Phase shifts in protein folding space: links to stress adaptation and disease

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Talks at the “Protein Folding, Misfolding and Neurodegeneration” Minisymposium gave new insights into protein misfolding, protein quality control, and how failure to control misfolded proteins may lead to disease. A newly emerging theme was the role of phase transitions in stress adaptation and disease.

Cytosolic pH changes in stress adaptation

Two talks focused on the role of cytosolic pH fluctuations in promoting stress adaptation in budding yeast. Acidification of the yeast cytoplasm was previously shown to be required for survival of starvation stress. However, whether the survival of other types of stresses also depends on cytosolic pH changes is unclear. Catherine Triantafillou (Drummond laboratory, University of Chicago) used a pH-sensitive variant of GFP and flow cytometry to quantify changes in cytosolic pH, addressing whether pH changes are required for survival of heat stress. She provided data showing that the cytosolic pH of yeast cells drops from 7.6 to less than 7.0 upon a relatively mild heat stress of 42°C. Preventing this cytosolic acidification with an ionophore led to an impairment of heat shock protein production and was associated with a significant fitness cost. These results suggest a more general role of cytosolic pH changes in stress adaptation. The molecular mechanism is still unclear, but previous work from the Drummond lab suggests that phase transitions of the RNA-binding protein Pab1 may be involved.

Simon Alberti (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany) continued on the theme of cytosolic pH and stress adaptation. Although acidification of the yeast cytoplasm is known to be required for survival of starvation, the molecular mechanisms are still unclear. Alberti showed that the translation termination factor and prion protein Sup35 may play an important role. Upon starvation stress, Sup35 undergoes pH-dependent phase separation and gelation. Gelation requires the N-terminal prion domain of Sup35 and involves the highly charged middle domain, which acts as a pH sensor. Importantly, gelation of Sup35 was required for starvation survival, because yeast lacking the gelation domain showed a strong growth impairment during recovery from starvation. This result suggests that prion domains are stress sensors that protect proteins from damage and facilitate rapid adaptation in unstable environments through phase separation and gelation.

Molecular mechanisms of desiccation tolerance and biofilm formation

Other talks examined the molecular mechanisms underlying dormancy and bacterial biofilm formation. Thomas Boothby (Pielak laboratory, University of North Carolina, Chapel Hill) focused on the role of intrinsically disordered proteins in tardigrades, a group of animals that can survive extreme desiccation. Boothby showed that there are tardigrade-specific proteins that promote a phase transition of the cytoplasm into a glass-like state, which is essential for desiccation tolerance. Additional data were provided demonstrating that these proteins form gels in vitro and that gel formation protects models enzymes such as lactate dehydrogenase from damage. However, the detailed molecular mechanism of how these gels protect biomolecules from desiccation-induced damage remains to be worked out. Ursula Jakob (University of Michigan) described the many ways in which polyphosphate can regulate the folding and misfolding of proteins. She provided data showing that polyphosphate stabilizes unfolded proteins in an amyloid-like conformation and discussed the important role of polyphosphate in amyloid-related processes, ranging from bacterial biofilm formation to neurodegenerative diseases. The data provided suggest that polyphosphate is a widely conserved and highly abundant mechanism that regulates various amyloidogenic processes in cells.

Aberrant phase transitions and age-related diseases

Relatively recent data have implicated membrane-less compartments such as protein/RNA (RNP) granules in age-related neurodegenerative disease. It has been hypothesized that these RNP granules undergo an aberrant phase transition from a liquid to a solid-like state that causes disease. However, the molecular mechanisms underlying these aberrant phase transitions are still unclear. Leeanne McGurk (Bonini laboratory, University of Pennsylvania) investigated the role of TDP-43 in this process, which forms protein inclusions in patients afflicted with amyotrophic lateral sclerosis (ALS). The presented work suggests that failure to regulate TDP-43 interaction with polyADP ribose may be a key mechanism underlying the conversion of physiological RNP granules into a pathological state.

Richard Wheeler (Hyman laboratory, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany) presented exciting work on new chemical modulators of phase transitions in cells. Wheeler used imaging-based approaches to identify chemicals that affect the formation of stress granules in vivo. Aberrant stress granule formation is thought to be one of the early events associated with ALS. Some of the identified chemicals were also effective against aberrant phase transitions in vitro and prevented early ALS phenotypes such as axonal degeneration. This suggests that protein phase behavior is a druggable target and that modulating protein phase separation could be a novel route for the treatment of ALS and related diseases.

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