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Review Article

Membrane Lipids: Implication for Diseases and Membrane Trafficking

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Abstract

Lipids play important roles in a variety of cellular trafficking and signaling pathways, and in maintaining homeostasis within eukaryotic cells. This review aims at discussing the various classes of lipids present in cellular membranes, as well as their roles, and an up-to-date discussion of the impact of membrane lipid composition on vesicular trafficking and associated diseases.

Overview of Lipids

Lipids are a diverse class of nonpolar or semipolar organic molecules that, in contrast to nucleic acids and carbohydrates, are insoluble in water but soluble in nonpolar organic solvents [1]. Within the cell, lipids have many roles, including signaling, structural composition of membranes, and energy storage [2]. Lipids can be synthesized de novo, or can be taken up from the environment, and used either directly or after modification [3].

The membranes that form the outer boundary of the cell and the limits of organelles are made of three main categories of lipids: phospholipids, sphingolipids, and sterols (cholesterol, or the yeast alternative, ergosterol) [4]. Within each of these broad groupings; however, there are many molecular alterations that result in a wide range of different lipids that behave in diverse ways and at various intracellular locations. Furthermore, cells alter the lipid composition within their membranes, based on the environment, in order to achieve optimal membrane performance [5].

Molecules in the first category of membrane lipids, phospholipids, consist of two fatty acid tails and a polar head group attached to a 3-carbon glycerol backbone. An extremely large number of different molecules with different physical properties can be formed within the phospholipid family by varying the length and degree of saturation of the fatty acid tails, or the molecular structure of the head group [6]. Important lipids in this family include phosphatidylinositol (PI), an important precursor to several other phospholipids found within membranes throughout the cell [7,8]. These downstream lipids include Phosphatidylinositol-4- Phosphate [PI(4)P], which is important in yeast for secretion and in mammalian cells for recruitment of the adaptor protein AP-1 to the Golgi [9]. In addition, Phosphatidylinositol (4,5)-Bisphosphate [PI(4,5)P2] is a phospholipid that has important roles at the plasma membrane bymodulating actin polymerization and vesicle formation [10], and additionally playing a role in signaling and cold tolerance [11]. PI(4,5)P2 is synthesized through the action of the lipid kinase Mss4 [12], and can be dephosphorylated back to PI(4)P or PI, through the action of the phosphatases Sjl1, Sjl2, and Sjl3 (also known as Inp51, Inp52, and Inp53), thus modulating the composition of each species of phospholipid in the membrane [13]. PI(4,5)P2 levels can be synthetically depleted using a temperature sensitive mutant, mss4ts, grown at elevated temperatures [12]. Additionally, accumulation of PI(4,5)P2 can be induced through deletion of SJL1, SJL2, or SJL3 [13].

The second category of membrane lipids, sphingolipids, is composed of the long chain base (a long carbon chain that terminates in an amine group and several hydroxyl groups) parent molecule sphingosine, as well as its derivatives: ceramides, sphingomyelins, cerebrosides, and gangliosides [14]. Sphingolipids are important parts of cell membranes, but also have signaling roles via regulating various aspects of the yeast cell cycle from cell division through apoptosis [15]. Additionally, sphingolipids have been shown to play a role in mitochondrial function and gene expression [16,17]. The first step in sphingolipid production is mediated by Lcb1 and Lcb2, which together form the serine palmitoyl transferase complex [18,19]. This step can be inhibited through addition of the atypical amino acid myriocin, resulting in a dose-dependent depletion of sphingolipids within the treated cells [20].

Molecules in the third category of membrane lipids, sterols, have a characteristic pattern of four interlocking hydrocarbon rings, rather than the long hydrocarbon chains present in phospholipids and sphingolipids. Sterols interact with sphingolipids in the cell membrane, playing an important role in endocytosis, transport of amino acids throughout the cell, energy production,

and maintenance of membrane stability during cellular stress [21-23]. Among the multiple sterols known to play important roles within the cell, cholesterol and ergosterol are the most prominent in mammalian and yeast cells, respectively [24].

