Emergent Behavior of Living Matter: Different Pathways of Liquid Condensate Engulfment and Endocytosis by Membrane

Rikhia Ghosh

Icahn School of Medicine Mount Sinai, New York, USA

rikhia.ghosh@mssm.edu

Biomolecular condensates (also known as membraneless organelles) formed by liquid liquid phase separation (LLPS) of proteins, are classic examples of liquid droplets in cell biology. Examples of such condensates include germ P-bodies, Cajal bodies, nucleoli, stress granules, to name a few [1]. The formation of biomolecular condensates in cells resembles the formation of molecular condensates in aqueous two-phase systems, that have been used for a long time in biochemical analysis and biotechnology. Similar to such molecular condensates, biomolecular condensates can potentially lead to wetting and remodeling of membranes. Evidence for membrane remodeling and endocytosis by condensate-membrane interactions has been provided for P-bodies that adhere to the outer nuclear membrane, for lipid vesicles within a synapsin-rich liquid phase, and for condensates at the plasma membrane.

In this talk, I will describe my efforts to understand the mechanism of membrane wetting by small, liquid droplets representative of molecular condensates in aqueous two-phase systems or biomolecular condensates in cell biology and their subsequent endocytosis [2]. Both for the partial and complete engulfment of these droplets by the membrane, we observe two different endocytic pathways. Complete engulfment leads to a closed membrane neck which may be formed in a circular or strongly non-circular manner. A closed circular neck undergoes fission, thereby generating two nested daughter vesicles whereas a non-circular neck hinders the fission process. Likewise, partial engulfment of larger droplets leads to open membrane necks which again have either a circular or a non-circular shape. The key, controlling parameters that determine the endocytic pathways, are the transbilayer asymmetry of the membrane and the line tension of the membrane-droplet contact line, which remarkably changes sign as a function of decreasing tension in the outer leaflet. The sign of the line tension along the membrane-droplet contact line determines the geometry of the droplet engulfment (circular or non-circular) and the fate of endocytosis.

In the second part of the talk, I will discuss a roadmap to the future direction of my research objective. *How do large-scale properties of living matter (organelles, cells, tissues) emerge from the complex interplay of their constituent molecules (DNA, proteins, lipids)? What are the mechanical forces that govern the remarkable organization in living matter? Can we understand the emergent dynamics of cellular machinery using existing physical and chemical laws?* — Even though there are enough evidences of stunning ordered dynamics in biology[1,3,4], the effort to explore this behavior using concepts of critical phenomena is still severely lacking. My goal is to identify the novel physical and chemical laws that govern the assembly, mechanical and dynamical properties of living matter and thereby connect the range of spatio-temporal scales encountered in biology.

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