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Self-assembly of lipid domains in the extracellular leaflet of the plasma membrane and models thereof

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ABSTRACT

Lipid domain formation and phase coexistence in biological membranes is a subject which has received considerable attention during the last two decades, especially the topic concerning so-called lipid rafts, a theory which has become as popular to confirm as to disproof. Regardless of the existence or precise composition and function of the classical rafts, the occurrence of lateral lipid segregation in biological membranes is indisputable. This review starts by focusing on state of the art findings concerning lipid domains and lateral heterogeneity in a biological context. Then, the physicochemical properties of lipid mixtures, phase properties and domain dynamics are considered. Canonical lipid models of the exofacial leaflet of the plasma membrane are treated in detail and the proper choices of model lipids are discussed. A special attention is given to polar lateral interactions (including carbohydrate–carbohydrate head group interactions), whose importance for spatial segregation and crystallization is commencing to be appreciated by the scientific community.

1. Introduction

Lipid bilayers are biologically essential self-assembled structure used by Nature to compartmentalize and segregate different biochemical constituents from each other (organelles) and from the surrounding environment (plasma membrane/cell walls). Ever since the fluid mosaic model was expanded to encompass lateral heterogeneities, a lot of research effort has been devoted towards elucidating their biological functions and physicochemical characteristics. In the literature, such biological lipid domains are usually synonymous with the so-called *lipid rafts*, which are supposed to reside in the exofacial leaflet of the plasma membrane [1]. In Fig. 1, the qualitative features and lipid composition of the plasma membrane containing different types of domains is envisaged, yet phase-segregated domains are found in most biological lipid bilayers [2•]. The lipid raft theory has been the subject of certain conjectural controversy during the last decade [3•]. Yet this review is not a contribution to that debate. Instead, focus will be on general phase segregation phenomena and phase coexistence in biological cell membranes, in particular the exofacial leaflet of the eukaryotic plasma membrane, and models thereof. Lipid tail as well as head group interactions will be considered, which both can be categorized as weak interactions (<1 k_BT) and the lipid membrane is consequently dominated by entropy effects.

2. Biological function

Lipid domains are necessary for the social life of cells. The social life encompasses essential functions such as intracellular or extracellular signalling, transmembrane signal transduction, cell–cell or cell–extracellular matrix adhesion which are involved in diseases, immune responses, cell proliferation, migration, differentiation, etc. In the following subsections, some state of the art findings, where lateral segregation is pivotal for the biological function, are presented.

2.1. Avidity

An important function of lipid domains is their ability to mobilize cell surface receptors/markers including membrane proteins (protein sorting) and glycolipids (lipid sorting). The protein sorting is not only limited to the partitioning of the proteins into different domains. Certain membrane proteins have affinity for the boundaries between different phases such as the HIV fusion protein [4]. The concentration of receptors/markers within a confined volume leads to significantly enhanced avidity, which is key since the monovalent peptide–peptide, peptide–carbohydrate, and in particular carbohydrate–carbohydrate interactions are very weak. Regarding peptide–peptide *trans* interactions (−(10, 100) k_BT), the cell–cell adhesion mediated via cd47-SIRPα

