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One and one is not two: Taking a fresh look at membrane interfaces

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Abstract

Plasma membranes sit at the divide – conceptually and literally – between the interior and exterior milieu of cells, coordinating communication between nearby cells and structuring surrounding tissue. While great effort over the last half century has advanced our understanding of the molecular organization of the plasma membrane, much of this work has focused on free plasma membranes that are not in contact with other cells. Recent studies have, however, highlighted unique and unexpected features of membrane interfaces between two cells, where the physical and chemical constraints of the interface conspire to create a system that is distinct from either plasma membrane alone. Inspired by this emerging view of cell-cell contacts, we propose classifying interfaces between cells as a distinct cellular compartment.

Comment

For centuries, scientists from multiple disciplines have marvelled at the exquisite organization of biological systems. The question of how order emerges from a collection of molecules has been the driving force behind landmark findings in the 20th and 21st centuries, including the discoveries of membrane-bound organelles in eukaryotes, DNA compaction into chromatin, and, more recently, phase-separated liquid-liquid compartments in the nucleus and cytoplasm. Similarly, organization within the plasma membrane has been the subject of intense interest from the first formulation of the fluid-mosaic model in 1972 to the development of the lipid raft theory in 1988 to the present day (see Additional information).

Evidence accumulated over the past several decades points to a model in which certain proteins and lipids, including sphingolipids and cholesterol, can associate with one another, leading to the formation of microdomains in live cells. Such ordered domains can, in theory, modulate the physical properties of membrane components, for example diffusivity and local concentration, and can consequently drive signal transduction through inclusion or exclusion of individual proteins (see Additional information). Although debate over the existence of microdomains in vivo continues, this concept of in-plane organization has

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Additional information

A comprehensive Review on composition, regulation and roles of lipid rafts: https://www.nature.com/articles/nrm.2017.16

provided a powerful framework for understanding the ways in which cells interact with the local environment through their plasma membrane. But what happens when that environment is not media or interstitial fluid or plasma but another cell? What principles govern lipid and protein organization and function when two plasma membranes interact? A fresh look at membrane interfaces – complete with a detailed picture of how the biochemistry and biophysics of diverse cell-cell contacts differ from that of single plasma membranes – is needed to achieve a mechanistic understanding of cell-cell communication and organization.

Cell-cell contacts are a fundamental part of multicellular organisms, where single cells are rarely found in isolation. In metazoans, cells constantly communicate with and monitor their surrounding neighbours: neutrophils climb around host cells and phagocytose pathogenic bacteria; endothelial cells interact tightly to limit plasma leakage; and neurons signal to muscle cells to elicit contraction. To do all of this, individual cells receive and transmit information to other cells and tissues, either indirectly through soluble ligands, so-called paracrine and endocrine signalling, or directly through cell-cell interfaces. Despite the critical role of cell-cell contacts in organismal development, homeostasis, and pathology, membrane interfaces joined by adhesive proteins are often approximated as the simple superposition of two free membranes, with each membrane behaving in either a fluid-like or raft-like manner, rather than as a distinct region with unique biochemical and biophysical constraints. However, the difference in size and dynamics of membrane microdomains in free plasma membranes (nm and μs-scale (see Additional information)) and at cell-cell interfaces (μm and hr-scale[1]) strongly suggest that the properties of one cannot be predicted from the properties of the other.

We propose that membrane interfaces be classified as specialized cellular compartments, similar to the nucleolus and lipid droplets. Several lines of evidence from recent investigations of protein mobility, membrane topology, mechanotransduction, and post-transcriptional gene regulation support the idea that membrane interfaces deserve their own designation in the pantheon of subcellular structures in multicellular organisms.

