GÖTEBORGS UNIVERSITET

Functional roles of protein phase separated assemblies in cellular stress response and proteinopathies

Michelle Lindström
Institutionen för kemi och molekylärbiologi
Naturvetenskapliga fakulteten

Akademisk avhandling för filosofie doktorsexamen i Naturvetenskap med inriktning biologi, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras fredagen den 9de december 2022 kl. 13:15 i sal 2118, Hus 2, HVB, Sahlgrenska Akademin, Arvid Wallgrens backe, Göteborg.

ISBN 978-91-8069-063-8 (PRINT)
ISBN 978-91-8069-064-5 (PDF)

GÖTEBORGS UNIVERSITET

ABSTRACT

For a long time, pertinent biological conundrums, such as the organization and compartmentalization of the cytoplasm and nucleoplasm, perplexed the scientific community. The organization of the complex biochemistry in an accurate space and time manner could not be explained without the enclosure of a membrane. In recent years, many of the processes relating to membraneless cellular organization and cytoplasmic regulation have become illuminated by the incorporation of liquid-liquid phase separation (LLPS) into biology. Phase separation entails a process by which a homogenous liquid solution of macromolecules, such as proteins or nucleic acids, separates into two distinct co-existing phases, a dense and dilute phase. LLPS thereby enables a spatiotemporal control over complex biochemical reactions, a vital process for cellular functions. Altered phase separation dynamics can lead to aberrant condensate assemblies that mature into a more solid-like state and are associated with disease. The list of cell compartments and biological processes thought to be formed and regulated through the process of phase separation has grown at a fast pace and includes a plethora of cellular functions, such as stress granule (SG) formation and disease associated protein aggregation. However, the mechanisms regulating the formation, and subsequent impact, of these phase-separated assemblies still remain elusive.

In this thesis, regulation of SG formation is explored using genome-wide phenomic screening. The results show a signaling cascade involving e.g. long-chain-base sphingolipids and ubiquitin, regulating the phase separation behavior of Lsm7 and further SG induction. Cellular consequences of cytotoxic aggregation of the ALS-associated disease protein FUS (fused in sarcoma) are also explored. A cytotoxic gain-of-function involving protein sequestration, resulting in delayed cell cycle progression, is identified. Overall, our findings elucidate the underlying mechanisms and cellular impacts of phase separated assemblies in health and disease.

Keywords: phase separation, LLPS, stress granules, Lsm7, FUS, Ccr4