Multi-author Review
Membrane traffic in the secretory pathway

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Abstract. During the last 20 years remarkable achievements have been made in the understanding of the molecular basis of membrane traffic in the secretory pathway. A combination of morphological, biochemical and genetical approaches revealed the identity of various compartments and transport intermediates, and provided basic functional insights into membrane trafficking. Recently, live cell imaging approaches further refined our understanding of the underlying mechanisms of budding, transport and fusion of transport containers, led to the discovery of new pathways and triggered new concepts as to how membrane traffic is orchestrated. This multi-author review highlights recent advances in membrane traffic by focusing on transport vesicles as the central mediators of communication in the secretory pathway. (Part of a Multi-author Review)

Keywords. Clathrin, COP protein, endocytic traffic, membrane fusion, myosin, phosphoinositide, Rab GTPase, secretory pathway, SNARE, transport vesicle.

Introduction

The secretory pathway of eukaryotic cells consists of a number of distinct membrane-bound compartments interconnected by vesicular traffic. Each compartment has a characteristic content of proteins and lipids, which must be maintained. Proteins destined for secretion first enter the endoplasmic reticulum (ER) and then undergo a vesicle budding and fusion journey to various cellular destinations, including the plasma membrane, the endocytic compartment and back to the ER for retrieval. At the same time, recycling of membranes and uptake of extracellular components are accomplished by the endosomal system. It is thought that vesicular transport is the basic communication mechanism between the various compartments and with the cellular environment [1 – 3]. Three types of transport vesicles have been characterized in detail so far: COPII-coated vesicles, which mediate exit from the ER; COPI-coated vesicles, which function within the early secretory pathway; and clathrin-coated vesicles, which shuttle between the trans-Golgi network, the endsomal/lysosomal system and the plasma membrane. These vesicle types are formed at the donor organelles and are transported to and fuse with target organelles. Vesicle biogenesis involves coat recruitment by small GTPases at donor membranes, Rab GTPases for COPI vesicles and Arf for both COPI vesicles and various clathrin vesicles. It emerges that, in addition to the well-characterized three classical coats, more types of vesicle coats exist.

Due to the constant flux of membrane material tight regulation of these vectorial vesicle transport processes is necessary to maintain a dynamic equilibrium between the various compartments of the secretory pathway. Rab GTPases are at the top of the hierarchy for this regulation. Besides driving cargo collections into nascent transport vesicles, Rab GTPases recruit vesicles to tethers to aid efficient and selective targeting. These tethers are either long, coiled coils or multimeric assemblies. Many tethering factors and Rab GTPases interact in concert with SNAREs to accomplish vesicle targeting and fusion with high fidelity. In many instances, Rab GTPases link vesicles to motor proteins to direct their transport. Furthermore, phosphoinositides serve as important regulators of intracellular trafficking and cell-signaling events. Thus, a long list of players in directing vesicle traffic becomes evident: more than 60 Rab GTPases, numer-

ous Rab effectors and tethers, phosphoinositides and other regulatory proteins. Endosomal traffic is mechanistically similar to the sorting and membrane-trafficking events in the secretory pathway. The only exception is the sorting of activated signaling receptors for degradation in the lysosome, which is accomplished by the inward budding of the endosomal membrane to create intraluminal vesicles.

Much work is needed to refine our understanding of membrane traffic machines and to elucidate how these machines work in a normal, cellular context. In particular, time-resolved imaging methods are required to analyze the cascades of protein interactions in a spatiotemporal manner. This will potentially provide answers in relation to the molecular mechanisms involved, the specificity of the transport steps and the regulation imposed by the cell. Although remarkable insights into basic principles of membrane traffic have been made to date, a growing number of burning questions remain. These include the following: How are specific proteins packaged into a forming transport vesicle in a highly selective manner? How is the timing of vesicle formation accomplished? How many different types of vesicles are present in a cell? How do transport intermediates identify their targets? What role does the cytoskeleton play in the targeting of transport vesicles? Which function do Rab proteins have in the formation of SNARE complexes and how does membrane fusion occur from the biophysical point of view? Much remains to be learned about these questions.

This multi-author review surveys some of these timely issues by focusing on important players and model systems of biosynthetic and endocytic membrane traffic. One subject deals with recruitment and shedding of coat proteins and the regulatory cascade of SNARE-dependent membrane fusion in the context of regulated exocytosis. Furthermore, the role of Rab proteins in the maturation, transport/recruitment and docking of secretory granules, the function of unconventional myosins in membrane traffic as processive motors and/or docking factors, and the role of phosphoinositides as spatial and temporal landmarks for organelle and sub-organelle domains are highlighted. In addition to the secretory traffic, the machinery and motifs governing endosomal sorting and membrane traffic are discussed. Finally, a novel pathway, involving Rab1-positive tubular membrane carriers and connecting the intermediate compartment with the cell periphery, is reported.

From these and other examples not included here, it emerges that the complexity of membrane traffic in the biosynthetic and endocytotic pathway is much greater than anticipated. First, the number of identified components of the transport machineries and the regulatory complexes underlying membrane traffic is constantly growing. Second, these functional complexes, operating by cascades of protein-protein interactions, are part of larger signaling networks integrating membrane-trafficking and cell-signaling events. Improved methods, including single-molecule imaging and new strategies such as the integrative approach of systems biology, are necessary to unravel this puzzle of 'Interactomics'.

Finally, I would like to thank my colleagues, who devoted their time to contribute to this multi-author review.

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