JB Minireview—Membrane Traffic in Physiology and Pathology

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Overview: Membrane Traffic in Multicellular Systems: More than Just a Housekeeper

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Membrane traffic is a fundamental cellular function by which molecules are transported between organelles in the post-Golgi network. Accumulating evidence supports the notion that membrane traffic is not only indispensable for normal cellular function and maintenance of cellular viability by playing housekeeping roles, but also critical for various functions characteristic of multicellular organisms. This Minireview series will focus on the latter aspects of membrane traffic. The topics discussed are: the pathophysiological impact of clathrin-associated adaptor protein (AP) complexes, the significance of membrane traffic in Alzheimer's disease, regulated exocytosis of insulin, secretory lysosomes in immune response, exosomes in physiology and pathology, viral and mammalian ubiquitin ligases modulating immune response, membrane traffic of bacterial toxins, and containment of bacterial infection by autophagy.

Key words: exocytosis, infectious microorganism, membrane traffic, multicellular organism, pathophysiology.

One of the most distinguishing characteristics of eukaryotic cells is the compartmentalization of their cytoplasm. By dividing the cytoplasm into an array of functionally distinct membrane-bound compartments, or organelles, cytosol can be separated from enclosed aqueous compartments where specialized functions are achieved. Each organelle contains a distinct set of enzymes and other specialized molecules, and it is these proteins that confer upon organelles their characteristic structural and functional properties. To maintain the organelle-specific composition of these proteins, the cells are equipped with complex distribution systems that transport specific proteins from one compartment to another. Cells could not even survive, not to mention function normally, unless the transport machinery operates properly.

Transport between the organelles in the secretory and endocytic pathways—including the endoplasmic reticulum, Golgi apparatus, endosomes, lysosomes and the plasma membrane—involves dynamic exchange of membrane and proteins, and is called "membrane traffic." Membrane traffic is generally mediated by small, membrane-bound transport vesicles. The transport vesicles are formed by budding off the membrane of the "donor" organelle that provides cargo molecules to be delivered to another compartment, the "target" organelle. Once vesicles are formed, they travel across the cytosol and specifically dock and fuse with the membrane of the target organelle to complete the transport.

The molecular understanding of membrane traffic has grown rapidly in the last decade or two. A Minireview series published in this journal in 2004–2005 examined this topic. More recently, accumulating evidence has unraveled the pathophysiological importance of membrane traffic in multicellular organisms. These findings are the focus of this Minireview series.

Membrane traffic and diseases

Breakdown in membrane traffic sometimes leads to certain disease states. Clathrin-associated adaptor protein (AP) complexes are a major coat component of clathrin-coated vesicles that regulate membrane traffic in the post-Golgi network connecting the *trans*-Golgi network, endosomes, lysosomes and the plasma membrane. This author will review mutations in the genes encoding the subunits of AP complexes, which lead to disorders ranging from hereditary diseases to embryonic lethality.

Neurons are highly specialized cells having a long axon and branched complex dendrites. To maintain their characteristic structures and functions, neurons have evolved distinct membrane trafficking machinery. Disorders of the machinery are thought to result in neurodegenerative diseases. Suzuki *et al.* will review one of the most popular neurodegenerative disorders, Alzheimer's disease, and the significance of membrane traffic in this disease.

Membrane traffic and regulated exocytosis

Regulated exocytosis is one of the important functions operated by membrane traffic in multicellular organisms. Neurotransmission mediated by synaptic vesicles is a typical example. Another well-studied example of regulated exocytosis is that of insulin by pancreatic β cells. Although advances in molecular biology and electrophysiology have greatly broadened our understanding of the molecular mechanisms of insulin release, the dynamic processes of membrane traffic in insulin exocytosis, such as

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translocation, docking and fusion of insulin granules, have remained elusive until recently. Ohara-Imaizumi and Nagamatsu will review recent insights into these processes that were elucidated with a new imaging technique, total internal reflection fluorescence microscopy.

Secretory lysosomes are lysosomes which are capable of undergoing regulated secretion in response to external stimuli. Many cells of the immune system use secretory lysosomes to release proteins involved in their specialized effector mechanisms. Holt *et al.* will discuss about secretory lysosomes and the regulatory mechanism of their secretion.

Exosomes are yet another, specialized means of regulated exocytosis by the cells. Exosomes are small vesicles that are contained in multivesicular bodies, or late endosomes, and are released by cells upon fusion of these organelles with the plasma membrane. van Niel *et al.* will review the implications of exosomes in intercellular communication under physiological as well as pathologic conditions such as tumors and prion diseases.

Membrane traffic in infection and immunity

Membrane traffic is also involved in infection and immunity. Viruses and bacteria often utilize the endocytic pathways of host cells for invasion of the cells. In addition, large DNA viruses such as adenovirus, herpes simplex viruses, Epstein-Barr virus and cytomegalovirus have evolved sophisticated mechanisms to evade host immune surveillance, mostly by perturbing the membrane traffic of host cells, thereby preventing antigen presentation of their own products. Ohmura-Hoshino *et al.* will review the recently discovered viral E3 ubiquitin ligases from Kaposi's sarcoma–associated herpes virus and their mammalian homologues.

A number of bacterial toxins also dexterously highjack membrane traffic of host cells to reach their specific target sites. Intracellular trafficking of bacterial toxins, especially cholera toxin and botulinum neurotoxin, will be reviewed by Fujinaga.

Autophagy is a fundamental cellular homeostatic mechanism that enables bulk degradation of a cell's own organelles and cytosolic proteins for reuse. It has recently been revealed that autophagy is important not only for cellular nutritional homeostasis but also for its involvement in pathophysiological conditions such as development, aging, cancer, neurodegeneration and myopathies. Furthermore, autophagy plays a role in containing infection by certain bacteria and viruses. Amano *et al.* will discuss this finding using Group A streptococcus as an example.