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Biomolecular Condensates at the Membrane Interface: Why the Boundary Between Fluid and Structure is where the Next Discoveries will Happen

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Editorial

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Abstract

For over a decade, biophysics framed liquid-liquid phase separation (LLPS) as the organizing principle of 'membraneless' organelles, establishing a strict conceptual dichotomy between phase-separated liquid droplets and classical lipid-bound compartments. Today, that dichotomy has broken down. The most critical biological phenomena do not occur in unconstrained bulk solution, but at the physical interface where liquid condensates meet lipid bilayers. Here, capillary wetting, interfacial energy, and reciprocal membrane remodelling dictate cellular function, disease pathogenesis, and synthetic biology. This editorial argues that the future of physical biology lies at this liquid-bilayer boundary.

Keywords: Biomolecular Condensates; Liquid-Liquid Phase Separation; Membrane Interface; Wetting Dynamics; Lipid Bilayers; Condensatopathies

Abbreviations

LLPS: Liquid-Liquid Phase Separation; ALS: Amyotrophic Lateral Sclerosis; FTD: Frontotemporal Dementia; Cryo-ET: Cryo-Electron Tomography; IDP: Intrinsically Disordered Proteins; MD: Molecular Dynamics.

Editorial

The Conceptual Irony of Membraneless Compartments

Scientific paradigms are often defined as much by what they reject as by what they affirm. When liquid–liquid phase separation (LLPS) emerged fifteen years ago as the dominant physical framework for intracellular organization, its central triumph was freeing cell biology from the absolute hegemony of lipid bilayers. Landmark studies on P granules, nucleoli, and stress granules demonstrated that cells could compartmentalize biochemical reactions without surrounding hydrophobic barriers. The term ‘membraneless organelles’ was coined precisely to contrast these dynamic, phase-separated protein and RNA droplets with traditional membrane-bound structures like the endoplasmic reticulum or Golgi apparatus.

Yet, a profound conceptual irony has unfolded across physical biology over the past three years. As biophysicists stepped away from idealized in vitro reconstitutions of bulk phase separation to examine live, intact cells, a stark reality emerged: ‘membrane less’ condensates almost never act in isolation from lipid membranes. From T-cell receptor signalling clusters at the plasma membrane to endosomal sorting complexes, RNA-transport granules riding along axonal vesicles, and autophagy initiation sites, condensates routinely nucleate, wet, and function directly at lipid bilayer interfaces.

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Reciprocal Mechanics: Capillary Wetting and Bilayer Remodeling

What makes the condensate-membrane interface so biophysically captivating is its inherent reciprocity. In bulk solution, condensate behaviour is governed primarily by protein multivalency, saturation concentrations, and bulk viscosity. However, at a membrane surface, the thermodynamic landscape is dominated by interfacial contact energy, capillary wetting, and line tension. The physical state of the interface determines whether a condensate forms a discrete, spherical droplet (partial wetting/dewetting) or spreads into a thin, functional surface film (complete wetting).

Crucially, this interaction is a two-way street. Adhering condensates exert soft capillary forces that actively deform the underlying lipid bilayer. Recent experimental and theoretical breakthroughs demonstrate that liquid droplet wetting can induce dramatic membrane morphological transformations including localized membrane bending, invagination, nanotube tubulation, and even endocytic-like scission without requiring ATP-driven motor proteins. Conversely, the biophysical properties of the membrane exert strict reciprocal control over condensate assembly. Variations in lipid packing density, acyl-chain saturation, cholesterol concentration, and local membrane curvature alter the interfacial adhesion energy, acting as a thermodynamic dial that tunes condensate wetting and functional activity.

The Pathological Spectrum of Condensatopathies

The recognition of condensate-membrane coupling has transformed our understanding of human pathology, spawning the concept of 'condensatopathies'. When phase separation goes awry, the consequence is rarely a simple loss of droplet volume; rather, it manifests as a pathological shift in phase behaviour specifically, the transition from functional, reversible liquid droplets into aberrant, toxic solid gels or amyloid-like aggregates.

This liquid-to-solid phase transition is exceptionally dangerous at membrane boundaries. In neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease, proteins like FUS, TDP-43, and Tau form aberrant condensates that adhere to organellar membranes. When these condensates solidify, their altered surface tension causes mechanical disruption of nuclear envelope pores, mitochondrial outer membranes, and synaptic vesicle pools. In oncology, super-enhancer transcriptional condensates (involving MED1 and MYC) interact with nuclear structural elements to drive oncogenic gene expression, while in cardiovascular disease, aberrant sarcomeric protein condensates alter mechanical force transmission across cardiac membranes.

Multiscale Methods: Resolving the Interface

Today, the synergy of cryo-electron tomography (cryo-ET) and advanced computer simulations has dissolved these barriers. Cryo-ET now enables researchers to visualize frozen-hydrated condensates contacting cellular membranes at sub-nanometer resolution in native intracellular environments, capturing real-time membrane bending and lipid reorganization. Concurrently, coarse-grained molecular dynamics (MD) simulations (such as Martini models) combined with continuum mechanics bridge the temporal and spatial gap, modeling how thousands of multivalent protein interactions generate macroscopic capillary forces on lipid leaflets. This multiscale arsenal has transformed condensate-membrane biophysics from speculative diagrams into a precise, quantitative science.

Synthetic Biology and the Future Horizon

Beyond unravelling natural physiology, the physical principles governing condensate-membrane interfaces are powering a revolution in synthetic biology. Researchers are no longer merely observing phase separation; they are engineering synthetic, membrane-anchored condensates to construct artificial cells and smart biomaterials. By designing artificial intrinsically disordered proteins (IDPs) equipped with specific lipid-binding domains, synthetic biophysicists can now program synthetic droplets that assemble on demand at target membrane sites. These engineered interfaces act as spatial catalytic hubs, concentrating enzymes to accelerate metabolic cascades, driving selective vesicle budding, or serving as drug delivery vehicles that fuse with target cell membranes upon sensing specific microenvironmental triggers.

Conclusion: Embracing the Boundary

The history of biophysics is marked by the continuous refinement of spatial boundaries. The initial decade of liquid-liquid phase separation research succeeded because it broke free from the rigid view that membranes were the sole organizers of the cell. However, the next frontier will not belong to bulk phase separation in isolation, nor to static membrane biology alone. The future belongs to the boundary the rich, complex, soft-matter interface where liquid droplets and lipid structures meet, deform, and mutually govern one another. It is precisely at this interface that the next generation of biophysical discoveries will take place.

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