Driving forces for phase separation, material properties and aging processes of condensates

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Stress granules (SGs) are biomolecular condensates that form in response to cellular stress. A plethora of genetic, cell biological and histopathological evidence have implicated SGs in the pathogenesis of neurodegenerative and neuromuscular disorders collectively known as multisystem proteinopathy (MSP), including amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD). Together, the combined evidence suggests that prolonged stress granule assembly promotes disease, and that mutations in RNA-binding proteins that favor fibril formation can short-circuit this process. Aging of stress granules, including fibril formation from condensates as well as dynamical arrest, have been proposed as mechanisms driving pathogenesis. Hence, SGs are widely viewed as crucibles or birthplaces of neurodegenerative diseases. Other evidence suggest that they could slow down fibril formation of disease relevant proteins such as TDP-43. Here, we will describe our recent work on understanding the driving forces for phase separation of proteins[1], how protein sequences encode material properties and timescales of condensate aging[2]. We will further tackle the mechanism of fibril formation from condensates with implications for our understanding of neurodegenerative diseases[3] .

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[2] I. Alshareedah#, W.M. Borcherds#, S.R. Cohen#, A. Singh, A.E. Posey, M. Farag, A. Bremer, G.W. Strout, D.T. Tomares, R.V. Pappu*, T. Mittag*, P.R. Banerjee*. Sequence-specific interactions determine viscoelasticity and aging dynamics of protein condensates. *Nature Physics*, in press. *bioRxiv* (2023)

[3] T. Das, F. Zaidi, M. Farag, K.M. Ruff, J. Messing, J.P. Taylor, R.V. Pappu*, T. Mittag*. Metastable condensates suppress conversion to amyloid fibrils. *bioRxiv* (2024)