteins and provide mechanistic insights into the contributions of structured and disordered domains to phase separation, enzymatic activity inside liquid organelles, and disruption of phase separation by disease mutations.

Host: Henning Urlaub



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