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Review on Regulation and Pathological Implications of Biomolecular Condensates

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Abstract: Biomolecular condensates formed through liquid–liquid phase separation (LLPS) represents a major mechanism of cellular organization without membranes. These structures participate in diverse physiological functions, including gene regulation, stress response, and signal transduction. However, aberrant condensate dynamics are increasingly linked to pathological conditions such as neurodegeneration, cancer, and immune deregulation. This review consolidates current knowledge on the regulation of phase separation, highlighting key biophysical parameters, molecular regulators, and posttranslational modifications (PTMs). We also explore recent findings on condensate involvement in disease mechanisms and emphasize significant research gaps that need to be addressed.

Index Terms **- liquid–liquid phase separation, posttranslational modifications**

1. INTRODUCTION

Intracellular organization is critical for maintaining cellular homeostasis and responding to environmental cues. Biomolecular condensates, which arise from LLPS, have emerged as central players in the compartmentalization of cellular processes without membrane boundaries. These condensates form through multivalent interactions among proteins, RNA, and other bimolecular. While their importance in normal physiology is increasingly appreciated, their deregulation has been implicated in disease states, including cancer and neurodegenerative disorders.

RESEARCH GAP: While in vitro studies highlight these parameters, their interplay in complex intracellular environments is not fully understood. The specificity and spatiotemporal control of chaperone-condensate interactions remain underexplored. The role of RNA sequence, structure, and modifications in condensate regulation is not well characterized. A systematic map of PTM-regulated condensates and their functional outcomes in vivo is still lacking. The molecular details of membrane-mediated regulation of condensates remain to be elucidated. Comprehensive profiling of virus–host condensate interactions is needed to inform therapeutic strategies. Distinguishing between physiological and pathological condensates in cancer contexts remains a challenge.

2. REGULATION OF PHASE SEPARATION

Understanding the mechanisms governing condensate assembly, disassembly, and functional specificity remains a significant research challenge. Various regulatory elements modulate the spatiotemporal dynamics of condensates.

2.1. BIOPHYSICAL PARAMETERS

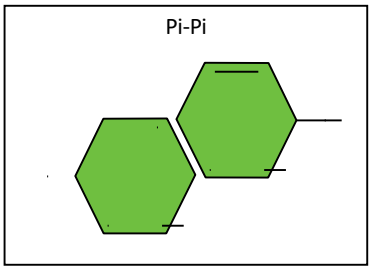
The concentration of phase-separating components is a key determinant of condensate formation, controlled through biosynthesis, degradation, and sub cellular localization. External factors such as salt concentration, pH, temperature, and molecular crowding influence phase behavior. For example, crowding agents like polyethylene glycol (PEG) and bovine serum albumin (BSA) promote phase separation. FUS condensates can undergo formation or dissolution with minimal temperature changes (1°C), demonstrating their physical sensitivity.

2.2. MOLECULAR CHAPERONES

Chaperones regulate proteotoxic and influence condensate dynamics. For instance, Hsp27 interferes with the transient interactions required for phase separation, modulating stress granules. Transporting prevents FUS aggregation by binding its nuclear localization signal in neuronal contexts.

Key Observation: Chaperones not only inhibit aberrant aggregation but also fine-tune condensate properties.

2.3. RNA AND RNA HELICASES



RNA helicases like DEAD-box proteins promote condensate formation in their ATP-bound state and drive disassembly upon ATP hydrolysis. RNA acts as both a scaffold and regulator: low concentrations promote LLPS, while high levels induce disassembly due to charge repulsion. Dhh1-RNA condensates show aging behavior, transitioning to a less dynamic state over time.
Key Finding: RNA content modulates the phase behavior and biophysical state of condensates.

2.4. POSTTRANSLATIONAL MODIFICATIONS (PTMS)

PTMs control condensate formation and disassembly by altering protein interaction domains. For instance, Simulation facilitates PML body formation, while Argentine methylation prevents LLPS by disrupting cation–π interactions. DYRK3 kinase regulates condensates during mitosis, and its perturbation results in cell cycle defects. Other PTMs like citrullination and phosphorylation dynamically modulate condensates depending on context.

