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Understanding membrane traffic from molecular ensemble, energetics, and the cell biology of participant components

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The COVID-19 pandemic that started in 2019 has left in its wake colossal devastation. While several countries continue to struggle with the second, third, and even the fourth waves of the pandemic and government agencies grapple with the difficult task of predicting how best to deal with emergent strains, vaccines have become available and are being deployed worldwide. This pandemic has only reinforced the redeeming quality of scientific research. Numerous research initiatives have culminated in providing knowledge on the viral genome, proteome, and protein structures that offer potentially druggable pathways for therapy. But a crucial ingredient to the success of the scientific endeavor has been the ability for communities of scientists to seamlessly disseminate data and thereby bring in fresh perspective. The sum total of all of these developments is that the world has witnessed a striking and unprecedent rapidity in scientific progress in tacking the pandemic. Its 2021 and we write this editorial with a sense of hope and promise of return to normal life. We would sincerely like to thank the commendable efforts of our contributing authors, who have come up with insightful reviews under circumstances that were anything but inspiring.

Compartmentalization is a defining feature of all living systems, and we are becoming increasingly aware of the complex organization of the intracellular space. The most pervasive means of achieving compartmentalization is by the self-assembly of richly functionalized lipid bilayers into self-contained units referred to as organelles. These units maintain specific form and composition and emerge from elaborate and coordinated membrane trafficking pathways that manifest either as explicit membrane-bound carriers or through regulated physical proximity of organelles. In this issue, we have gathered viewpoints from investigators trying to understand membrane trafficking across organelles from a biological, physical, and engineering perspective.

Cellular traffic is orchestrated on membrane templates that undergo regulated alterations in their chemical composition. This is best exemplified by the phosphoinositide lipids that turnover their identity by an

elaborate control of their phosphorylation status by kinases and phosphatases. Such turnover serves to organize specific reactions on membranes, which in turn regulates membrane traffic. The phosphatidylinositol-5-phosphate 4-kinase phosphorylates phosphatidylinositol-5-phosphate to generate the well-known lipid phosphatidylinositol-4,5-bisphosphate. Padinjat [1] reviews recent developments linking the biochemical activity of phosphatidylinositol-5-phosphate 4-kinase to metabolism, immune functions, and growth control.

Phosphoinositide lipids are just one component of the vastly complex membrane template and a new and emerging field of molecular dynamics simulations of membranes, incorporating the rich chemical diversity of lipids in the native membrane and providing fascinating insights into how such heterogeneity determines the shape and form of organelles. Pezeshkian and Marrink [2] review a diverse range of computational techniques that are able to capture this complexity at increasing levels of accuracy and connect molecular-level protein—lipid interactions to macroscopic organelle morphologies.

Cellular traffic involves the budding, fission, and fusion of membranes, but the membrane template itself presents a tall energy barrier for such shape distortions. In this context, modeling becomes critical because it incorporates membrane mechanics. Lee et al [3] discuss the contributions made by models to our understanding of membrane budding and identify opportunities for a unified view of cellular traffic, moving beyond molecular complexity to offering testable models that can predict the success or failure of trafficking events based on energetics.

Endocytosis is a specialized from of membrane traffic by which extracellular proteins, micronutrients, and transmembrane cell surface proteins are internalized by the cell. The best understood endocytic pathway is clathrin-mediated endocytosis. But current models explaining protein sorting during this process assume a vectorial chain of molecular recognition and binding events. Wu and Wu [4] provide fresh perspectives on how kinetic proofreading that prune the specificity and sensitivity of biochemical reactions allow for the disassembly of unwanted intermediates and can provide better models to explain cargo sorting during this endocytic process.

Renard and Boucrot [5] survey more enigmatic, unconventional pathways of endocytosis that are used by many viruses, toxins, and bacteria to infect cells. These clathrin-independent endocytic routes use distinct principles of a signaling-induced membrane remodeling — akin to that seen during macropinocytosis, direct cargo capture and local membrane deformation by noncoat-like cytosolic proteins, and lipid clustering-induced budding of membranes. The importance of signaling in the regulation of endocytic trafficking is further highlighted by Kunselman et al [6] as they describe how trafficking of G-protein—coupled receptors to different membrane compartments is a critical determinant for signaling.

An additional layer of regulation of endocytic transport occurs by the content of respective compartments. Protons determine the movement and maturation of endocytic vesicles, calcium contributes to vesicular fusion and fission, and monovalent ions are key determinants of hydrostatic pressure and endomembrane tension. Chadwick et al [7] provide an interesting overview of this intimate association between luminal ions and endocytic trafficking and address the mechanisms but also our gap in knowledge to convert ion concentrations into membrane trafficking events.

Caveolae are specialized endocytic structures, appearing as bulb-shaped pits at the plasma membrane with a specialized lipid composition. Caveolae can bud from the plasma membrane to bring specific cargoes to endosomes, but they also have the ability to flatten into the plasma membrane in case of membrane tension. Parton et al [8] present a model in which the filamentous cavin proteins help to generate a lipid domain that is favorable for insertion of caveolin proteins, forming a metastable membrane domain that can readily be disassembled in response to cellular stress or induction of endocytosis.

Endocytosis is counteracted by the biosynthetic pathway. Soluble proteins destined for secretion were long thought to follow the so-called bulk flow or secretory pathway from the endoplasmic reticulum (ER) to Golgi to trans-Golgi network (TGN) to the plasma membrane. Recent research, however, indicates that at the TGN, soluble proteins are actively sorted into this pathway. Ramazanov et al [9] describe the emerging view that cisternal TGN membranes represent functional subdomains from which different types of carriers are formed. The internal TGN milieu may induce concentration of cargo, whereas cholesterol- and sphingolipid-rich membrane nanodomains serve as protein sorting platforms. Interestingly, the lipid environment and the TGN milieu are at least partly controlled by ER—TGN membrane contact sites (MSCs).

