Current Topics

Lipid Dynamics and Pathobiology in Membrane Lipid Rafts

Foreword

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The lipids in biological membranes are an important component of the cell, and are involved in functions such as membrane permeability, signal transduction, cellular homeostasis, and so on. The membrane is composed of an enormous number of different lipid species arranged in an animal species-, organ-, and organelle-specific manner. In the "fluid mosaic model" proposed by Singer-Nicholson in 1972, the lipid in the plasma membrane is characterized as a sea where the lipid is distributed randomly and proteins float like islands. In this model, the chemical diversity of the membrane lipid is not taken into account. Some 25 years later, Simons proposed a new concept, the "lipid raft." In this model, the membrane lipids such as cholesterol and glycosphingolipids (GSLs) are not homogeneously distributed, but rather, form distinct and functional micro-domains and/or nano-domains (1997). Lipid rafts have been proposed to play a key role in cellular signaling domains. Crosslinking of the IgE receptor on mast cells, for example, causes recruitment of the receptor to the lipid raft, which in turn triggers allergic reactions. The non-receptor type of the Src-family kinase, Lyn, is localized in the lipid raft to protect from inactivation (dephosphorylation) of crosslinked IgE receptors by a transmembrane phosphatase. Thus, the lipid raft is essential for maintaining the integrity of signaling complexes (Holowka *et al.*, 2005).

The lipid raft hypothesis is still a matter of heavy debate. Brown and London (2000) suggested the liquid-ordered phase of lipids composed of GSLs and cholesterol in the membrane to be essential for the detergent (cold Triton X-100)-insolubility (DI) of lipid rafts or microdomains. Based upon the physical properties, most biochemists or cell biologists isolate and characterize lipid microdomains from cells or tissues to perform compositional analyses of the lipid microdomains, in spite of the fact they know that DI membranes (DIMs) are not the same as lipid rafts in their native state. Nevertheless, the biochemical approaches have revealed the presence of new glycolipids and signaling molecules in mammals. Very recently, Nagatsuka *et al.* identified a novel glycolipid, phosphatidylglucoside, in the DIMs fraction of developing brains (2006). Very importantly, brain phosphatidylglucoside is exclusively composed of saturated fatty acids (C18:0/C20:0) in its diacylglycerol moiety. It is speculated that there are additional still unrecognized but biologically important membrane lipids present in nature. Development of a new method using mass spectrometry (MS) to identify structurally diverse lipids is definitely needed and, indeed, MS-based approaches such as "sphingolipidomics" have already been initiated (Merrill, 2005). It is also impor-

tant to develop methods to visualize lipid rafts. Filipin and cholera toxin subunit B are most commonly used for the detection of cholesterol and ganglioside GM1 in the lipid rafts, respectively. Recently, new probes and inhibitors have been shown to be useful to advance the investigation (Kobayashi *et al.*, this issue). All these results show that lipid rafts or microdomains are heterogeneous in terms of their composition and function. For a deeper understanding of lipid rafts, live-cell imaging technology using fluorescent probes will need to be further developed.

Recent extensive studies have suggested that lipid rafts play significant roles in the pathogenesis of various diseases such as the lipid storage diseases, Alzheimer disease, and disorders associated with metabolic syndrome. Here, Inokuchi *et al.*, suggest a possible link between lipid rafts and insulin resistance (type 2 diabetes) in adipose tissues. Host-parasite interaction through lipid rafts is also an important issue for the understanding the mechanisms of infectious disease and their treatment (Suzuki *et al.*, this issue).

Another important feature of membrane lipids is that they are distributed asymmetrically between the two leaflets of the bilayer. A typical example is seen in GSLs that exclusively reside in the outer leaflet exposing sugar chains to the extracellular space. Glucosylceramide (GlcCer), a precursor lipid for most all GSLs, is synthesized on the cytosolic side and then is translocated to the luminal side of the ER/Golgi membranes. This translocation process is extremely important because it determines the membrane topology of GSL as well as the formation of more complex type of GSLs. However, in spite of its importance, it has been difficult to study, mainly because there is no reliable method to measure the activity of the translocase *in vitro*. ABCB1/MDR1, one of the ABC transporters, is suggested to function as the translocase for GlcCer (Ikeda *et al.*, this issue).

Plasma membrane translocases are required both to generate and maintain the asymmetric structure of biological membranes. Phosphatidylserine and phosphatidylethanolamine are two non-rafts phospholipids which are mainly localized in the inner leaflet and this topology is regulated by multiple factors: P-type ATPase, ABC transporter and scramblase (Yamaji *et al.* and Ikeda *et al.*, this issue). Advances in basic research in this field will greatly facilitate our understanding of the membrane-associated human diseases.

The following 5 review articles provide the most recent overview of membrane lipid organization, the underlying molecular mechanisms, and the related pathogenesis in a number of pathologies.