Implication of derailed phase separation and molecular chaperones in the stress response and in age-related neurodegenerative diseases

In mammalian cells, proteins with intrinsically disordered regions trigger the formation of membrane-less organelles via a process known as liquid-liquid phase separation (LLPS). Examples of membrane-less organelles are cytoplasmic ribonucleoprotein granules, such as stress granules, nuclear bodies and nucleoli. Derailed LLPS is emerging as a pathomechanism that may contribute to several age-related neurodegenerative diseases. Here we report two examples of how derailed phase separation may contribute to these diseases. We also discuss how molecular chaperones, by avoiding irreversible phase transition and irreversible protein aggregation may regulate essential cellular functions, thereby maintaining protein and RNA homeostasis, as well as cell fitness. Stress granules (SGs) are ribonucleoprotein particles that assemble, via LLPS, when translation is inhibited. In amyotrophic lateral sclerosis and inclusion body myopathy, the SG components TDP-43, FUS, hnRNPA1 accumulate in the form of protein aggregates. We investigated the mechanisms that drive the conversion of physiological SGs into aggregates. We find that liquid-like SGs can sequester misfolded proteins, which promote the aberrant conversion of SGs into solid aggregates. We identify a specific protein quality control process that prevents the accumulation of misfolding-prone proteins in SGs and, by doing so, preserves SG dynamics. This quality control process is referred to as granulostasis, and relies on the action of the HSPB8-BAG3-HSP70 chaperone complex. Next, we report a novel property of HSPB2, a molecular chaperone that contains an IDR and is expressed in skeletal and cardiac muscle cells. We find that, in cells, HSPB2 phase separates to form nuclear assemblies that behave as liquid droplets. These HSPB2 nuclear droplets sequester lamin A and displace chromatin, with detrimental consequences for nuclear function and integrity. Importantly, aberrant phase separation of HSPB2 is negatively regulated by its partner HSPB3, but not by two HSPB3 mutations associated with myopathy. These results suggest that HSPB2 might participate in cellular reorganization during myoblast differentiation and that deregulation of this property might contribute to neuromuscular diseases.