Most steroids are synthesized in the ER and then trafficked to their final destination. For example, cholesterol can be incorporated into lipid droplets present in the cytoplasm, and then trafficked to the mitochondria by SNARE proteins [25]. Ergosterol is similar to cholesterol but has a slightly altered structure and function, and is synthesized from its precursor, zymosterol, via a complex multi-step process involving the *ERG* genes [26]. Knockout or overexpression of these genes can result in an accumulation of the ergosterol precursors or ergosterol within the cell membrane, altering cellular behavior and function [27]. The final steps of ergosterol synthesis are catalyzed by *ERG6*, *ERG2*, *ERG3*, *ERG5* and *ERG4*, and knockout of these genes results in cells that are viable, but have abnormal phenotypes of varying degrees of severity due to the accumulation of ergosterol precursors [28]. Of these five genes, *ERG6*, *ERG3*, and *ERG4* have the greatest impact on cell physiology. In strains with any of these genes deleted, plasma membrane stability is compromised, resulting in increased sensitivity to changes in environmental water (*erg6*Δ cells), decreased ability of the cell to maintain membrane potential (*erg6*Δ and *erg4*Δcells), variations in size and morphology (*erg4*Δcells), and altered susceptibility to antifungal agents (*erg6*Δ, *erg3*Δ and *erg4*Δcells) [21,29].

Roles of Lipid Classes

Each class of lipids has unique and important roles in maintaining proper cellular and organismal function. For example, phospholipids play important roles nutritionally in brain development [30,31] as well as possibly playing roles in proper brain function and in the prevention of neurodegenerative diseases [32,33]. Phospholipid consumption has also been linked to resistance against certain kinds of bacteria and viruses [34,35]. Interestingly, certain kinds of phospholipids have also been found to have anti-proliferative properties, leading to speculation about the possible applications for lipids in cancer therapies [36,37].

Sphingolipids have been found to have various roles in signaling and regulation of cellular processes. Specifically, sphingolipids play a role in regulating the cell cycle, apoptosis, cell survival [38,39], and inflammation [40,41]. Some examples of sphingolipids as signaling molecules include their role in regulating survival and apoptosis of murine neuroblasts [42], and their postulated role in development of diabetes through contributing to apoptosis of pancreatic β-cells [39]. Sphingolipids also have a role in recycling of endocytic membranes [43], and in intracellular trafficking during the life cycle of some viruses, including hepatitis B and C viruses [44]. Overall, sphingolipids play important roles as biological signaling molecules, and their imbalance would be likely to cause defects in cell function.

Cholesterol (ergosterol) has important roles in many membranes, as well as being important as a precursor of steroid hormones [45]. The concentration of cholesterol in various organelles has been shown to be important in the trafficking of African swine flu virus [46], and trafficking of hedgehog ligands, which are important in the regulation of developmental processes [47], and integrins, which are important for interaction of cells with the extra-cellular matrix [48]. Improper accumulation of cholesterol in the mitochondria has been one factor implicated in the ability of cells to avoid apoptosis, leading to cancer [45,49].

Lipid-Associated Diseases

Alteration of membrane lipid concentrations is known to play a role in a variety of diseases. For example, cystic fibrosis causes lipid imbalances which impair surfactant ability in the lungs and promotes bacterial growth, leading to decreased breathing ability [50,51]. In mouse models of cystic fibrosis, membrane lipid imbalance was found in affected organs, but administration of docosahexaenoic acid [39], remedied both the lipid imbalances and disease pathology [52] and administration of myriocin, a sphingolipid synthesis inhibitor, reduced inflammation and bacterial growth [53]. Additionally, alterations in lipid concentration and cholesterol structure have been found to activate signaling pathways and allow for recruitment of proteins that play a role in amyloid formation, which can contribute to damage of pancreatic β-cells, leading to type 2 diabetes [54] or to the death of neurons, leading to Alzheimer's disease [55-57]. Furthermore, alterations of membrane lipids have been implicated in multiple sclerosis and in the progressive neurodegenerative condition Niemann-Pick C Disease, suggesting that lipid imbalance is toxic for neural cells [58,59], but administration of a sphingosine homologue which allows for SNARE association with the cellular membrane has proven promising for treatment of multiple sclerosis [60].

Altered membrane lipid concentration has been reported in other diseases, although the imbalance may be a result, rather than a cause, of the disease. One of these findings is that levels of cholesterol and unsaturated fatty acids increased in the membranes of platelets isolated from women with preeclampsia [61]. Patients with sickle cell anemia were found to have a lack of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid [39] making up the membranes of their erythrocytes, and supplementation of EPA and DHA has been proposed as a therapy to reduce the severity of the anemia in these patients [62,63]. Additionally, membrane lipid imbalance, specifically in immune cells such as macrophages, has been proposed to be involved in the development of atherosclerosis [64].

