Department of Physiological Chemistry

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Research Projects:

1) Studies of intracellular membrane traffic and intraflagellar transport:

Normal functions of a human body, which consists of ~3.7 × 10^{13} cells, rely strictly on the normal function of every cell. There are a variety of intracellular organelles, in which specific proteins are localized (Figure 2). Furthermore, it is essential for each cell to function properly that each protein is transported from an organelle where it is synthesized to another organelle or the plasma membrane where it fulfills its function. We are studying protein and lipid transport systems called membrane traffic mediated by membrane-enclosed structures.

We are working to elucidate the mechanism of protein transport in an organelle called primary cilium. Primary cilia serve as "cellular antennae", because they contain many receptors for extracellular signals. Defects in trafficking of ciliary proteins prevent the cilia from functioning as antennae, leading to a variety of hereditary disorders, generally called the "ciliopathies." The primary cilium has an axoneme composed of microtubules. The intraflagellar transport (IFT) machinery powered by motor proteins, kinesin and dynein, regulates anterograde and retrograde protein trafficking along the axoneme (Figure 1). The IFT machinery is a highly complicated molecular machine containing 5 multiprotein complexes composed of ~40 subunits in total. We are revealing the molecular basis of regulation of ciliary protein trafficking by elucidating the architectures of the multiprotein complexes in the IFT machinery, the roles of each subunit, and the recognition mechanisms of cargo proteins. Our research will also lead to the elucidation of the molecular basis of the ciliopathies.

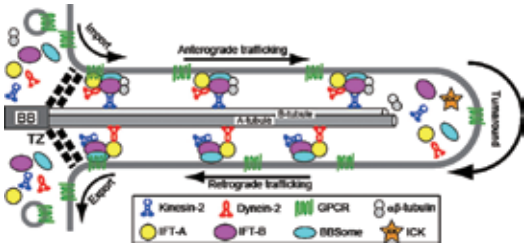

Figure 1. Bidirectional ciliary protein trafficking mediated by the IFT machinery

2) Roles of transbilayer lipid dynamics in cellular functions:

Lipids are asymmetrically distributed between lipid bilayers of biological membranes. In the plasma membrane, PS, PE, and PI are primarily confined to the cytoplasmic leaflet, and PC and SM are enriched on the exoplasmic leaflet. The transbilayer lipid asymmetry is regulated by ATP-dependent flippases (translocate phospholipids from the exoplasmic to the cytoplasmic leaflet; red) and floppases (translocate phospholipids in the opposite direction; blue) (Figure 2), and scramblases (ATP-independent bidirectional transporters). Spatiotemporal transbilayer lipid asymmetry plays a crucial role in many cellular processes (*e.g.*, thrombogenesis, immune response, clearance of apoptotic cells and erythrocytes, fusion of myocytes, cell division, cell migration, sperm capacitation, and membrane traffic), however, the regulatory mechanisms underlying the asymmetry remain unknown. We aim at elucidating roles of P4-ATPases (flippases) in cellular functions, such as membrane traffic, cell migration, and cell polarity, *etc.* Since some mutations of P4-ATPases are responsible for genetic diseases, we also aim at understanding how lipid dynamics are committed to pathophysiological conditions.

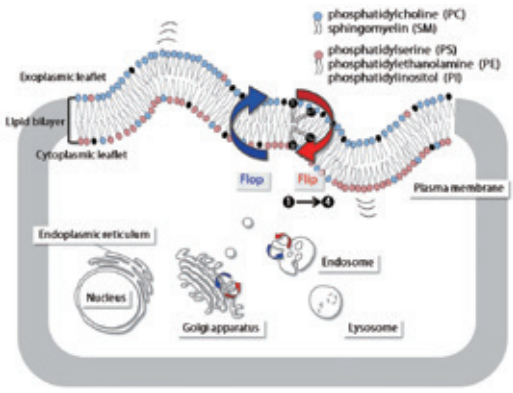

Figure 2. Regulation of transbilayer lipid asymmetry in biological membranes

Recent publications

- Tsurumi, Y. *et al.* (2019) Interactions of the dynein-2 intermediate chain WDR34 with the light chains are required for ciliary retrograde protein trafficking. ***Mol. Biol. Cell*, 30,** 658-670.
- Funabashi, T. *et al.* (2018) Interaction of heterotrimeric kinesin-II with IFT-B-connecting tetramer is crucial for ciliogenesis. ***J. Cell Biol.*, 217,** 2867-2876.
- Hamada, Y. *et al.* (2018) Interaction of WDR60 intermediate chain with TCTEX1D2 light chain of the dynein-2 complex is crucial for ciliary protein trafficking. ***Mol. Biol. Cell*, 29,** 1628-1639.
- Takahara, M. *et al.* (2018) Ciliopathy-associated mutations of IFT122 impair ciliary protein trafficking but not ciliogenesis. ***Hum. Mol. Genet.*, 27,** 516-528.
- Takada, N. *et al.* (2018) Phospholipid-flipping activity of P4-ATPase drives membrane curvature. ***EMBO J.*, 37,** e97705.
- Takatsu, H. *et al.* (2017) Phospholipid flippase ATP11C is endocytosed and downregulated by Ca^{2+}-mediated protein kinase C (PKC) activation. ***Nat. Commun.*, 8,** 1423.