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Editorial

Introduction: Phase Separation

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Eukaryotic cells are comprised of a series of canonical membrane-delimited organelles, such as lysosomes, peroxisomes, nuclei, and mitochondria. However, there are also many membraneless organelles or biomolecular condensates, including nucleoli and speckles in the nucleus, and stress granules (SGs) and processing bodies in the cytoplasm. These condensates can have complex architectures with liquid or gel-like material properties and are suggested to form via phase separation, a process by which molecules in solution spontaneously separate into at least two distinct phases with different compositions.

Biomolecular condensates can assemble and disassemble spontaneously in response to environmental changes. The rapid coalescence and dissolution of condensates can be precisely controlled by tightly regulating the multivalent interactions between their constituent macromolecules, including proteins and nucleic acids. This dynamic mode of compartmentalization empowers cells to organize essential biochemical and functional modalities in space and time, including nuclear import, RNA metabolism, DNA repair, transcription, and signal transduction. Moreover, hysteresis in condensate disassembly can also yield important mechanisms for biochemical timekeeping and molecular memories.

There is great interest in defining the phase-separation mechanisms that may underlie the biogenesis and composition of specific biomolecular condensates such that subcellular physiology can be accurately understood, and synthetic biomolecular condensates can be engineered for beneficial purposes. Importantly, aberrations in biomolecular condensates can be debilitating and are connected to several fatal disorders including neurodegenerative diseases and cancer, which can have limited therapeutic options. Hence, there is also great interest in understanding how to mitigate and reverse aberrations in biomolecular condensates such that effective therapeutics can be developed and implemented.

This thematic issue on phase separation brings together several cutting-edge reviews that provide the latest insights from several leaders in the field on how biomolecular condensates form, how they contribute to physiology, and how they may go awry in human disease. Collectively, these pieces provide a detailed and comprehensive overview of several important functional and mechanistic aspects of phase separation in physiology and disease.

Pappu and co-workers lead off this thematic issue with a compelling review on how multivalent associative biomacromolecules, including proteins and nucleic acids, can drive the biogenesis of biomolecular condensates. They detail a series of complex, equilibrium phase transitions that they term coupled associative and segregative phase transitions (COAST). Under this umbrella, they review the key concepts of phase separation coupled to percolation and complex coacervation. They also deploy the COAST framework to address several recent critiques in the literature regarding the relevance of phase separation to the formation of biomolecular condensates in vivo.

In the next review, Knowles and co-workers focus on recent advances in theoretical methods, physics-driven simulations, and machine learning models to understand the molecular forces that underpin biomolecular condensate form and function. They emphasize the importance of acquiring accurate measurements of phase-separating systems as a critical prerequisite for the validation of these computational approaches. The integration of cross-disciplinary computational models and experimental measurements coupled to active learning mechanisms is anticipated to yield rich insights into several pressing questions in the field, such as how small-molecule drugs or oligonucleotides might affect phase separation of specific proteins.

Next, Boeynaems and co-workers review how intrinsically disordered proteins can protect the cellular environment from desiccation stress, including how reversible biomolecular condensates allow plants to sense water stress. For example, in the thale cress, *Arabidopsis thaliana*, a prion-like protein, FLOE1, forms biomolecular condensates upon seed hydration, which permit germination, whereas these FLOE1 condensates disperse upon desiccation stress to prevent germination. Thus, FLOE1 condensation serves as a water sensor that enables germination once hydration conditions are appropriate. Importantly, a survey of *Arabidopsis thaliana* ecotypes revealed that FLOE1 expression was correlated with local climate and germination phenotypes, indicating that FLOE1 might serve as a tunable sensor for water stress. The FLOE gene family is conserved across green plants, indicating a broad role in sensing water stress, which could have important implications for crop design and responses to climate change.

In the next review, Youn and co-workers cover the molecular composition and regulatory dynamics of mammalian SGs. SGs are biomolecular condensates that form in the cytoplasm in response to diverse stresses. They are implicated in cytoprotective processes such as antiviral responses but may

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also serve as crucibles for neurodegenerative disease pathogenesis via facilitating the assembly of TDP-43 and FUS fibrils in amyotrophic lateral sclerosis and frontotemporal dementia. Thus, there is great interest in unveiling the mechanism of SG formation and function. Youn et al. provide an update on the SG proteome and an analysis of how SG protein residents may be prone to phase separation and aggregation. They also survey how modifications of protein and RNA residents of SGs might alter SG composition and dynamics. Understanding the intricacies of SGs will help to establish how SGs can enable stress-specific adaptation and promote disease pathogenesis in a context-specific manner.

Next, in our review with Rhine and Odeh we focus on the regulation of biomolecular condensates by the nucleic-acid-like polymer poly(ADP-ribose) (PAR). We provide a primer on how PAR is synthesized and regulated, the diverse structures and chemistries of ADP-ribosylation modifications, and protein−PAR interactions. We showcase recent advances in understanding the mechanism of PAR-mediated phase separation, which contributes to the formation of DNA-repair condensates and SGs. We discuss how PAR polymerase inhibitors with specific properties may be effective treatments for neurodegenerative diseases. We also highlight the need for rigorous biochemical interrogation of ADP-ribosylation events to clarify the exact pathways from PARylation to condensate formation.

Finally, Silva and co-workers review accumulating evidence that the tumor suppressor protein and multifunctional transcription factor p53 forms aberrant biomolecular condensates that may contribute to cancer via multiple mechanisms, including loss of p53 function. They also review potential therapeutic strategies that might antagonize formation of aberrant p53 condensates. For example, the newly appreciated protein-disaggregase activity of the polyD/E protein DAXX might be exploited to reverse aberrant p53 condensation in cancer cells and restore the tumor suppression activity of p53.

In organizing this thematic issue, we have compiled several exciting reviews that bring a timely aerial view of several bleeding edges of phase separation and biomolecular condensate research. This flourishing field is rapidly expanding and evolving, and it now seems that phase separation impacts almost every corner of biology, which makes it difficult to cover the entire breadth of the area. Due to the challenges of the pandemic, submission of some articles has been delayed. Nevertheless, these manuscripts will be published in the future and linked to this thematic issue. We hope that readers will take delight in the eclectic sample of important topics covered. We also hope to inspire readers to advance the field to a stage that enables game-changing therapeutic strategies to mitigate aberrations in biomolecular condensation that underlie several fatal human diseases.

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Notes

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