Key Observation: PTMs offer a rapid, reversible mechanism to regulate phase separation.

2.5. MEMBRANE INTERACTIONS

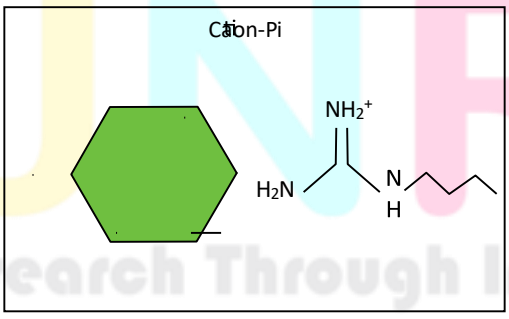
Membranes provide a platform for condensate nucleation by reducing the critical concentration required for LLPS. This interaction is seen across diverse compartments, including the plasma membrane, mitochondria, and endoplasmic reticulum.
Observation: Membranes spatially guide condensate formation and regulate their activity.

3. PATHOLOGICAL FUNCTIONS OF BIMOLECULAR CONDENSATES

Given their regulatory roles, disruption of condensate dynamics can result in pathological consequences.

3.1. IMMUNE SIGNALING AND VIRAL INFECTION

Viral proteins often co-opt or disrupt host condensates to evade immune responses. For instance, SARS-CoV-2 nucleocapsid protein forms condensates with G3BP1 and RNA, impairing cGAS and RIG-I signaling. Similarly, herpes virus and EBV proteins target



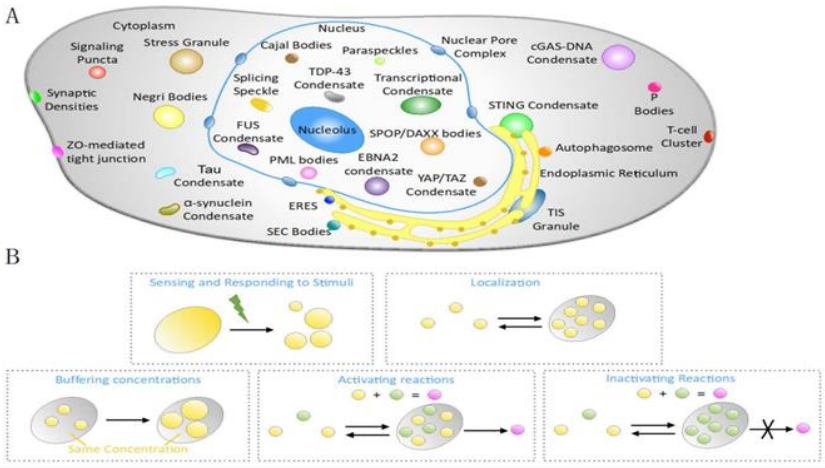
host condensates to modulate gene expression and evade detection.

Key Finding: Pathogens exploit phase separation to interfere with host immunity.

3.2. CANCER

Altered phase separation contributes to ontogenesis. SPOP mutations disrupt nuclear condensate formation, leading to accumulation of ontogeny proteins. SHP2 mutations promote stable MAPK-associated condensates, driving uncontrolled cell signaling. Other transcriptional regulators like YAP/TAZ, SRC-1, and AKAP95 form pro-tumorigenic condensates.

