Phase separation as a survival strategy: stress protection by translation factor condensates

Climate change is threatening the health and survival of many organisms. While most organisms can tolerate a wide range of temperatures, they typically have a narrow temperature window in which they thrive. However, environmental temperatures increasingly deviate from this optimal growth temperature, and small temperature deviations can significantly impair organismal fitness. Heat stress constitutes a significant threat to organismal fitness and **efficient and effective molecular mechanisms are required to ensure growth and survival** in the face of elevated temperature.

The formation of **biomolecular condensates** provides a novel way by which organisms sense and respond to changes in temperature. Condensates are large assemblies without membranes, which often form by the physical process of phase separation. The Alberti group has been at the forefront of the field of biomolecular condensates and has made significant contributions to understanding the role of condensates in stress responses. We recently showed that the yeast **translation factor Ded1p assembles into condensates** in response to heat stress and that this inactivates the helicase activity of Ded1p and **promotes a switch in translation from housekeeping to stress protein production**. The concept of protein condensation provides a novel way to think about how cells sense stress and mount an appropriate response for survival. Work so far has barely touched the surface of this novel principle and we have yet to learn of the contributions it can make to understanding stress responses and the evolution and ecology of organisms.

Recent evidence suggests that Ded1p interacts with the translation initiation complex eIF4F during translation initiation. Like for Ded1p, we have found that **eIF4F assembles into condensates in a heat-dependent manner**. We hypothesize that eIF4F inactivation by condensation promotes an additional switch in translation which serves to downregulate specific sets of mRNAs. The purpose of the work program is therefore to uncover the molecular events underlying the formation of heat-induced condensates by Ded1p and eIF4F and to pinpoint the adaptive functions that are associated with condensation. More specifically, we will 1) study the molecular events underlying heat-induced condensation, 2) determine critical amino acid motifs underlying thermal sensitivity and analyze how evolution has tuned protein condensation to different thermal environments, 3) study how condensate assembly and disassembly is regulated and how condensate dynamics and properties affect the stress response, and 4) establish the physiological function of translation factor condensates and determine how condensation promotes stress survival. We envisage that this research project will provide a **much-needed deeper understanding of temperature-regulated condensation**, thus providing a **template for temperature regulation of other fundamental cellular processes such as transcription and signaling**.

References

Alberti S, Hyman AA (2021). Biomolecular condensates at the nexus of cellular stress, protein aggregation disease and ageing. ***Nature Reviews Molecular Cellular Biology***, 22(3):196-213.

Iserman C, Desroches Altamirano C, …, Alberti S (2020). Condensation of Ded1p Promotes a Translational Switch from Housekeeping to Stress Protein Production. ***Cell***, 14;181(4):818-831.e19. doi: 10.1016/j.cell.2020.04.009.

Franzmann TM, Alberti S (2019). Protein Phase Separation as a Stress Survival Strategy. ***Cold Spring Harb Perspect Biol***, doi: 10.1101/cshperspect.a034058.