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Review

Cholesterol, sphingolipids, and glycolipids: What do we know about their role in raft-like membranes?

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ABSTRACT

Lipids rafts are considered to be functional nanoscale membrane domains enriched in cholesterol and sphingolipids, characteristic in particular of the external leaflet of cell membranes. Lipids, together with membrane-associated proteins, are therefore considered to form nanoscale units with potential specific functions. Although the understanding of the structure of rafts in living cells is quite limited, the possible functions of rafts are widely discussed in the literature, highlighting their importance in cellular functions. In this review, we discuss the understanding of rafts that has emerged based on recent atomistic and coarse-grained molecular dynamics simulation studies on the key lipid raft components, which include cholesterol, sphingolipids, glycolipids, and the proteins interacting with these classes of lipids. The simulation results are compared to experiments when possible.

Contents

Abbreviations: SM, sphingomyelin; OSM, oleoyl-SM; PC, phosphatidylcholine; POPC, 1-palmitoyl-2-oleoyl-PC; DOPC, dioleoyl-PC; DMPC, dimyristoyl-PC; DPPC, dipalmitoyl-PC; PGPC, 1-palmitoyl-2-glutaryl-sn-glycero-3-phosphocholine; POPE, 1-palmitoyl-2-oleoyl-phosphatidylethanolamine; GalCer, galactosyl-cerebroside; GM1, Gal5-β1,3-GalNAc4-β1,4-(NeuAc3-α2,3)-Gal2-β1,4-Glc1-β1,1-Cer; GM3, NeuAc3-α2,3-Gal2-β1,4-Glc1-β1,1-Cer; LPS, Lipopolysaccharide; MD, molecular dynamics; CG, coarse-grained; QM, quantum mechanical; L_o, liquid-ordered; L_d, liquid-disordered; NBD, nitrobenzoxadiazole; PEG, poly(ethylene) glycol; NH, amide group; OC, carbonyl group; OH, hydroxyl group; NMR, nuclear magnetic resonance.

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1. Introduction

Biological membranes contain a complex mixture of numerous lipid species (Niemela et al., 2009). For instance, in a very recent study, thousands of lipid species were found in a single sample of adipose tissue (Pietilainen et al., 2011). This huge diversity of lipids arises from, for example, variations in polar headgroups (neutral, charged, or carbohydrate), variations in length and (un) saturation of the hydrocarbon chains, variations in the main lipid backbone (glycerol vs. sphingosine), and all possible combinations of these variants.

Lipids are not randomly distributed in cells (van Meer et al., 2008) but they are highly organized according to their function. For instance, on a cellular level charged cardiolipins are typically found only in mitochondria, while sphingolipids are mainly found in the external leaflet of cell membranes. The well-defined organization of lipids also relates to how the lipids are distributed in the membranes themselves. For example, many cellular membranes are asymmetric. The internal (intracellular, cytosolic) leaflet of plasma membranes is typically composed of charged phosphatidylserines, large amounts of phosphatidylethanolamines, and a smaller number of phosphatidylcholines (PCs). In contrast, the outer (extracellular) leaflet is largely composed of sphingolipids, which include a great fraction of glycolipids, and PCs. Cholesterol, being present in both leaflets, is also an important component of the cell membrane, though the details of its transmembrane distribution remain debated (Maxfield and Mondal, 2006).

Because sphingolipids have predominantly saturated chains, and PCs are predominately unsaturated, the composition of the extracellular leaflet can be approximated as a mixture of cholesterol, saturated lipids, and unsaturated lipids. In model membranes, the behavior of this lipid mixture is well characterized (Almeida, 2009). It is known that cholesterol separates with the saturated lipids into a liquid-ordered (L_o) phase while unsaturated lipids segregate into a liquid-disordered (L_d) phase (Rheinstädter and Mouritsen, 2013). In model membranes, the domains in question are relatively large and can hence be visualized quite easily. In membranes of living cells, the situation is more complicated as the discussion below brings out.

The existence of domains enriched in cholesterol and sphingolipids was postulated already decades ago. Eventually, they became known as lipid rafts, and nowadays they are known or suggested to be associated with numerous cellular functions (Lingwood et al., 2009; Lingwood and Simons, 2010). Yet as biological membranes are much more complex than model membranes, the characterization and visualization of lipid rafts in cells have been largely incomplete. This lack of identifiable lipid rafts in cells may be explained by the presence of membrane proteins, which can interfere with lipid-lipid interactions and thus reduce the tendency of lipids to phase separate (Yethiraj and Weisshaar, 2007). It is also known that proteins alter the dynamics of lipids around them, and consequently there are protein-lipid complexes containing of the order of hundreds of lipids migrating together with individual proteins (Niemelä et al., 2009). It is possible that these are the smallest functional units able to carry out the functions in cell membranes. Given that the size of such complexes is about 10 nm or less, the challenge to identify them with even super-resolution microscopy techniques has been too demanding until now. For the same reason, the structure of nanoscale rafts in cell membranes remains unclear.

Molecular dynamics (MD) simulations have become an important tool in structural biology. The MD method can provide information about atomic-scale mechanisms that are often inaccessible with current experimental techniques, thus atomistic simulations are often used to complement experimental studies (Lyubartsev and Rabinovich, 2011; Vattulainen and Róg, 2011; Hug, 2012). MD simulations can also yield important insight into large-scale behavior such as phase separation and diffusion, when simplified (coarse-grained) molecular models are used instead of atomistic ones. The information emerging from atomistic and molecular simulations can be highly useful in interpreting experimental results. For example, MD simulations of fluorescent probes or spin labels can show how the presence of the probe changes the properties of a biological system, and how the behavior of the probe might differ from that of the surrounding lipids (Loura and Ramalho, 2011; Jurkiewicz et al., 2012; Kemmerer et al., 2013; Timr et al., 2014). Also, atomistic simulations can be carried out under conditions that match the ones used in experiments, and hence simulation data can reveal nanoscale mechanisms that are out of reach through experiments. Recently, this strategy was used to identify the mechanism how cholesterol is able to inhibit the function of a glycoreceptor in a lipid membrane (Lingwood et al., 2011b).

The primary limitations of MD simulations have been the small time and length scales for modeling objects of interest. However, significant advances over the last decade have improved the scales that can be reached through simulations. For example, atomic MD simulations of β2-adrenergic receptors embedded in a lipid bilayer recently achieved a timeframe of 30 μs (Rosenbaum et al., 2011). Also, the size capacity of simulated systems has increased to allow simulations of objects as large as lipoproteins (Murtola et al., 2011) or polymer-coated bilayers that are relevant to drug delivery (Lehtinen et al., 2012). Further, the models developed for MD simulations are constantly under intensive development. For