Membrane Traffic in the Post-Golgi Network: Toward A Better Understanding of the Higher Order Functioning Systems

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Inside the eukaryotic cell is filled with various organelles. In order for the cells to function normally, tens of thousands of proteins synthesized in the cell must be properly delivered to the organelles of their final destination. Cells have developed several different machineries for protein targeting to realize the complex evolution of protein transport network connecting the various organelles. In the secretory and endocytic pathways, this is basically achieved with a cellular mechanism called vesicular transport or membrane traffic, where small membrane-bound vesicles derived from the donor organelle membrane act as a carrier in which cargo proteins to be delivered are selectively concentrated. Once the transport vesicles are pinched off from the donor organelle membrane, they travel across the cytosol, and specifically recognize, tether and fuse with the target organelle membrane to deliver the cargo molecules. Membrane traffic has recently been recognized to be involved in sophisticated higher order functioning systems characteristic of higher, multicellular organisms, as typified by the immune system as well as the nervous system, to say nothing of its importance for the life of cells as a fundamental cellular function. It is not surprising, therefore, that membrane traffic has been drawing more and more attention from researchers outside the field in recent years. A good indication of this is the fact that the Nobel Prize in Physiology or Medicine in 1999 has been awarded to Dr. Günter Blobel for his pioneering work on “the discovery of proteins have intrinsic signals that govern their transport and localization in the cell” (Blobel and Dobberstein, 1975a; Blobel and Dobberstein, 1975b). Thus, it is pertinent at this point of time to organize a review cluster for Cell Structure and Function dealing with membrane traffic. In higher organisms including ourselves, membrane traffic connecting the various post-Golgi membrane compartments such as the trans-Golgi network (TGN), endosomes, lysosomes and the plasma membrane has been particularly well-developed: it is now proposed to call this membrane traffic system the “post-Golgi network”.

The complicated evolution of the post-Golgi network is thought to be attributable to the need to support the transmission of vast amounts of information to and from the cells across the plasma membrane in various aspects of activity in multicellular organisms. In this cluster, all articles will be concerned with the membrane traffic operating in the post-Golgi network, with the aim of helping us to better understand the importance of membrane traffic in higher order functioning Systems.

Over the past decade or two, the elucidation of the molecular mechanisms for membrane traffic has been accelerated by taking advantage of the powerful genetic analyses of a model organism, Saccharomyces cerevisiae. Using these approaches, groups of genes have been identified whose products are required for sorting and transport of proteins to the vacuole, the yeast counterpart of lysosomes (Rothman et al., 1989). Another model organism, the fission yeast Schizosaccharomyces pombe possesses more similarities to mammalian cells in some features than does S. cerevisiae (Moreno et al., 1991). Takegawa et al. will review vacuolar transport pathways in S. pombe in contrast with those in S. cerevisiae (Takegawa et al., this issue).

Transport vesicles are covered with coat components, distinct sets of peripheral membrane proteins, responsible for the formation of vesicles (by membrane deformation) as well as cargo selection (by specific interaction with the cargo proteins). Three classes of coated vesicles have been well-described to date: COP-I, COP-II, and clathrin-coated vesicles (Kirchhausen, 2000). Of those, clathrin-coated vesicles are involved in the membrane traffic connecting the post-Golgi compartments. Two articles are invited in this review cluster to introduce the contrasting, but inextricable, family of proteins constituting the clathrincoats. Adaptor protein (AP) complexes are classic coat components of the clathrin-coated vesicle and participate in several distinct transport pathways in the post-Golgi network such as endocytosis and lysosomal targeting. Some members of the family are exclusively expressed in certain cell types and play a role in cell-type specific transport pathways. Nakatsu and Ohno will review the recent advances in understanding of molecular mechanisms in cargo selection and clathrin-
coated vesicle formation, as well as of the roles in orga-
isms, of AP complexes (Nakatsu and Ohno, this issue). GGAs are the latest addition to the list of clathrin-coat com-
ponents, which are thought to be involved in sorting at the TGN of the cargos bound for endosomes. It has recently been suggested that GGAs operate the endosomal sorting in concert with an AP complex family member, AP-1A. Molecular function of GGAs will be discussed, including the recent flourishing contribution by the authors in struct-
ural analyses of GGAs with X-ray crystallography (Nakayama and Wakatsuki, this issue).

Although it is well known that polyubiquitin targets cyto-
solic and nuclear proteins for proteasomal degradation by covalently binding to them, recent studies shed light on a novel role of ubiquitin: monoubiquitination of membrane proteins as a lysosomal targeting signal along the endocytic pathway (Bonifacino and Weissman, 1998). Moreover, it has recently been revealed that the same cellular compo-
ments required for recognition and sorting of ubiquitinated proteins into inner vesicles of the multivesicular bodies en route to lysosomes are also involved in budding of certain viruses, including HIV, from the plasma membrane of infected cells (Amara and Littman, 2003). Lipids are also important for, and in some cases may collaborate with ubiqui-
quitin in, the membrane traffic in the endosomal/lysosomal compartments. Here, Umebayashi will discuss the roles of ubiquitin and lipids in this aspect (Umebayashi, this issue).

Lysosomes, filled with a variety of hydrolytic enzymes, have long been believed to be a site of terminal degradation. Growing evidence now tells us that lysosomes are more than we imagined: they not only digest, but also can store and secrete. In certain tissues and cell types, lysosomes differen-
tiate into organelles with specialized functions, termed lysosome-related organelles (Dell’Angelica et al., 2000), or secretory lysosomes (Blott and Griffiths, 2002). A character-
istic feature of the lysosomes and lysosome-related organelles (as well as endosomes) is their acidic luminal pH, and the acidic internal milieu is tightly correlated with their functions. The acidification is achieved by a subset of proton pumps, the vacuolar-type proton ATPase (v-
ATPase). Roles of lysosomes and lysosome-related organelles in higher organisms will be reviewed with the emphasis on v-ATPase functions (Sun-Wada et al., this issue).

The secretory pathways can be divided into two types: constitutive and regulated secretion (Burgess and Kelly, 1987). The latter pathway is highly developed in multicellu-
lar organisms as a strategy for intercellular communication, and are mediated by ‘conventional’ secretory granules as well as secretory lysosomes. These organelles are morpho-
logically distinct, but the features shared among them, including the association of rab27 on their membranes, sug-
gest their phylogenetic commonality. Izumi et al. will discuss the mechanisms of regulated secretion with a focus on rab27 and its effectors exophilins (also known as Slp/Slac2) (Izumi et al., this issue).

Another important activity of membrane traffic in the post-Golgi network is autophagy. Autophagy has started to be dissected at the molecular level in an accelerating pace for the last several years, and has been extensively described in the review cluster of the Cell Structure and Function organized by T. Yoshimori a year ago (Huang and Klionsky, 2002; Mizushima et al., 2002; Petiot et al., 2002).

Multiple complexities of the post-Golgi network and their relationships with the functions as multicellular organ-
isms have just begun to be addressed, and a long, although promising, way awaits us before we can capture the whole of the field. Hopefully the articles in this review cluster will offer us subtle glimpses of these future directions.

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