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– Supramolecular Biology –

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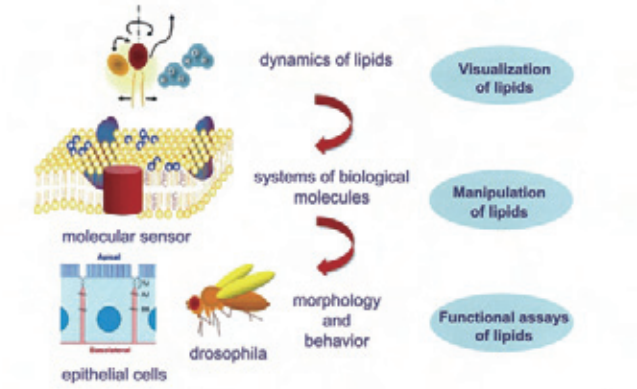
Scope of Research

We have undertaken the molecular biology, cell biology and behavioral genetics approaches to study the role of biological membrane systems in controlling animal morphogenesis and behavior. The membrane is a complex supramolecular complex formed by a noncovalent self-assembly of proteins, lipids, and carbohydrates. Our long term objective is to understand the fundamental principles underlying the dynamism of complex membrane systems and to provide a clue to reconstruct an artificial supramolecular membrane complex. Current research topics are as follows:

(1) Identification of a series of proteins that regulate molecular motion of lipid molecules and elucidation of their role in cellular and animal morphogenesis.

(2) Establishment of a series of *Drosophila* mutants with aberrant temperature preference (*atsugari*, *samugari*, etc) and elucidation of the molecular relationship between the temperature-responding membrane systems and animal behaviors.



KEYWORDS

Lipid Cell Biology Membrane

Selected Publications

Ikenouchi J, Umeda M: FRMD4A Regulates Epithelial Polarity by Connecting Arf6 Activation with the PAR Complex, *Proc. Natl. Acad. SCi. USA*, **107,** 748-753 (2010).

Takeuchi K, Nakano Y, Kaneda M, Aizu M, Yamaguchi A, Kato U, Awano W, Kiyonaka S, Mori S, Yamamoto D, Umeda M: Changes in Temperature Preference and Energy Homeostasis in Dystroglycan Mutants, *Science*, **323,** 1740-1743 (2009).

Ikenouchi J, Sasaki H, Tsukita S, Furuse M, Tsukita S: Loss of Occludin Affects Tricellular Localization of Tricellulin, *Mol. Biol. Cell.*, **19(11),** 4687-4693 (2008).

Ikenouchi J, Umeda K, Tsukita S, Furuse M, Tsukita S: Requirement of ZO-1 for the Formation of Belt-like Adherens Junctions during Epithelial Cell Polarization, *J. Cell Biol.*, **176,** 779-786 (2007).

Emoto K, Inadome H, Kanaho Y, Narumiya S, Umeda M: Local Change in Phospholipid Composition at the Cleavage Furrow is Essential for Completion of Cytokinesis, *J. Biol. Chem.*, **280,** 37901-37907 (2005).

Regulation of Membrane Phospholipid Dynamics and Its Role in Cell Migration

The basic structure of biological membranes is the lipid bilayer in which phospholipids distribute asymmetrically between the two leaflets of the bilayer. This asymmetry is regulated by the transbilayer movement of phospholipids, but its physiological significance and molecular mechanisms are largely unknown. Previously we have identified a putative aminophospholipid translocase complex responsible for the inward movement of aminophospholipids, P-type ATPase (ATP8A1) and its non-catalytic subunit mROS3. Depletion of either mROS3 or ATP8A1 inhibited cell migration as well as the inward movement of aminophospholipids across the plasma membrane. ATP8A1 localized at the leading edge of migrating cells and contributes to the formation of membrane ruffles by regulating actin cytoskeleton. Furthermore, PE is exclusively located in the inner leaflet of the plasma membrane at the leading edge (Figure 1). Immobilization of cell-surface PE by a PE-binding peptide inhibited the formation of membrane ruffles, causing a severe defect in cell migration. These results indicate that organized movement of cell-surface PE mediated by ATP8A1 plays an important role in cell migration by regulating actin reorganization and membrane ruffling.

