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Structural determinants of protein partitioning into ordered membrane domains and lipid rafts

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ABSTRACT

Increasing evidence supports the existence of lateral nanoscopic lipid domains in plasma membranes, known as lipid rafts. These domains preferentially recruit membrane proteins and lipids to facilitate their interactions and thereby regulate transmembrane signaling and cellular homeostasis. The functionality of raft domains is intrinsically dependent on their selectivity for specific membrane components; however, while the physicochemical determinants of raft association for lipids are known, very few systematic studies have focused on the structural aspects that guide raft partitioning of proteins. In this review, we describe biophysical and thermodynamic aspects of raft-mimetic liquid ordered phases, focusing on those most relevant for protein partitioning. Further, we detail the variety of experimental models used to study protein-raft interactions. Finally, we review the existing literature on mechanisms for raft targeting, including lipid post-translational modifications, lipid binding, and transmembrane domain features. We conclude that while protein palmitoylation is a clear raft-targeting signal, few other general structural determinants for raft partitioning have been revealed, suggesting that many discoveries lie ahead in this burgeoning field.

1. Introduction

Biological membranes are relatively impermeable barriers between aqueous compartments, with membrane-spanning proteins representing the central mechanism for transport of materials and signals across the membrane. Such transmembrane proteins comprise approximately 30% of the human genome (Wallin and von Heijne, 1998), underlining their functional ubiquity. An early model of cellular membranes described membrane proteins as freely diffusing in a two-dimensional solvent of bilayer lipids (Singer and Nicolson, 1972). Since then, a plethora of experimental observations have amended this model to provide a more complex picture of membrane protein organization. Most of these measurements have focused on the plasma membrane, both because it is the major site for extracellular signal transduction and because it is the only membrane readily accessible to external labeling and observation. A major takeaway is that very few proteins distribute homogeneously in the plasma membrane. Some – including GPI-anchored proteins (Sharma et al., 2004; Suzuki et al., 2012) and Ras GTPases (Prior and Hancock, 2011; Zhou et al., 2013) – appear to form small, dynamic oligomers. Others show free diffusion on short length/time scales, but remain corralled by a membrane-associated cytoskeleton (Kusumi et al., 2005).

In addition to these, one of the most widely studied mechanisms for organizing the plasma membrane are lipid-driven membrane domains known as lipid rafts. These structures are believed to arise from preferred interactions between saturated lipids, glycosphingolipids, sphingomyelin, and cholesterol that give rise to a sterol-dependent liquid ordered phase (L_o) which can coexist with a liquid disordered (L_d) phase under physiological conditions (Lingwood and Simons, 2010). Proteins and lipids partitioning to this phase would then interact preferentially with each other, thereby spatially confining signaling reactions. Despite a growing body of evidence to support the hypothesis that lipid interactions drive domains in live cells, direct observation remains extremely difficult due to the purported size (tens to hundreds of nanometers) and time (millisecond lifetimes) scales of the putative domains. However, recent developments in isolated plasma membranes have confirmed that liquid–liquid phase coexistence is accessible in biological membranes and that its behavior is consistent with many aspects of the raft hypothesis (Kaiser et al., 2012; Levental and Levental, 2015a,b).

Perhaps the key feature underlying the functionality of lipid rafts is their selectivity for specific proteins. Despite this importance, very few studies have experimentally addressed the

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molecular mechanisms by which this selectivity is mediated. In this review, we will elaborate the characteristics of lipid rafts that may influence protein partitioning, discuss experimental models and techniques for investigation of raft association, and attempt an inclusive overview of the known mechanisms for protein partitioning to ordered membrane domains. Finally, we will address the physicochemical bases behind these results to provide mechanistic, structural insights in the determinants of protein partitioning to lipid rafts.

2. Characteristics of the liquid ordered phase relevant for protein partitioning

The features that bias proteins for preferential partitioning to raft domains are likely those that impart preferential interactions with either the unique lipid composition or physical environment of membrane rafts (Fig. 1A). The L_o phase of synthetic membranes is the most well accepted model for such domains, and the unique properties of this phase have been extensively characterized.

