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Editorial overview: Membrane traffic in the time of COVID-19

Frances M. Brodsky and Jennifer L. Stow

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Edited by **Frances M. Brodsky** and **Jennifer L. Stow**

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Frances M. Brodsky
Division of Biosciences, University College London, Gower Street, London, WC1E 6BT, UK
*Corresponding author: Brodsky, Frances M.
e-mail: f.brodsky@ucl.ac.uk

Prof. Frances Brodsky is Director of the Division of Biosciences at UCL. Her laboratory focuses on how intracellular clathrin-mediated pathways influence glucose metabolism, the immune system, and neuronal function. This research, currently supported by the Wellcome Trust and the UKRI, emerges from a career studying the biochemistry, genetic diversity, and evolution of clathrin proteins, at the University of California, San Francisco, until 2014, then at UCL.

Jennifer L. Stow
Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, 4072, Australia
*Corresponding author: Stow, Jennifer L.
e-mail: j.stow@imb.uq.edu.au

Prof. Jenny Stow is a group leader, NHMRC Leadership Research Fellow, Deputy Director (Research), and head of IMB microscopy, at IMB, the University of Queensland. Her research has explored both secretory and endocytic pathways in epithelial cells and macrophages, using live cell imaging and biochemistry to uncover GTPases, SNAREs, scaffolds, and kinases as key regulators of inflammation and disease.

We write this editorial emerging from lockdown in countries across the world in the face of the COVID-19 pandemic. These have been challenging, frightening, and too often catastrophic times for many. Such times lead to evaluation of one's own enterprise in the context of a global emergency. The mandated reliance of the world on scientific data and judgment has now placed research that has often been treated by governments as obscure, in these increasingly anti-intellectual times, at center stage. We hope that a silver lining to the current pandemic will be a renewed recognition of the place of science in society and redoubled efforts by governments to appropriately fund and support scientific research that will protect us now and into the future.

As the pandemic has evolved, the use of modeling and mathematical epidemiology and our knowledge of coronavirus biology and human immunity have directly impacted government and medical decisions. These fields absolutely rely on a foundation of fundamental cell and molecular biology, biochemistry, and microbiology, and an advanced understanding of membrane traffic is needed for insights into how and where SARS-CoV-2 infects different human cells and how our immune system responds to the infection. Likewise, research on membrane traffic was vital over the past decades for understanding the pathogenesis of HIV [1], and new insights into clathrin-mediated transport [2] and how it is subverted by HIV [3–5] will continue to inform the development of effective treatments. Indeed, many of the historical and recent discoveries in membrane traffic have emerged from studies using viruses, bacteria, and other pathogens as tools to probe cell pathways and molecular mechanisms (reviewed in this issue by Noack and Mukherjee [6]). The articles in this issue were written in the period just before the global escalation of COVID-19, and the science they review is highly topical for the field of membrane traffic. However, they will also be vital for current investigations around the world to understand SARS-CoV-2, its mode of infection in different tissues, disease manifestations, and resulting immune responses and for the development of vaccines and treatments.

The reviews selected for this issue are written by experts across membrane traffic, contemporizing issues such as sorting, sensing, scaffolding, and recognition of proteins, lipids, and cargo in trafficking pathways. Organelle

formation, regulation, and interactions are surveyed. Importantly, environmental, metabolic, and microbicidal influences on membrane traffic and vice versa are also appraised and updated. Here we summarize the emerging themes in membrane traffic covered by the reviews in this issue. We sincerely thank the authors for their comprehensive updates, expert insights, and their ongoing, pioneering research contributions.

While membrane traffic focuses on mechanisms of intracellular transport, the end result of import and export of membrane-associated proteins and of membrane itself is to influence the interaction of cells with their environment. The importance of mechanosensing in this process and the involvement of membrane traffic in response to membrane stress or injury is highlighted in several reviews in this issue. The review by Vassilopoulos [7] describes membrane traffic pathways in muscle cells, which have caveolae and clathrin-coated plaques to help manage intense stress at membranes and have dysferlin-mediated mechanisms for constant repair. Bohannan and Hanson [8] discuss roles for ESCRT proteins and calcium in repair of both internal and external membrane injury from pathogens, particulates, and metabolic or chemical stresses. The review by Parton et al [9] is focused on the molecular mechanisms of caveolae formation, discussing how these structures regulate membrane tension and respond to UV-induced stress through rapid disassembly. Babst [10] describes how lipid fluidity in the yeast membrane, in response to environmental changes, alters the membrane traffic of nutrient transporters during metabolic stress, focusing on how eisosome formation regulates transporters. The review by Day and Stachowiak [11] discusses the biophysical requirements for membrane bending and considers how the influence of cargo on lipid fluidity leads to the recruitment and necessary combination of different mechanical forces to regulate membrane curvature and vesiculation during membrane traffic.

