Liquid-Liquid Phase Separation in Biology:
Protein interactions, Function and Disease Implications
by Tanja Mittag

Liquid-liquid phase separation drives the formation of dozens of biomolecular condensates in cells. Phase separation is mediated by multivalent interactions, and these can be encoded via domain-motif systems or as homotypic interactions in intrinsically disordered protein regions (IDRs). While multivalent domain-motif systems are fairly well understood thanks to our knowledge of the structural basis of these interactions, our understanding of phase separation of IDRs is immature. I will discuss our work towards the unbiased identification of adhesive motifs, so-called “stickers”, in IDRs and the determination of their pairwise interaction strengths. We find that the valence and patterning of stickers determines the phase behavior of IDRs (1). They therefore behave conceptually similarly to domain-motif systems. I will discuss different protein architectures that encode multivalency and how this affects the material properties of assemblies (2, 3). The sensitivity of proteins for phase separation can be modulated by external signals via post-translational modifications, and I will briefly discuss insights into the structural basis for such mechanisms (4).

Martin EW[#], Holehouse AS[#], Peran I[#], Farag M, Incicco JJ, Bremer A, Grace CR, Soranno A, Pappu RV*, **Mittag T***. Valence and patterning of aromatic residues determine the phase behavior of disordered prion-like domains, ***Science*** 367: 694-699, 2020.

Bouchard JJ, Otero JH, Scott DC, Szulc EM, Martin EW, Sabri N, Granata D, Marzahn MR, Lindorff-Larsen K, Salvatella X, Schulman BA, **Mittag T**. Cancer mutations of the tumor suppressor SPOP disrupt the formation of active, phase-separated compartments. ***Mol Cell*** 27: 19-36, 2018. PMC6179159

J.D. Schmit*, J.J. Bouchard, E.W. Martin, **T. Mittag**. (2020) Protein network structure enables switching between liquid and gel states. ***JACS*** 142 (2): 874-883. PMID: 31845799

Yang P, Mathieu C, Kolaitis RM, Zhang P, Messing J, Yurtsever U, Yang Z, Wu J, Li Y, Pan Q, Yu J, Martin EW, **Mittag T**, Kim HJ, Taylor JP. G3BP1 is a tunable switch that triggers phase separation to assemble stress granules, ***Cell*** 181, 325-345, 2020.