Title

Modeling aberrant protein phase transitions during stress and aging in *C. elegans*

Hosting team

Protein Homeostasis in Development and Aging (Department of Cell Biology, Ambre Sala)

Project summary

Our group is interested in protein homeostasis (proteostasis) which corresponds to the capacity of cells and organisms to maintain the integrity of their proteome. This relies on an extensive network of conserved cellular machineries that includes molecular chaperones and degradation pathways that together prevent the accumulation of aberrant proteins. Failure of these systems during aging is a major driver of cellular dysfunction, and many age-related diseases are characterized by pathological protein misfolding and aggregation. Several proteins that are found in pathological aggregates can undergo liquid-liquid phase separation (LLPS) in physiological stress conditions, and it has been proposed that aberrant transition to a solid state underlies the protein aggregation observed in certain neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD).

The M2 project will take advantage of the short-lived *C. elegans* model system to investigate the influence of aging and proteostasis modulation on proteins that naturally undergo LLPS. For this, we will use a series of strains expressing fluorescently tagged proteins that are associated with disease and/or known components of stress granules. The subcellular localization and aggregation status of these proteins during stress and aging will be studied using confocal microscopy and fractionation assays. The second part of the project will involve manipulation of molecular chaperones and degradation machineries using genetics approaches to investigate how individual components contribute to the aggregation process. This work will provide insights into the mechanism of aggregation of phase separated proteins and pave the way for future studies to gain a mechanistic understanding of this pathological process.

References

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