

Phase separation of RNA-binding proteins in physiology and disease: An introduction to the JBC Reviews thematic series

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In recent years, there has been a jarring awakening that liquid–liquid phase separation (LLPS) of key protein and nucleic acid scaffolds underpins the biogenesis of diverse membraneless organelles, including P granules and stress granules in the cytoplasm and nucleoli and paraspeckles in the nucleus. These biomolecular condensates are proposed to be critical organizers of subcellular biochemistry and to control the flow of information from genotype to phenotype. Despite clear biological utility, LLPS can also have deleterious outcomes. Phase-separated compartments can concentrate specific RNA-binding proteins (RBPs), such as TDP-43 and fused in sarcoma (FUS), that through low-complexity, prion-like domains have an intrinsic tendency to form self-templating fibrils that are closely tied to fatal neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia. This series of reviews illuminates the molecular language underlying membraneless organelle biogenesis, how prion-like domains and post-translational modifications regulate phase behavior, how cells exploit the phase-separation process for adaptive modalities, and how phase separation is corrupted in neurodegenerative diseases. Collectively, these pieces provide a cutting-edge view of our functional and mechanistic understanding of phase separation in physiology and disease.

Eukaryotic cells compartmentalize distinct facets of their biochemistry into tailored microenvironments that are established and maintained by canonical membrane-delimited organelles. However, it is ever clearer that another type of compartmentalization is achieved by self-organizing membraneless organelles, including P bodies and stress granules in the cytoplasm as well as various subnuclear compartments such as nucleoli, speckles, and Cajal bodies. This arsenal of biomolecular condensates is now understood to originate via liquid–liquid phase separation (LLPS)² of key protein and nucleic acid scaffolds, which recruit and retain various resident clients. The material properties of these compartments can be tuned in terms of viscoelasticity according to precise functional and cel-

lular needs. LLPS likely also empowers prokaryotes to organize specific aspects of their biochemistry in membraneless organelles.

Although critical for various features of cellular architecture and physiology, LLPS also has a dark side. Liquid droplets that form at the wrong time or in the wrong place can be detrimental. LLPS can concentrate certain RNA-binding proteins (RBPs), including TDP-43, FUS, ataxin 2, hnRNPA1, and hnRNPA2. These RBPs contain low-complexity, prion-like domains that can spontaneously morph into self-templating, amyloid-like fibrils. Although these self-templating fibrils may have beneficial properties in defined contexts, they are primarily linked with devastating neurodegenerative diseases, including ALS and frontotemporal dementia. The close apposition and concentration of prion-like domains within phase-separated liquid compartments may promote deleterious fibrillization. Thus, it is of great interest to understand how cells maintain beneficial phases and simultaneously prevent pathological LLPS and fibrillization. This series of five reviews provides a panoramic overview of the mechanisms and benefits of LLPS and membraneless organelle biogenesis, how these processes are regulated, and how they can go awry in neurodegenerative disease.

In the article by Edward Gomes and myself (1), we discuss the molecular language of membraneless organelles. We survey eukaryotic membraneless organelles and describe how they can tune biochemical reactions and enhance cellular fitness. We describe the molecular underpinnings of their formation and regulation. We discuss how disturbances in LLPS and membraneless organelles may lead to neurodegenerative disease and how these disturbances might be countered by molecular disaggregases.

In the article by Titus Franzmann and Simon Alberti (2), the authors discuss various low-complexity prion-like domains and how they help drive functional LLPS of the proteins in which they are found. Although these domains can assemble into self-templating fibrils under some conditions, they can also play important roles in regulating phase behavior and can even protect proteins against proteotoxic damage. The authors suggest that evolution has likely harnessed prion-like domains and other intrinsically disordered regions for a variety of beneficial purposes.

Mario Hofweber and Dorothee Dormann (3) review recent advances in our understanding of how post-translational modifications (PTMs) of RBPs can regulate their LLPS and the

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² The abbreviations used are: LLPS, liquid–liquid phase separation; RBP, RNA-binding protein; FUS, fused in sarcoma; ALS, amyotrophic lateral sclerosis; PTM, post-translational modification.

dynamics of membraneless organelles. They focus primarily on the importance of arginine methylation and serine/threonine/tyrosine phosphorylation. Interestingly, the authors highlight that depending on context, these PTMs can weaken or enhance the multivalent interactions that elicit LLPS. Consequently, disruptions in PTMs can dysregulate LLPS and promote damaging transitions that underlie neurodegenerative disease.

Haneul Yoo, Catherine Triandafillou, and Allan Drummond (4) focus our attention on how cells utilize LLPS to sense alterations in the intracellular and extracellular environment. They showcase seminal examples of sensory phase separation and discuss how this mechanism endows cells with an exquisite sensitivity to respond rapidly and adaptively to environmental perturbations. Here, it is the very process of phase separation rather than the material properties of the resulting condensates that is of paramount importance.

In the review “Matter over mind: liquid phase separation and neurodegeneration,” Shana Elbaum-Garfinkle (5) provides an elegant summary of the link between LLPS and neurodegeneration. In particular, the pathological role of altered phase behavior and material properties of condensates are discussed. The author discusses several opportunities for therapeutic intervention and for understanding the molecular etiology of neurodegenerative disease.

In summary, this collection of reviews provides a state-of-the-art overview of our understanding of adaptive and deleterious phase separation. It will be exciting to watch how this rapidly exploding field develops. A more complete understanding of the functional repertoire of LLPS deployed by cells will be highly enlightening. Moreover, by gaining an accurate understanding of how cells prevent pathological phase separation, it is hoped that we will finally be able to develop therapeutics for several debilitating and invariably fatal neurodegenerative disorders.

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