Nutrient availability is a significant stress that regulates membrane traffic in a variety of pathways. Bryant and Gould [12] take a broad view of the trafficking and translocation leading to insulin-induced GLUT4 clearance of blood glucose. Their review considers how this trafficking is dictated by physiological determinants and metabolic needs, which vary across cell types and across species. As an intracellular starvation response, autophagosome formation from phagophore assembly sites is reviewed by Hollstein and Kraft [13] with updates on molecular regulation and the roles of the endoplasmic reticulum and vacuoles in autophagy. Microenvironmental triggers, nutrient stress, and gene mutations can induce the uptake of fluid, nutrients, and debris by macropinocytosis. Stow et al [14] review newly identified molecular regulators in immune cells and cancer cells that govern macropinosome formation and downstream cargo sorting, receptor signaling, and cell survival.

Interactions between organelles mediated by lipid exchange and lipid regulation, which were highlighted in Volume 59 in this series, continue as very active areas in membrane traffic. Here the review by Lees and Reinisch [15] provides new perspectives on the molecules that regulate lipid exchange at organelle contact sites. Harper et al [16] provide updates on the protein complexes that mediate small-molecule exchange between mitochondria and other organelles and the review from van den Boomen et al [17] addresses regulation of sterol homeostasis by ubiquitination.

Cargo sorting at appropriate cellular locations has been a theme of membrane traffic since the discovery of coat proteins and their ability to select cargo for sequestration. The importance of sorting integrity to the health of a whole organism, as well to the function of a single cell, is becoming increasingly apparent. The recent progress in understanding regulation of clathrin-coated vesicle formation reviewed by Briant et al [2] demonstrates how clathrin-mediated pathways affect tissue development and differentiation, as well as disease. The review by Phillips et al [18] discusses quality control mechanisms in the endoplasmic reticulum that are absolutely critical for the health of a cell and whose malfunction accounts for toxicity in protein folding diseases. The formation of protein sorting domains and tubules on endosomes for selective degradation or recycling is emerging as a key mechanism of cargo sorting, as described at the molecular and structural levels in the review by Weeratunga et al [19] and as reviewed for the endosomal pathway of *C. elegans* by Norris and Grant [20].

Sorting and trafficking of cargo in the secretory pathway and moving through the Golgi have been studied by live imaging, and the revelations from such studies are reviewed here by Thomas and Fromme [21], with a focus on Rab GTPase cascades and counter currents that regulate this transport. The review by Shafaq-Zadah et al [22] provides a comprehensive update on clathrin-independent pathways for endocytosis that contribute to apico-basolateral polarity in epithelia, front-rear polarity in migrating cells, and synapse formation in neurons and immune cells. The review highlights how these endocytic pathways coordinate with secretory traffic to deploy proteins to specific membrane domains in a highly targeted fashion. Continuing on the theme of highly targeted traffic, Naslavsky and Caplan [23] review endocytic traffic that helps to regulate organelles without membranes, such as cilia and the centrosome, which are supported by endocytic machinery throughout the cell cycle. The review by Noack and Mukherjee [6] highlights recent examples of sorting and trafficking events that are highjacked by bacterial

and viral pathogens, including mechanisms for subverting traffic at the level of the endoplasmic reticulum and in mitophagy.

We close this editorial with a heartfelt tribute to three giants in the membrane traffic field whom we have lost during this past year, both to COVID-19 and to cancer, Marilyn Farquhar, Kathryn Howell, and Ernst Ungewickell. The career contributions of Marilyn and Kathryn laid much of the foundation for our current understanding of the ultrastructure, pathways, and molecules of the Golgi apparatus [24,25]. Ernst was a pioneer in the field of clathrin biochemistry, from his identification of clathrin's triskelion morphology [26] to his in vitro reconstitution of clathrin coat formation [27]. All three were strong characters, of staunch integrity, with passion for their research. They leave a legacy of several generations of trainees who continue to push the field of membrane traffic forward. And their work, similar to much of that described in this issue, has set the stage for progress in molecular biology that will eventually overcome the diseases that removed them from our community.

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