True Cell Simulations Inc.
cell blog
Nov/05/2025, Kazuhisa Ichikawa

18. Lipid droplet and membrane systems

Descriptions of lipids and membrane systems, including cell membrane and those of organellar membranes, in a textbook of molecular cell biology are limited in comparison to those of proteins or genes (e.g., Molecular Cell Biology, Lodish, H., et al., 2016, W.H. Freeman and Company). We tend to recognize membrane systems as compartments or places of local biochemical reactions. This is not surprising, because such a view emerges intuitively into our understanding when we view electron micrography of a cell. When we study the change in the cell shape or organelle creation/destruction, however, we need to know the mechanisms of the membrane expansion/retraction [1)]. In addition, we find many reports on the membrane contact site (MCS), where membranes of two organelles are closely apposed. In this blog, the membrane system of a cell, including mitochondria, Golgi membranes, and lipid droplets (LD), is discussed.

1) Once, it was popular to simulate the cell membrane based on modeling a membrane as a spring network. However, the force acting on two amphipathic lipid molecules is not inversely proportional to the distance for a wider range of distances. Thus, we should say such a model is phenomenological.

More than 1,000 lipid species are synthesized. LD also exists in the nucleus. No blueprint like genes for proteins exists for lipids. These various lipids are synthesized and degraded through chains of biochemical reactions. The fluid-mosaic model by Singer, S.J. and Nicolson, G.I. (1972, Science) is still the basis for the understanding of the membrane system.

Membrane constituents and their synthesis and breakdown: Almost all neutral lipids are synthesized on the ER [2)]. This is because enzymes that synthesize neutral lipids are localized on the ER. Thus, synthesized lipids are transferred to other membrane systems via MCS (Mathiowetz, A.J., et al., Nat. Cell Biol., 2024). Lipid synthesis proceeds on the outer leaflet of the phospholipid bilayer of the ER membrane, where triacylglycerol (TAG) is synthesized from glycerol-3-phosphate (G3P) and phospholipids in the following steps. Synthesized TAGs diffuse within the hydrophilic inner layer of the lipid bilayer, being accumulated in a region forming LD.

G3P → MAG → PA → DAG ↘
TAG → Used as constituents of the LD core
phospholipid/FA ↗

Breakdown of TAGs in LD proceeds by the pathway above in the inverse direction, and finally generates fatty acids (FAs) and glycerol, which is recruited to the cytoplasm. ATGL protein on a lipid monolayer of LD is responsible for the process.

*2 It is known that the phospholipids are synthesized on the mitochondrial membrane.

Structure, roles, and creation of LD: A LD is observed in a spherical shape. The core occupies most volume of an LD, and its constituents are hydrophobic neutral lipids with no proteins. The core is surrounded by an amphiphilic phospholipid monolayer. LDs regulate lipid fluxes, act as lipid buffers, and exchange lipids with other membrane systems, including cell and organellar membranes.

LDs are generated on ER membranes (Mathiowetz, A.J., et al., Nat. Cell Biol., 2024). Diffusing TAGs are accumulated in a region that is created by transmembrane proteins called seipin, where TAGs are condensed. The TAG-condensed region is called the lens. By the further accumulation of

TAGs into the lens, it buds into the cytoplasm, generating an LD. Thus, TAGs are condensed in an LD. Since budding occurs at the cytoplasmic lumen, which is possibly due to the asymmetry of seipin, the membrane at the surface of an LD is a monolayer of amphiphilic lipids. This is because we see a thinner surface membrane of LDs in an electron micrograph*3. During this LD-generating process, proteins are embedded on the surface of LDs. Constituents of lipids in the core are altered by the differences in cell types and metabolic conditions.

*3 See Fig.1 in Cell Blog #9. Large white circles are LDs whose surface membranes are thin. The center region around a large LD is left black because of imperfect staining.

Exchange of lipid at MCS: Lipids are exchanged between ER/LD – cell membrane, ER/LD – mitochondria, ER/LD – Golgi apparatus, endosome – Golgi apparatus, LD – peroxisome, and LD – LD (Mathiowetz, A.J., et al., Nat. Cell Biol., 2024; Iglesias-Artola, J.M., et al., Nature, 2025). Recently, lipid exchange at MCS without the help of LD has been focused (Reinisch, K.M., et al., JCB, 2021). The exchange rate in this system is surprisingly high, reaching 10^6 dehydroergosterol (DHE) molecules exchanged between organelles in 1 sec. This corresponds to exchanging all cell membrane cholesterol molecules within 5 min (Reinisch, K.M., et al., JCB, 2021).

Lipid exchange at MSC is accomplished by lipid transport protein (LTP). There are two mechanisms in this exchange, "bridge" and "shuttle" (Reinisch, K.M., et al., JCB, 2021). Two proteins of Vps13 and Atg2 are known to the bridge mechanism. The length of both proteins is long enough (10 – 30 nm) for bridging the gap between two membranes in MCS. Bulk transfer of lipids is thought to proceed by the bridge mechanism.

LD-related diseases: It is reported that LD deficiency causes cancer, neurodegenerative diseases, and cell-stress-related diseases. It is also known that LD dysregulation relates to health and life span.

In this blog, we discussed lipid synthesis, degradation, transportation/exchange, and LDs. There are many topics left, among them, a simulation of LD generation was reported (Holzhutter, H-. G., FEBS J., 2025). The lipids and LD dynamics are the basis for the change in cell shape, which will be discussed in a later blog.

Proteins exist at the lipid layer and local regions in/on the lipid bilayer. Among these, the raft is well known for its localization of specific proteins. It is known that glycosphingolipids and cholesterol are enriched in rafts. Are these enrichment bases for the localization of specific proteins? What is the mechanism to localize proteins to a specific region of a lipid layer? Proteins are sorted into the lipid bilayer/layer of different organelles. What is the mechanism for such sorting? If different lipid components result in the localization and sorting of proteins, what is the mechanism of localization/sorting of lipids? Obviously, this argument suffers from the infinite regress theory. How can we avoid this trip?