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Probing the importance of lipid diversity in cell membranes *via* molecular simulation

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ABSTRACT

Lipid membranes in prokaryotes and eukaryotes have a wide array of lipids that are necessary for proper membrane structure and function. In this paper, an introduction to lipid diversity in biology and a mini-review on how molecular simulations have been used to model biological membranes (primarily limited to one to three lipid types in most simulation-based models) is provided, which motivates the use of all-atom molecular dynamics (MD) simulations to study the effect of lipid diversity on properties of realistic membrane models of prokaryotes and eukaryotes. As an example, cytoplasmic membrane models of *Escherichia coli* were developed at different stages of the colony growth cycle (early-log, mid-log, stationary and overnight). The main difference between lipid compositions at each stage was the concentration of a cyclopropane-containing moiety on the *sn*-2 lipid acyl chain (cyC17:0). Triplicate MD simulations for each stage were run for 300 ns to study the influence of lipid diversity on the surface area per lipid, area compressibility modulus, deuterium order parameters, and electron density profiles. The overnight stage (also known as the death stage) had the highest average surface area per lipid, highest rigidity, and lowest bilayer thickness compare to other stages of *E. coli* cytoplasmic membrane. Although bilayer thickness did depend on the growth stage, the changes between these were small suggesting that the hydrophobic core of transmembrane proteins fit well with the membrane in all growth stages. Although it is still common practise in MD simulations of membrane proteins to use simple one- or two-component membranes, it can be important to use diverse lipid model membranes when membrane protein structure and function are influenced by changes in lipid membrane composition.

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1. Introduction

Lipids are one of the four main building blocks in biology and many are amphiphilic molecules, *i.e.*, they have a portion that likes water and a portion that dislikes water. In general, lipids are molecules that are synthesized by either or both of the two following routes: carbanion-based condensations from thioesters or carbocation-based condensations of isoprene moieties (Fahy et al., 2005). The function of lipids can be classified into three categories, *i.e.*, energy storage, membrane formers, and biological signaling (van Meer et al., 2008). Lipids are used by cells to store calories for future use in molecules such as tyiacylglycerol and steryl esters (van Meer et al., 2008). The most common and ultimate use for lipids is to form membrane structures in the cell due to their ability to self-associate in aqueous environments. The amphiphilic character of these lipids at the appropriate concentration will result in bilayer formation that encapsulates cells and/or various organelles. The properties of these lipid membranes vary and go beyond cell protection and are important in cell division, membrane protein function, and protein aggregation (van Meer et al., 2008). Certain lipids in the membrane can also serve as signal transduction and recruiters of proteins. Some proteins are known to respond to signals in the membrane in the transmembrane domains and propagate these to cytosolic portions of a protein (van Meer et al., 2008). Other proteins are known to selectively bind to certain lipids that are segregated into different cell organelles, domains of sterol-rich membranes, or other unique membrane properties (Cho and Stahelin, 2005; Drin et al., 2007; Leventis and Grinstein, 2010).

Although lipids have the same general properties, there is a wide variety of lipid diversity that exists in cells. These can be classified into eight categories that are associated with common chemical structures, *i.e.*, fatty acyl, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids and polyketides (Fahy et al., 2005). In cells, glycerophospholipids,

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sphingolipids and sterol lipids are the most common but can contain a wide variety of acyl chains and hydrophilic head groups. These head groups can be polar, zwitterionic (having both negative and positive charges), or anionic. The head groups also vary in size, *i.e.*, small (hydroxyl in sterols or glycerols), moderate (phosphocholines and phosphoinositols) or large (glycerolipids with polysaccharides). In addition to head group diversity, there is also a wide range of non-polar chemical structures. Fully saturated acyl chains and monounsaturated chains are the most common for non-sterol lipids but these can vary in length with 14- to 26-carbons. However, depending on the species and its diet lipid chains can also exist with branched, polyunsaturated, cyclic or cyclic-containing chains. For sterols, a variety exists in the steroidal fused ring structures and the attached short chain. This wide diversity is used by cells for its function and structural stability.