At the cellular level, membrane lipids play an important role, especially at the plasma membrane. Lipids are important for determining the curvature of the membrane, which may influence interactions with nearby cells [65], as well as impacting the secondary structure of proteins that interact with the membrane from outside the cell. Membrane lipid imbalance can also disrupt proper functioning of membrane proteins, including G Protein-Coupled Receptors (GPCRs), because proteins that are embedded in the membrane interact with membrane lipid components.

Membrane Trafficking Pathways Impacted by Lipid Composition

Membrane lipid concentration is crucial for proper functioning of membrane trafficking pathways, specifically endocytosis and the secretory pathway. In urothelial cells, excesses of oleic and linoleic acids have been found to reduce endocytosis [66], and altered sterol structure and composition can inhibit endocytosis [67], indicating lipid homeostasis is important for proper uptake of materials from the environment. Conversely, defects in the low density lipoprotein receptor can result in impaired uptake of cholesterol from the

blood, leading to hypercholesterolemia and atherosclerosis [68]. Additionally, a high fat diet can also interfere with formation of lipid rafts required for uptake of components such as insulin from the blood [69]. Mechanistically, this occurs because proteins required to initiate the endocytic process are recruited to the membrane by the presence of specific lipids. For example, local PIP2 enrichment in the plasma membrane results in recruitment of SNX9 [70], which then activates other proteins, such as dynamin, that are important for completion of the endocytic process [71]. Other lipids, such as sterols, also play important roles in lipid raft formation, and can impact the rates of both clathrin-dependent and clathrin-independent endocytosis [67].

Lipid balance also plays a role in proper secretory transport from the Golgi to the plasma membrane. The levels of lipids in the membranes of each organelle vary, allowing the vesicular trafficking to proceed properly, and alterations of these compositions result in defects in various pathways [72]. In particular, target membrane SNAP receptors (t-SNAREs) rely on a proper balance of cholesterol in the endosomes and Golgi in order to be trafficked properly [73,74]. Specifically, defects in the endosome/Golgi lipid balance results in accumulation of Syntaxin 6, a protein important in trafficking from the TGN [75]. When cholesterol accumulates in the endosomes rather than being transported to the Golgi, localization of t-SNAREs important in the exocytic process is impaired, but this localization and transport pathway is rescued when proper cholesterol balance is restored [76]. Sphingolipid depletion also results in improper targeting of the v-SNARE Snc1 [77]. Additionally, SNAREs are unable to function properly when membrane fluidity is disrupted due to altered membrane lipid compositions, resulting in failure of vesicles to fuse with their target membranes, inhibiting many vesicular trafficking pathways, including recycling, secretory, and degradation pathways [78]. Alterations in lipid transport from the endosomes to the Golgi have also been implicated in the progressive neurological Niemann-Pick C disease, potentially due to impairing the transport of a variety of proteins within the cell [59].

Lipids are also important in regulating exocytosis. For example, exocytosis during sperm development is triggered by a change in cholesterol concentration, which serves as a signal that result in alterations in calcium concentrations and activation of phospholipase B, an enzymeimportant in the hydrolysis of the fatty acid tails of phospholipids [79]. Since the curvature of membranes depends on the relative area occupied by the lipid heads and tails, hydrolysis of lipid tails reduces the space occupied by the lipid tails, resulting in curvature of the membrane, which allows for exocytosis to occur [79]. Additionally, specific lipids are required for the formation of lipid rafts containing a variety of proteins needed in the exocytic process [80]. Specifically, PI4P enrichment allows for recruitment of proteins such as synaptotagmin and SNAREs, which are essential for exocytosis to occur [81-83]. Mechanistically, the membrane phospholipid concentration is important for actin polymerization, and imbalances result in defects in actin polymerization and thus in exocytosis [84]. Through regulation of lipid concentrations, cells can regulate rates of exocytosis. This is particularly important in maintaining proper rates of material movement across cells at the border of the blood brain barrier [85].

Since lipid imbalance is characteristic of diseases such as Alzheimer's, Niemann-Pick type C Disease, and cardiovascular disease [86], a deeper understanding of the role of lipids within the cell is crucial. Future work should investigate in greater detail the mechanisms by which membrane lipid imbalance results in defects in intracellular trafficking. Additionally, a greater understanding of the relationship between membrane dynamics and protein recruitment is needed. Elucidation of the role of lipids in intracellular processes will lead to a greater understanding of therapeutic targets, which will enable more sophisticated treatment options for a variety of lipid-related diseases.

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