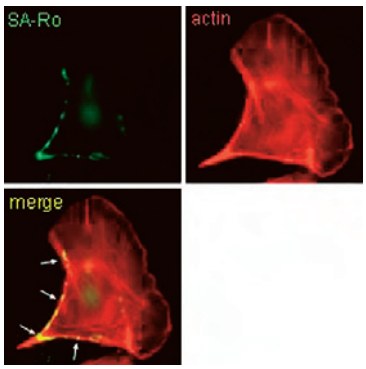


Figure 1. Cell-surface PE distributes in the inner leaflet of the ruffling membranes in migrating cells. The serum-stimulated cells were incubated with 10 μg/ml PE-binding peptide (SA-Ro) for 30 min at 37 °C, and then fixed and stained for SA-Ro and actin. Arrows indicate the colocalization of SA-Ro and actin at the rear membrane.

Elucidation of Molecular Mechanisms which Generate and Maintain Discrete Membrane Domains in Polarized Cells

The plasma membranes of cells are fundamental components of our body. They are composed of discrete membrane domains in which membrane proteins and lipids are differentially partitioned. Compared to plasma membrane proteins which have been investigated by many researchers, plasma membrane lipids are less well understood, even though they are the other main component of membranes. Using epithelial cells as an experimental model, we aim to clarify what kind of lipids and lipid metabolites are enriched in the apical as well as the basolateral membrane, and how these asymmetric membrane domains are maintained to be separated (Figure 2).

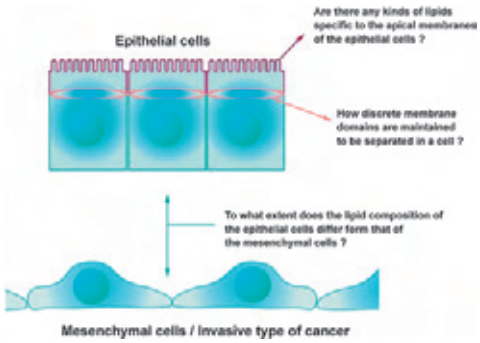


Figure 2.

Drosophila Stearoyl-CoA Desaturase in Energy Metabolism

In many animals, energy-rich components are converted into glycogen and triacylglycerol (TAG), the storage forms of carbohydrate and fat, respectively. TAG is deposited in the adipose tissue in mammals or the fat body in *Drosophila*, and is metabolized during periods of energy need such as nutrient depletion. The regulatory mechanisms of energy homeostasis are still not fully understood. Stearoyl-CoA desaturase, catalyzing introduction of the *cis* double bond in the Δ9 position of fatty acyl-CoA substrates, is a rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids (Figure 3A). We generated a series of *Drosophila* mutants that showed a defective expression of stearoyl-CoA desaturase (desat1). One of them, designated *desat1#42*, showed dramatic reduction in TAG content and was defective in survival during starvation (Figure 3B). In the *desat1#42* mutant, the expression of desat1 was specifically reduced in oenocyte, an organ analogous to mammalian liver. The *desat1#42* mutant will provide a unique model for studying the physiological functions of desat1 in energy metabolism.

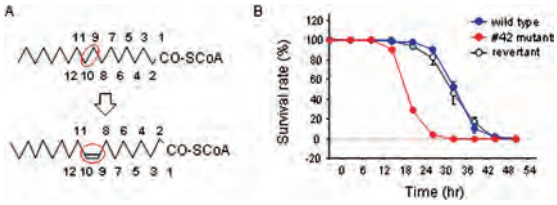


Figure 3. Starvation resistance was reduced in the *desat1#42* mutant flies.
A) Double bond introduction by stearoyl-CoA desaturase.
B) Survival rate of wild type and *desat1#42* mutant flies during starvation.