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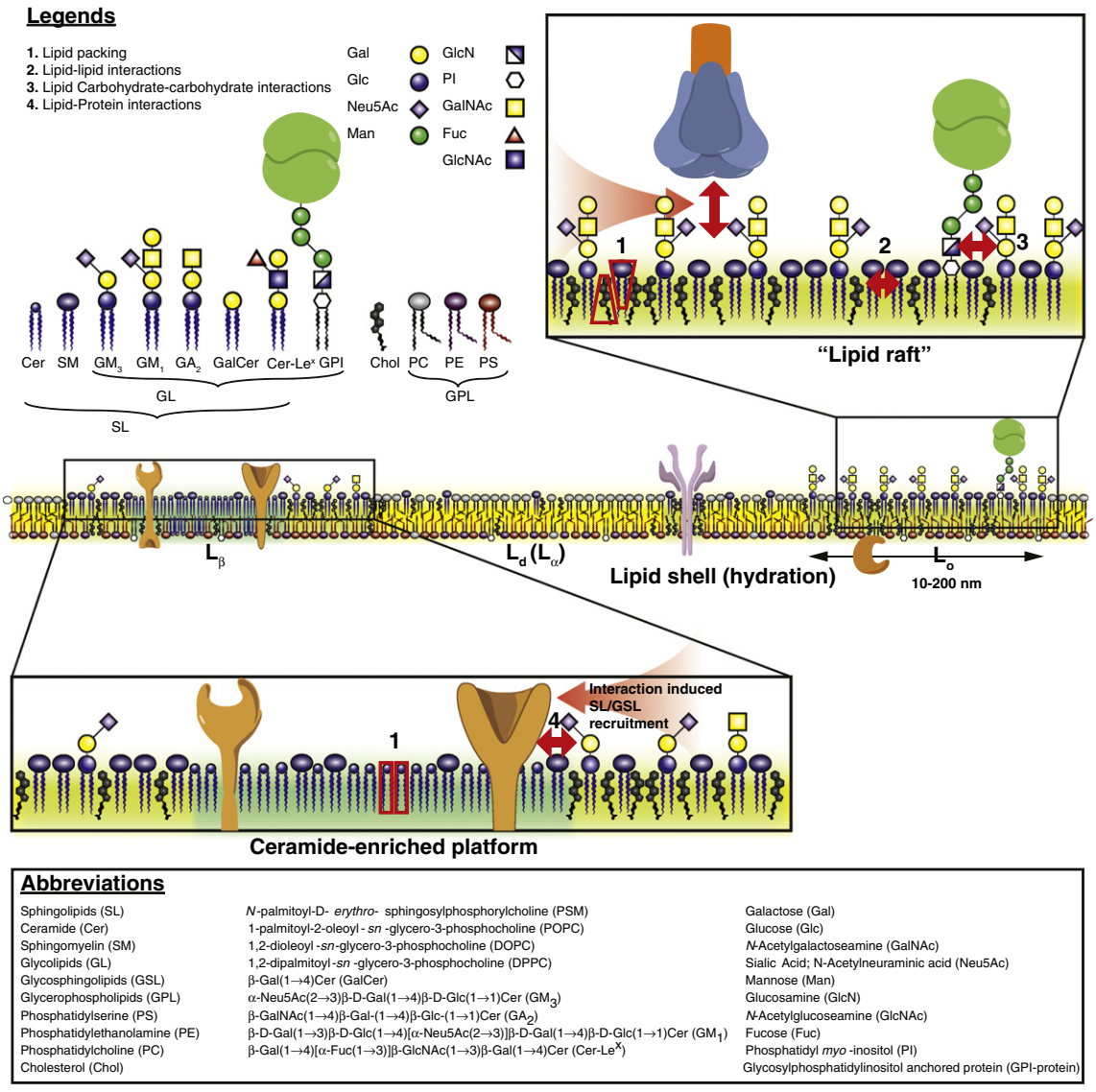