The first defining feature of membrane interfaces relates to the mobility of proteins, namely that their diffusivity at interfaces decreases dramatically. A prerequisite for forming membrane interfaces is the presence of ligands and receptors that juxtapose two membranes together. This is usually accomplished by adhesion proteins in vivo. As these adhesion components move from free membrane regions to interfaces, trans-interacting proteins, like E-cadherin of the epithelial adherens junction and claudin-1 of the tight junction, are known to undergo extreme and dramatic transitions in diffusivity – both transition from highly mobile in free membrane regions, fitting well to models of 2-D random walks, to highly immobile, with decreased diffusivity, at interfaces. And while there is strong evidence that coupling to cytoskeletal structures in the cell is involved in these differences, in vitro studies of membrane interfaces between supported lipid bilayers and giant unilamellar vesicles also show similar phenomena. Reconstituted interfacial proteins display features of anomalous diffusion, leading to descriptions of their behavior as gel-like. Thus, the physical environment created by two bilayers coupled together through adhesive proteins is distinct from that of liquid-ordered microdomains of free membranes.

Second, local membrane topology is altered by adhesions at cell-cell interfaces, creating physical constraints that affect protein organization and function (for example in signalling). A series of recent papers has begun to shed light on how defined spatial separation between two adhered membranes can influence protein organization, transport, and binding kinetics. One study showed that only particular membrane species with defined molecular characteristics (such as a molecular dimensions of proteins) have access to these topologically-distinct regions.[2] In another example, typically well-defined second order rate constants for receptor:ligand interactions were found to be augmented at interfaces, where the rate constant of association between individual T cell receptors (TCRs) and major histocompatibility complexes (MHCs) increases locally due to membrane bending.[3] This in turn drives a feedback loop: accelerated TCR-MHC binding causes clustering of TCR proteins, further deforming and bending the membrane locally, which leads to exclusion of large inhibitory signaling proteins, such as the CD45 phosphatase, out of interfaces, thereby allowing robust T cell activation. Many of these mechanisms, though, are not specific to T cells. They are similar in other immune cell encounters, in epithelial adhesions and in neuronal contacts, suggesting a more unified picture of the mechanisms that regulate signaling at membrane interfaces.

Third, membrane interfaces transmit physical forces between cells, triggering a range of mechanical responses. Recent work on adherens junctions in epithelial tissue has shown that E-cadherin-mediated interfaces sense interfacial tension and respond to tissue-level strain. Minimal interfacial strain leads to sequestration of the transcription factors, YAP-1 and β-catenin, near the membrane.[4] In doing so, interfaces direct the majority of epithelial cells to remain quiescent and non-proliferative for a cell's lifetime. However, in response to elevated strain, these transcription factors are released and translocate to the nucleus, where they promote cell cycle re-entry. Cells clearly rely on the specialized features of interfaces to integrate the surrounding mechanics of tissue and specify cell fate.

Finally, the long-lived nature of interfaces may be co-opted by cells in surprising ways. Recently, membrane interfaces have been described as hubs for post-transcriptional gene regulation. RNA interference machinery and native micro RNAs appear to be recruited to and enriched at cadherin-based interfaces, where their silencing activity is turned on against drivers of pluripotency, such as SOX2 and MYC. Here, membrane interfaces play the role of impairing the dedifferentiation of epithelial cells.[5] By virtue of their unique physical and biological properties, cell-cell contacts are therefore emerging as key control centres of cell identity.

What then lies ahead? Recognizing that membrane interfaces formed at cell-cell contacts are distinct compartments with their own underlying physical and chemical properties is a crucial starting point. Steps beyond that include detailed characterization of the lipidomics, proteomics, and mechanical forces at cell-cell interfaces, as well as investigation of how localized energy consumption steers specific out-of-equilibrium configurations of interfacial lipids and proteins. Hybrid in vitro-in vivo systems comprised of custom-built synthetic membranes interfacing with live cell plasma membranes will continue to play a crucial role in advancing the field by allowing researchers to connect specific physical or chemical inputs with functional cellular outputs. The focused study of in-plane organization of free

membranes over the last few decades, both in vitro and in vivo, must now be extended to membrane interfaces in order to dissect the unique properties of this specialized compartment in systems that include but go beyond immune cells and epithelial cells. If we are successful as a community, membrane interfaces may one day earn their own section in biology textbooks highlighting how, in biology at least, one and one is not always two.

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