Eukaryotes have cells that contain an outer plasma membrane (PM) and membranes that enclose various organelles. These organelles are known to have a wide variety of lipids (see Fig. 1 for a few examples) and concentrations (van Meer et al., 2008). If we consider yeast, phosphatidylcholine (PC) lipids are the most common in the endoplasmic reticulum, trans-Golgi network (TGN), and mitochondrion (MIT), but a minor lipid in the PM (Fig. 2) (Daum et al., 1999; Klemm et al., 2009; Schneiter et al., 1999; Tuller et al., 1999). As shown in Fig. 2, the distribution of lipids is not uniform between organelles of yeast. The TGN and PM have the highest amounts of anionic lipids, *i.e.*, phosphatidylinstol (PI) and phosphitdylserine (PS) lipids. The ergosterol levels increase along the secretory pathway of yeast (ER to TGN to PM). The MIT membranes contain cardiolipin which is common in many membranes with high curvature. Glycosphingolipids, such as, galactosylceramide (GalCer, Fig. 1) are known to exist at lower

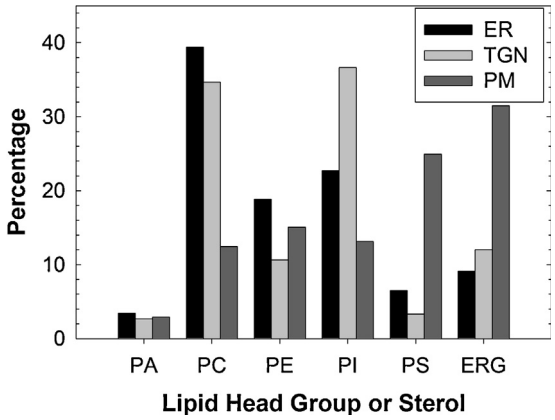

Fig. 2. The head group composition of lipids of the ER (endoplasmic reticulum), TGN (trans-Golgi Network) and PM (Plasma Membrane) in *Saccharomyces cerevisiae* based off experimental measures (Daum et al., 1999; Klemm et al., 2009; Schneiter et al., 1999; Tuller et al., 1999) and ignoring inositol sphingolipids in the PM and TGN.

concentrations in the ER and TGN (van Meer et al., 2008). In addition to the uneven distribution of lipids between organelles, many organelles (excluding the ER) have asymmetrical leaflets. For example, the outer leaflet of the PM is enriched in PC, sphingomyelin (SM), and glycopshingolipids, whereas the inner leaflet contains mainly phosphidylethanolamine (PE), PS and PI lipids (van Meer et al., 2008).

Eukaryotes may have varying lipid compositions in their organelles, but prokaryotes also have a wide array of lipids. In gram-negative bacteria, the viscous periplasm (Ruiz et al., 2006;

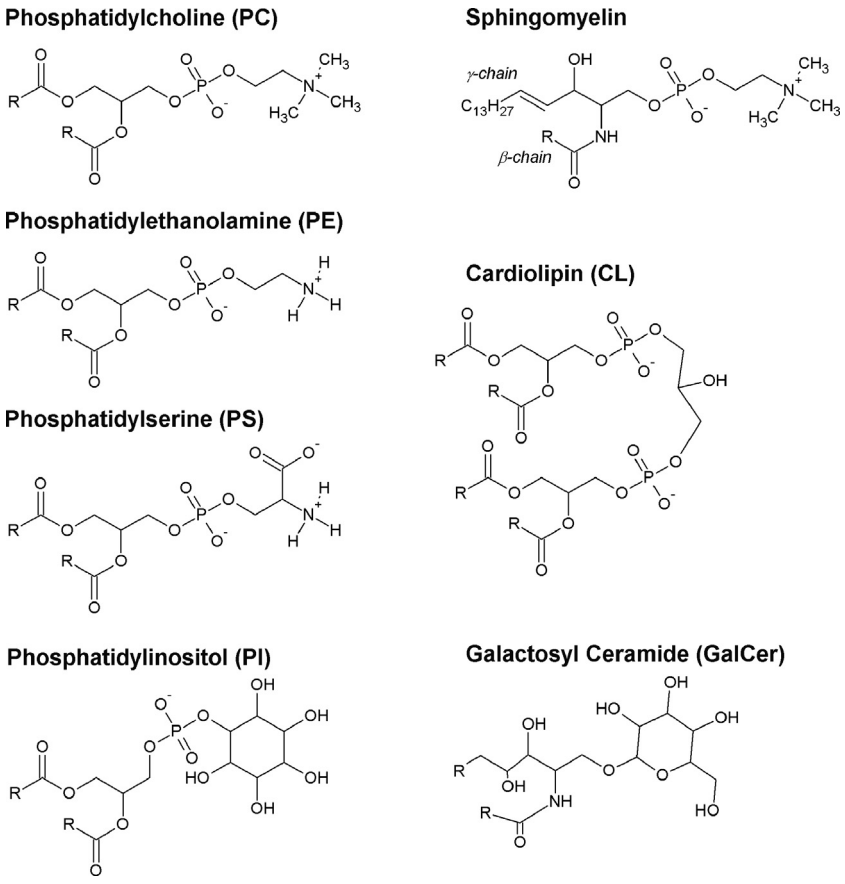

Fig. 1. Chemical structures of seven common lipids.

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