Abbreviations

Sphingolipids (SL)	*N*-palmitoyl-D- *erythro*- sphingosylphosphorylcholine (PSM)	Galactose (Gal)
Ceramide (Cer)	1-palmitoyl-2-oleoyl- *sn* -glycero-3-phosphocholine (POPC)	Glucose (Glc)
Sphingomyelin (SM)	1,2-dioleoyl -*sn*-glycero-3-phosphocholine (DOPC)	*N*-Acetylgalactoseamine (GalNAc)
Glycolipids (GL)	1,2-dipalmitoyl -*sn* -glycero-3-phosphocholine (DPPC)	Sialic Acid; N-Acetylneuraminic acid (Neu5Ac)
Glycosphingolipids (GSL)	β-Gal(1→4)Cer (GalCer)	Mannose (Man)
Glycerophospholipids (GPL)	α-Neu5Ac(2→3)β-D-Gal(1→4)β-D-Glc(1→1)Cer (GM_3)	Glucosamine (GlcN)
Phosphatidylserine (PS)	β-GalNAc(1→4)β-Gal-(1→4)β-Glc-(1→1)Cer (GA_2)	*N*-Acetylglucoseamine (GlcNAc)
Phosphatidylethanolamine (PE)	β-D-Gal(1→3)β-D-Glc(1→4)[α-Neu5Ac(2→3)]β-D-Gal(1→4)β-D-Glc(1→1)Cer (GM_1)	Fucose (Fuc)
Phosphatidylcholine (PC)	β-Gal(1→4)[α-Fuc(1→3)]β-GlcNAc(1→3)β-Gal(1→4)Cer (Cer-Le^x)	Phosphatidyl *myo* -inositol (PI)
Cholesterol (Chol)		Glycosylphosphatidylinositol anchored protein (GPI-protein)

Fig. 1. Schematic illustration of the spatial heterogeneity in the plasma membrane. Its major lipid constituents are portrayed in the legends as well as the glycolipids that are relevant for this review. The SL and GPL tails are colored blue and black, respectively. Regarding the major GPL lipids, the *cis*-monounsaturated tail is displayed by a chain kink. Different types of lateral (*cis*) and vertical (*trans*) interactions are shown as red double-headed arrows. A distinction is made between lipid–lipid interactions which rely on geometrical constraints (**1**, lipid packing) in contrast to other types of lateral interactions (**2**, e.g., hydrogen bonding or electrostatic repulsion).

necessitates SIRPα clustering in lipid domains [5]. Peptide–carbohydrate interactions are important for cellular recognition and immunoresponses (e.g., lectin-mediated carbohydrate recognition) as well as for a variety of diseases, e.g., HIV [6] and norovirus infection [7] (≈ -5 k_BT for the monovalent interaction with GalCer or H type 1 antigen [8]). A classic example is the multivalent and clustering-inducing interaction between GM_1 and cholera toxin (see Fig. 1) [9], which is one of the strongest known peptide–carbohydrate interactions (≈ -30 k_BT) [10]. GM_1 is also known to interact with amyloid-β peptides inducing fibrillation [11], a molecular process which has been linked to Alzheimer's disease [12]. The clustering is particularly important for carbohydrate–carbohydrate interactions to exert biological functions. The monovalent interaction strength is typically in the order of 0.2–0.5 k_BT. Cellular aggregation during embryogenesis relies on the Ca^{2+}-dependent homotypic *trans* Le^X-Le^X [13•], which was one of the first multivalent carbohydrate–carbohydrate interactions to be studied, inter alia, due to its comparably high strength (≈ -1 k_BT) [14]. The heterotypic *trans* GM_3–GA_2 interaction ($<|-1$ $k_BT|$) [15,16•] mediates cellular adhesion of melanoma to lymphoma cells and plays accordingly a role in cancer and metastasis.

2.2. Transmembrane signal transduction

Another important lipid domain function is the formation of transmembrane signal transducing platforms [1]. The clustering of GSLs, GPI, and transmembrane proteins induced *via cis* or *trans* lipid–lipid, lipid–protein and protein–protein interactions is subsequently part of the signalling cascade. For example, the *trans* GM_3–GA_2 interactions mentioned above activates the signalling proteins Ras and Rho [17]. Transmembrane signal transduction necessitates reciprocal domain formation on the cytoplasmic leaflet. However, lipid bilayer or monolayer models representing the cytoplasmic leaflet (see Fig. 1) display no phase segregation and this leaflet resides in a fluid state at thermodynamic equilibrium. Yet recent findings of asymmetric lipid vesicles have revealed that domain formation in the exoplasmic phase induces ordering in the cytoplasmic leaflet [18], and the effect has been attributed to long-tailed SMs