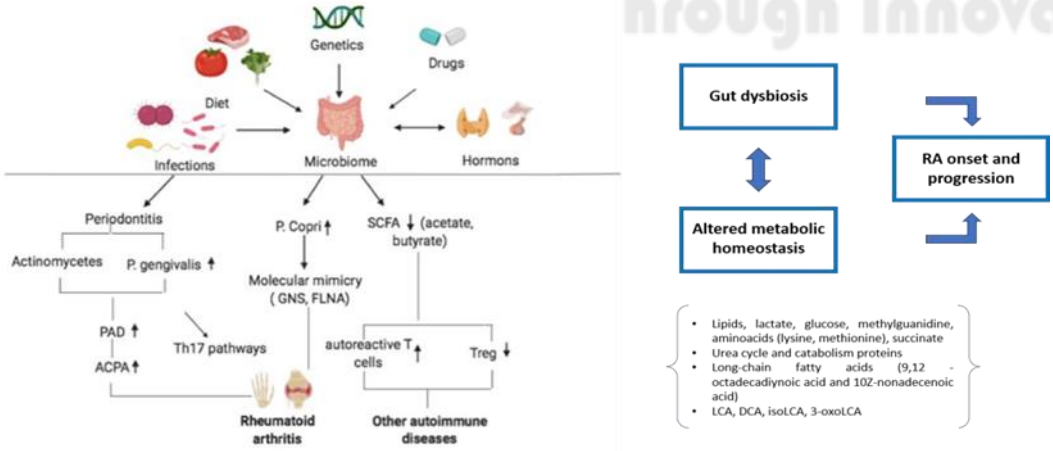
Key Observation: Aberrant condensate behavior supports ontogeny pathways and offers druggable targets.



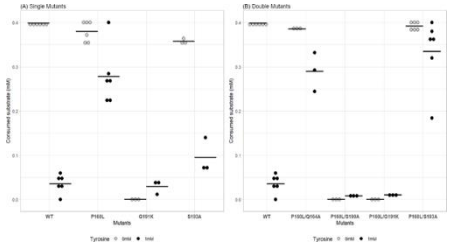
The compartmentalization of cellular biochemistry without physical membranes is a key feature of intracellular organization, achieved through the formation of bimolecular condensates. These dynamic assemblies emerge via phase separation driven by multivalent interactions among proteins, nucleic acids, and other bimolecular. Such organization allows for the spatial and temporal regulation of signaling pathways, metabolic processes, and stress responses. The regulation of condensate dynamics is critical for maintaining cellular homeostasis, and its deregulations has been implicated in various diseases, including cancer, neurodegeneration, and immune disorders.

A central mechanism regulating the formation, dissolution, and properties of bimolecular condensates involves post-translational modifications (PTMs) of constituent proteins. PTMs such as phosphorylation, methylation, acetylating, ubiquitination, and Simulation can modulate the interaction valence, charge, and conformation of proteins, thereby influencing their phase separation behavior. For instance, phosphorylation often introduces negative charges that weaken protein–protein or protein–RNA interactions, leading to condensate dissolution, while methylation may promote condensate maturation or hardening depending on the context.

Recent research has shed light on the role of PTMs in tuning condensate properties in response to cellular cues. During immune activation, for example, specific kinesis phosphor late components of signaling condensates, altering their assembly and signaling outputs. Similarly, in cancer, ontogeny signaling pathways frequently hijack PTM machinery to stabilize aberrant condensates that promote uncontrolled proliferation or stress resistance. In neurodegenerative diseases, mutations that alter PTM sites or the enzymes responsible for them often lead to the formation of persistent, toxic condensates associated with pathological protein aggregation.