2.1. Structure and composition of the L_o phase

In synthetic systems, and also in more complex cell-derived membranes (Levental et al., 2009), the formation of the L_o phase depends on the unique structural properties of sterols (cholesterol in mammalian membranes) and their interactions with diacyl membrane lipids. In fluid membranes, the rigid, planar ring of cholesterol (and other sterols) inhibits trans-gauche isomerization of lipid acyl chains, enforcing more extended lipid conformations. This acyl chain ordering effect leads to a reduction of lipid molecular area and thickening of the membrane (reviewed in (Rog et al., 2009; Rog and Vattulainen, 2014)). Conversely, cholesterol fluidizes the lipid gel phase (L_β) by intercalating between lipids, with the methylated β-side of the molecule forcing apart closely packed phospholipids. Certain compositions permit the formation of a distinct liquid phase with properties intermediate between the gel and liquid crystalline state, termed the liquid ordered (L_o) phase. The detailed physicochemical interactions that drive the formation of a L_o phase are only partly understood. Interactions between cholesterol and saturated acyl chains have been shown to be energetically favored over interactions with unsaturated acyl chains (Almeida, 2009). Hydrogen bonding between the hydroxyl group of cholesterol and the amide group of sphingolipids might stabilize such preferential interactions, favoring the formation of ordered assemblies (Rog et al., 2009). Other effects, like the umbrella effect induced by the large headgroups of glycolipids could shield hydrophobic cholesterol and thereby contribute to preferential sterol–lipid interactions (Huang and Feigenson, 1999). Finally, stoichiometric 'condensed complexes' of phospholipids and cholesterol have been proposed based on the non-linear reduction of lipid molecular area induced by cholesterol (Radhakrishnan and McConnell, 1999).

In model membranes, the L_o and Lα phases coexist at thermodynamic equilibrium through a large range of lipid compositions and temperatures (Brown and London, 1998; London, 2005). Such behavior can be directly observed by conventional fluorescence microscopy (Korlach et al., 1999; Veatch and Keller, 2003) and atomic force microscopy (Garcia-Saez et al., 2007), or inferred from NMR (Heberle et al., 2013) or FRET (Pathak and London, 2011) data. Despite being reliant on cholesterol for its formation, the L_o phase is believed to be modestly enriched in cholesterol (Feigenson and Buboltz, 2001; Veatch et al., 2006); rather, strong enrichments are expected for saturated lipids and sphingolipids (Niemela et al., 2009; Rog and Vattulainen, 2014).

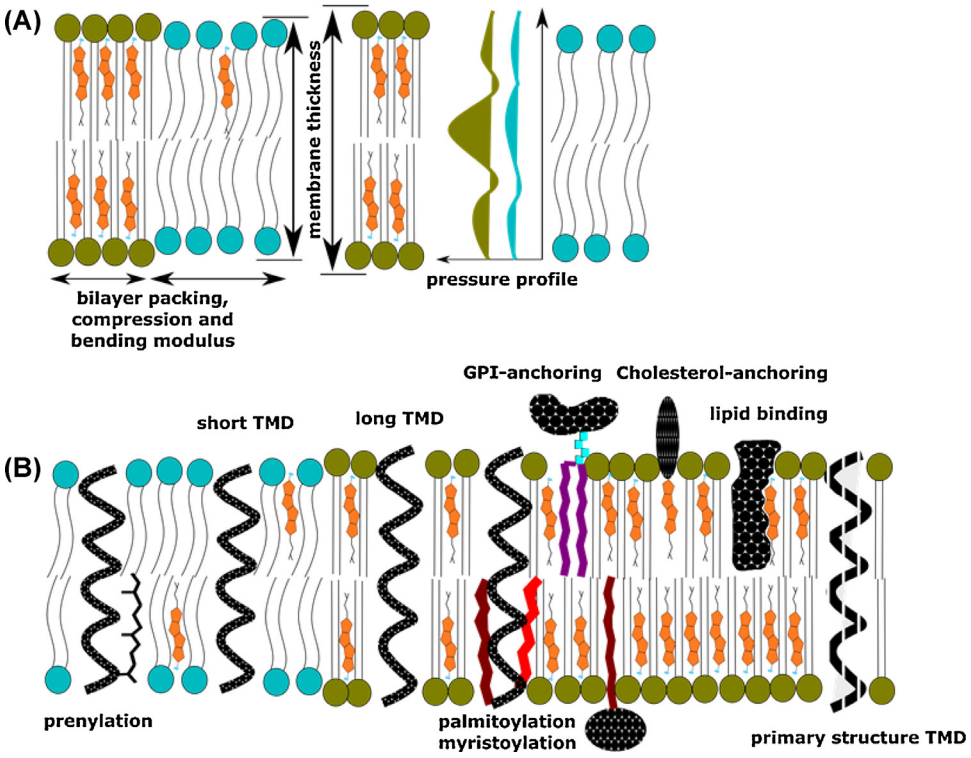

Fig. 1. Biophysical determinants of raft partitioning. (A) Ordered (raft-like) phases in biomimetic and biological membranes are distinguished from disordered (non-raft) by a variety of biophysical characteristics, including their compressibility, bending modulus, hydrophobic thickness, and transbilayer pressure profile. (B) Proteins preferentially interact with one of these phases by a variety of mechanisms, including matching the transmembrane domain length to the thickness of the membrane, post-translational saturated lipid modifications that impart order phase affinity, and specific binding of raft lipids, among others.