MCSs are defined as areas of close apposition between two membranous organelles that are connected via protein tethers but do not fuse. Through exchange of materials, MCSs are important for organelle function, structure, and positioning. Venditti et al [10] give a highly interesting overview on the dynamic molecular regulation of MSCs in response to specific stimuli and then use this knowledge to highlight an as yet unexplored role of MSCs in development and disease of multicellular systems. Lujan et al [11] review recent advances on interorganelle communication and how they control the shape, identity,

and export functions of the two main organelles of the early secretory pathway: the ER and the Golgi complex. Sun et al [12] review recent advances in the mechanism of selective cargo packaging and its relevance to ER morphological dynamics.

Regulation of membrane transport is especially challenging in polarized cells, such as mature neurons and immune cells. Mature neurons consist of two morphologically distinct domains, the somatodendritic domain and axonal domain, which are also functionally different. Interacting immune cells form an immunological synapse with target or other immune cells, a transient, polarized membrane domain destined for secretion of toxic or immunoregulatory proteins. An outstanding question is how transport of selective organelles and cargoes to these functionally different subdomains is regulated. Koppers and Farías [13] provide a comprehensive overview on domain-specific inclusion and exclusion mechanisms in neurons and highlight the role and mechanisms by which the microtubule cytoskeleton is necessary for fine regulation of polarized membrane transport. Moreover, they discuss the emerging role of MCSs in organelle positioning. Douanne and Griffiths [14] describe how polarization of the centrosome and rapid actin dynamics are required to form the immune synapse. In addition, they provide an overview of different types of immune synapses and their distinct functions.

Autophagy is a catabolic pathway that targets cytoplasmic proteins and organelles by sequestering them into double-membrane vesicles called autophagosomes. How autophagosomes are formed has long remained enigmatic, but the pieces of the puzzle are now coming together. Gómez-Sánchez et al [15] present in a compelling review how different organelles donate membranes in the form of vesicles that fuse together to form the initial phagophore, whereas expansion and closure of the membrane into an autophagosome is realized by establishment of different types of MCSs. Autophagosomes then fuse with lysosomes, which contain a set of acid hydrolases that are capable of digesting cellular macromolecules obtained by autophagy or endocytosis. Massive leakage of these lysosomal hydrolases into the cytoplasm causes cells death. However, as discussed by Stahl-Meyer et al [16], emerging evidence indicates that spatially and temporally controlled leakage of lysosomal hydrolases may act as a key regulator of fundamental cellular processes as mitosis, inflammation signaling, and cellular motility. Their review demonstrates that the versatile lysosome can still amaze us with novel, unexpected functions.

While MSCs are clearly in the center of interest as mode to exchange materials within cells, tunneling nanotubes (TNTs) represent a novel way of communication between cells. TNTs are open membrane channels by which cells exchange various cellular materials, such as signaling proteins, genetic material, organelles, and pathogens. Zurzolo [17] reviews the current definitions and fundamental properties of TNTs and addresses the major questions and confusions in this field. Furthermore, they propose the interesting hypothesis that nonsynaptic communication by TNTs may precede synaptogenesis in the brain and may be instrumental in establishing functional neural circuits.

In neurons, synapses can contain up to thousands of synaptic vesicles that are grouped in the vicinity of the active zone. The classical view is that these vesicles form a reservoir for neurotransmitter release upon the proper stimulus. Reshetniak and Rizzoli [18] present an alternative view, suggesting the synaptic vesicle cluster as a central organizer of synaptic composition and dynamics. Via various protein interactions, the synaptic vesicle cluster acts as a buffer for cytoplasmic cofactors involved in neurotransmission, while at the same time controls their localization, copy numbers, and mobility by regulating actin polymerization.

Progress in imaging technology is key to further understand the intricate complexity of dynamic membrane trafficking events. Many of the reviews in this issue highlight the need for advancing light and electron microscopy imaging techniques to boost our understanding of ultrastructure, protein distribution, membrane dynamics, tissue organization, and more. An important innovation in imaging is correlative light electron microscopy techniques, and Sochacki and Taraska [19] discuss how emerging correlative light electron microscopy techniques have been used to study the assembly of protein coats inside cells. Passmore et al [20] take imaging one step further by using microscopy to control cells. They present an overview of technologies alter organelle positioning, membrane trafficking pathways, and organelle interactions in live cells. Their exciting outlook for further optimization and developments in the field make a compelling case of how microscopy can change from an observing to a controlling technology.

Clearly, the field of cytoplasmic compartmentalization into organelles is burgeoning with important discoveries and breakthroughs. We have learned a lot from cataloging the diversity and reconstituting the function of organelles, and these developments together have resulted in remarkable insights into unique and specialized membrane trafficking pathways to facilitate specific physiological needs. The actions of sophisticated protein machines that bend, fuse, and divide organelles and the design of robust iterative sorting principles that manage to maintain organelle composition throughout the entire life of a cell are key regulatory mechanisms that often are subverted in pathophysiology. Moreover, research into membrane trafficking has inspired important technological advances in

experimental techniques and the development of smart materials or templates that embody principles of self-replicating living matter. Together, these developments portend a bright future for membrane traffic and offer unparalleled opportunities for bright young colleagues to invest in a research career.

Conflict of interest statement

Nothing declared.

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