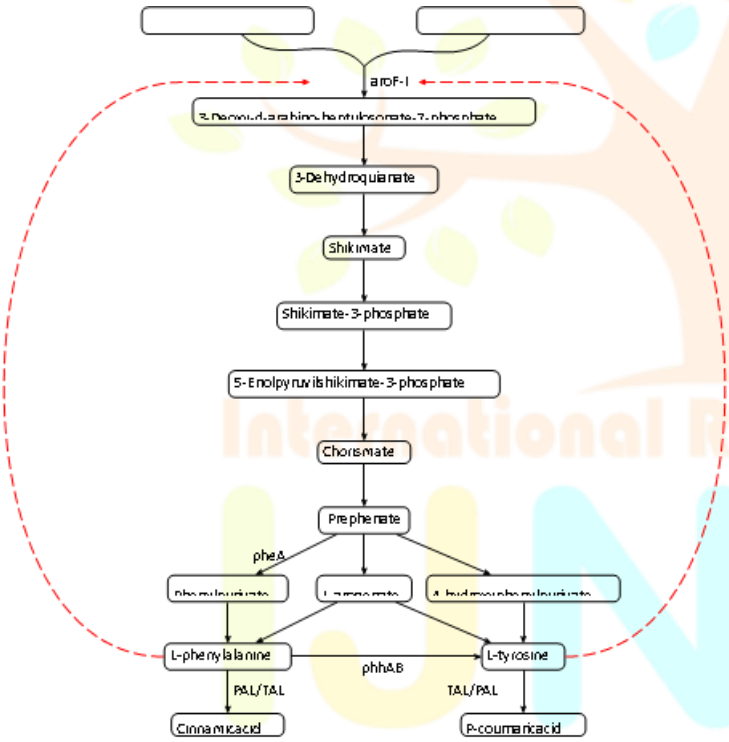


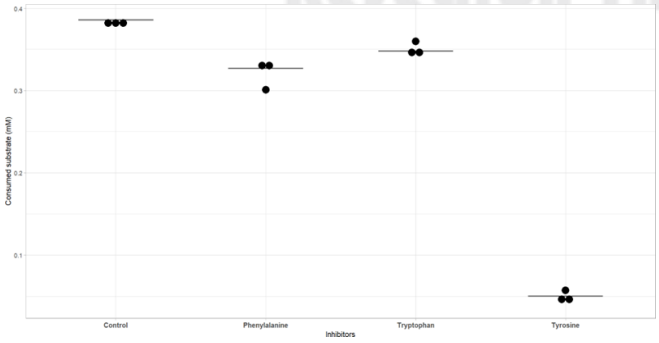
The regulation of condensates is not solely dependent on PTMs but also involves a network of biophysical and molecular factors. RNA molecules can act as scaffolds or regulators, influencing condensate nucleation, stability, and composition. Molecular chaperones and ATP-dependent remodeling complexes can dissolve aberrant assemblies or maintain condensate fluidity. In addition, cellular factors such as ionic strength, temperature, and macromolecular crowding play key roles in modulating phase behavior.



A growing body of evidence highlights the importance of kinesis such as DYRK family members in controlling condensate dynamics. DYRK1A and DYRK3, for example, have been shown to phosphor late key condensate constituents, thus regulating stress granule dissolution, transcriptional condensates, and mitotic transitions. These kinesis act as rheostats, tuning condensate states in accordance with developmental or stress-related signals, and represent potential therapeutic targets for modulating pathological condensates.

Despite these advances, several challenges and knowledge gaps remain. Many studies have focused on simplified in vitro systems, and translating these findings to the complex cellular environment requires careful validation. Additionally, the interplay between multiple PTMs on the same protein—so-called PTM crosstalk—remains poorly understood in the context of condensate regulation. Future research must also address how cells distinguish functional condensates from pathological ones and how they selectively degrade or repair the latter.





In general, the regulation of bimolecular condensates via PTMs and other molecular mechanisms represents a fundamental principle of intracellular organization with broad implications for cell biology and disease. Understanding these

processes at the molecular and systems levels will be critical for developing targeted strategies to manipulate condensates therapeutically in diseases where their regulation goes awry.

4. CONCLUSION

Recent advances have illuminated the diverse regulatory mechanisms and pathological roles of biomolecular condensates, yet several key questions remain unresolved. A major future direction involves constructing a comprehensive atlas of condensate types, their regulators, and disease associations using high-throughput proteomics and transcriptomics. Additionally, super-resolution live-cell imaging and single-molecule tracking technologies will be pivotal in dissecting the spatiotemporal behavior of condensates in vivo. Emerging tools such as artificial intelligence and machine learning hold promise for predicting phase-separating regions and understanding condensate behavior under perturbation. Furthermore, the development of small molecules or engineered peptides that modulate LLPS opens new avenues for therapeutic intervention, particularly in cancer and neurodegeneration. Moving forward, interdisciplinary approaches integrating cell biology, biophysics, and systems biology will be essential to unravel the multifaceted roles of bimolecular condensates. Biomolecular condensates represent a paradigm shift in our understanding of intracellular organization. Despite major advances, crucial questions remain regarding their regulation, composition, and pathological transitions. Future studies must integrate high-resolution imaging, quantitative proteomics, and genetic tools to map condensate dynamics under physiological and disease conditions. A more comprehensive understanding could lead to novel

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