Around 25% of the human genome encodes for integral membrane proteins. The study of those molecular processes that control the intracellular transport of these proteins (and associated proteins and lipids) during organelle biogenesis, organelle maintenance and organelle quality control is an extensive field that includes the secretory, endocytic and autophagic pathways, all fundamental features of eukaryotic cells. In this issue, leading experts discuss latest advances in our understanding of these membrane trafficking pathways and their essential roles in cellular organisation and cell, tissue and organism-level physiology.

Membrane trafficking is a highly dynamic process with organelles needing to be correctly positioned and transport carriers needing to be moved to their correct destinations. Cross and Dodding [1] provide the foundations for such dynamic behaviour by discussing how these events are regulated by dynein, kinesin and myosin motor proteins and in particular the new insights that have emerged into the mechanisms and regulations of motor-–organelle interactions. Gillingham and Munro [2] discuss recent progress in the identification of the molecular mechanisms that allow highly dynamic cargo-enriched transport carriers to be recognised and docked at their correct acceptor organelle. These tethering concepts are further explored by Lamber et al. [3] who focus on the role of active forms of Rab GTPases as ‘transient landmarks’ for providing compartment identity cues during vesicle tethering including new evidence for a direct role of Rab guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) in the tethering process. The importance of correct Rab GTPase switching for orchestrating efficient membrane trafficking within a neuronal context is dissected by Bonet-Ponce and Cookson [4] who explore the recent identification of Rab’s as major phosphorylation targets for the LRRK2 kinase and as regulators of α-synuclein clearance during the pathobiology of Parkinson’s disease. Mattie et al. [5] expand the discussion of GTPase switches through an exploration of their role in controlling the dynamics of the interconnected mitochondrial reticulum.

A series of reviews serve to highlight recent advances in our appreciation of lipid signalling and lipid metabolism in membrane trafficking. Wang et al. [6] discuss the switching in phosphoinositide signatures within the endocytic and endo-lysosomal network and how defects in the efficiency and timing of these switches are increasingly linked to pathophysiolgy. The under-appreciated role of other lipid species is explored by Wang et al. [7] they discuss recent advances in dissecting the interface between glycerol-based phospholipid and sphingolipid metabolism in membrane trafficking through the TGN/endosomal network. Best et al. [8] go on to describe the exciting new advances in understanding the role of phospholipid flippases in lipid flipping between the membrane bilayer thereby generating lipid asymmetry during the biogenesis of vesicular and tubular transport carriers. Moving away from the vesicular transport model of lipid movement, Henne [9] explores the increasing appreciation of inter-organelle lipid transport through membrane contact sites by discussing the crosstalk between endoplasmic reticulum, lysosomes and lipid droplets. Recent advances into the fascinating mechanistic question of how monolayer enclosed lipid droplets are formed from specialised regions of the endoplasmic reticulum and how this process is regulated and may be de-regulated in lipid storage diseases are discussed by Jackson [10].

As discussed at the outset, the central role of membrane trafficking is the transport of integral proteins during organelle biogenesis and the delivery and removal of these proteins during organelle maintenance and adaptive remodelling of organelle function in response to physiological demand. Hutchings and Zanetti [11] explore the fundamental question of how bulky integral proteins, such as procollagens, are efficiently sorted through the secretory pathway and the emerging view that this may be achieved through

flexibility in coat complexes. Baños-Mateos et al. [12] extend the theme of coat complexes by exploring the common features and unique differences between two functionally distinct endosome associated coat complexes, retromer and retriever, both of which are involved in the sorting of a wide array of integral proteins away from the lysosomal degradative fate for recycling principally back to the cell surface. Gatta and Carlton [13] discuss the role of the endosomal associated ESCRT coat complexes in sorting of integral proteins into the degradative fate, and in particular the recent and unexpected insight into the role of the ESCRT-III complex in membrane remodelling during membrane repair. The question of how membrane trafficking pathways can be manipulated to remodelled organelle function in response to changing physiological demand is explored by Hartwig et al. [14], who discuss the switching in the endomembrane distribution of copper pumping ATPases in response to copper availability and how this is providing new insight into neuropsychiatric phenotypes associated with copper dyshomeostasis. Carter and Blacque [15] provide further insight into directed membrane trafficking and the integration of secretory and endocytic pathways during organelle biogenesis, in this case cilium, and the recent observation that released extracellular vesicles are associated with ciliary control. Concepts of directed membrane trafficking are further explored by Delevoy et al. [16] through the functional adaptation of lysosomal-related organelles.

It has long been appreciated that viruses and bacterial pathogens have developed an array of ingenious mechanisms to hijack and manipulate the membrane trafficking pathways of their host cells in order to establish their replicative niche. Bugnon Valdano et al. [17] describe how the capsid proteins of non-enveloped DNA tumour viruses exploit different entry routes into host cells and manipulate different endosome associated coat complexes to promote their transport through the TGN and ER to reach the nucleus. The other side of the host:pathogen battle is explored by Taguchi and Mukai [18], who discuss membrane trafficking of Toll-like receptors and STING as part of the innate immune response to invading pathogens, dysregulation of which can lead to infection and autoinflammatory disease. Finally, the need to study such membrane trafficking pathways in an in vivo context is highlighted by Ebrahim and Weigert [19], who discuss how advances in intravital subcellular microscopy coupled with genetically modified mouse models have provided much insight into trafficking pathways in living tissues.

Overall, through this series of reviews the authors provide insight into a range of exciting advances and developments in the study of membrane trafficking. Through an increased understanding of molecular mechanism has stemmed an increased level of appreciation that dysregulation of membrane trafficking pathways plays an important role during the initiation and development of human disease that span from host:pathogen interactions through to age-related inflammatory and neurodegenerative diseases. Further dissection of the molecular mechanisms of membrane trafficking is certain to provide additional new insight into these and other human diseases.

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