Targeted Project / AY 2023 -2024

Establishing a structure-function relationship between biomolecular condensates and protein degradation

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Department/Institute: Pharmacology

Research area: Biomolecular condensates, protein homeostasis, protein engineering

Project outline:

Liquid-liquid phase separation (LLPS) is an emerging phenomenon linked to biological processes including stress response, thermosensing and disease-related protein aggregation. By controlling the spatiotemporal organisation of intracellular components, cells can promote specific processes. This often involves the physical segregation by membranes; however, non-membrane enclosed, subcellular structures are formed and maintained by LLPS. These biomolecular condensates (BCs) act as specialised compartments possessing distinct properties, composition and functions, from the cytoplasm. The dynamics and physical attributes of BCs are linked with their biological roles. Stress-induced condensation and dissolution is a hallmark of stress granules, whereas the liquid-like to gel-like conversion of p62 bodies influences autophagic degradation. These tightly regulated processes depend on changes in the BC composition, specifically that of the non-scaffold components (ligands).

Determining how ligands affect phase boundaries within live cells is crucial for understanding how BC formation occurs in the right place and at the right time. LLPS is well-studied within polymer and colloidal sciences, but to truly understand its role in biological systems requires an interdisciplinary approach. We will utilise protein engineering, cell biology, biophysics and computational modelling to relate the BC's physico-chemical properties with their cellular function. Using BCs engineered with different structural attributes capable of targeting autophagy, we will characterise their structures in vitro and introduce them to cell models to link their underlying physico-chemical properties with efficient targeted degradation in cellulo. Understanding how Nature utilises LLPS for efficient protein degradation will provide strategies to control and drive the clearance of disease-associated proteins from the cell.

BBSRC DTP main strategic theme: Understanding the rules of life