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Review

Lipid-protein interplay and lateral organization in biomembranes

Thomas K.M. Nyholm*

Biochemistry, Biosciences, Faculty of Science and Engineering, Åbo Akademi University, Tykistökatu 6A, FIN-20520 Turku, Finland

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ABSTRACT

The distribution of lipids and membrane proteins within and between cellular membranes is carefully regulated. This sorting of lipids and proteins results in compositional differences between membrane compartments, bilayer leaflets, and lateral domains in the bilayer plane. The lateral organization of lipids and proteins has proven challenging to investigate, and the driving mechanisms remains unclear. Lipid self-organization has an essential role in the formation of lateral membrane structure, but the role of transmembrane proteins is not well known. This review focuses on how lateral lipid structure can affect the lateral distribution of proteins and how proteins could influence the organization of lipids in biomembranes.

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1. Introduction

Proteins and lipids are the major building blocks of all biological membranes. These membranes have significant roles both as structural and functional units of the cell. Membrane proteins are the working units in the ensemble, but without the right lipid environment the proteins do not function properly. Historically, the lipid environment has been considered a rather simple solvent for hydrophobic proteins, but during the latest decades its complexity has started to be appreciated. This complexity arises from the wide structural range of lipids that are found in cellular membranes. Usually the membranes are composed of several different classes of lipids, which in themselves most often are structurally rather heterogeneous, having different acyl chain compositions.

Lipids are not randomly distributed in cellular membranes, but rather they seem to be organized carefully between the different membrane compartments of the cell (reviewed in (van Meer et al., 2008)). For example, sphingolipids and cholesterol are found predominantly in the plasma membrane. The cholesterol content in the membranes increases along the exocytic pathway of eukaryotic cells. This cholesterol gradient has been considered to be of importance in the trafficking of proteins along the pathway (Munro, 1995; Munro, 1991). Further, eukaryotic membranes have a transbilayer organization, which is required for proper cell function (van Meer, 2011). The main focus in this review, however, will be on the lateral organization of membrane components, and especially on how proteins participate in the lateral sorting. After a general discussion about lateral organization in biological membranes the review will continue with a discussion about membrane proteins and lateral membrane structure. Although the lateral sorting of proteins and lipids into domains is most likely a mutual interplay between lipids and proteins, this part of the review has been divided into two parts: the first focuses on the

* Corresponding author.
E-mail address: tnyholm@abo.fi (T.K.M. Nyholm).

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partitioning of proteins between lateral domains in membranes, and the second focuses on how proteins could influence the lateral organization of lipids.

2. Lateral organization in membranes

It is well established that lipid self-organization can give rise to lateral structure in lipid bilayers. This sorting of lipids into lateral domains in the bilayer is mainly dependent on the thermotropic phase behavior of phospholipids (see e.g. (van Meer et al., 2008)). However, other factors like e.g., curvature preferences arising from the shape of the lipid may also be important determinants of lateral organization (Callan-Jones et al., 2011). From a biological perspective the liquid–liquid phase separation induced by cholesterol in phospholipid bilayers has been of special interest. The liquid ordered phase, which is formed by cholesterol and phospholipids, could separate from the liquid disordered phase in cell membranes, forming lateral functional domains in the membrane. Such domains rich in sphingolipids and cholesterol, called membrane rafts, have been proposed to be involved in a variety of cellular processes like e.g., membrane trafficking, immune responses, and cell signaling (Simons and Ikonen, 1997).

Liquid–liquid phase separation has been observed in model membranes with a variety of methods (Veatch et al., 2004; Mills et al., 2008; Petruzielo et al., 2013). However, in cellular membranes the presence of membrane raft like domains has proven so challenging to detect that the existence of membrane rafts has been debated (Munro, 2003). Due to their elusiveness membrane rafts have been thought to be small and dynamic. Yet, results from experiments with giant plasma membranes vesicles (GPMVs) have suggested that the plasma membrane possess the ability to phase separate into ordered and disordered domains (Lingwood et al., 2008; Baumgart et al., 2007), and it has been suggested that mammalian plasma membranes may exist near critical miscibility points, which would result in fluctuations in heterogeneity (Veatch et al., 2008).

Originally, membrane rafts were associated with the co-transport of membrane proteins and sphingolipids from the trans Golgi network to the plasma membrane in polarized cells (Simons and van Meer, 1988; Diaz-Rohrer et al., 2014a). Still, perhaps the strongest evidence for the lateral organization of lipids and proteins in cell membranes is observed by looking at membrane trafficking. It has already long been known that the plasma membrane in eukaryotic cells is thicker than the inner membrane compartments like e.g., the endoplasmic reticulum and Golgi membranes, and that the transmembrane segments of proteins are tuned to match the thickness of the membrane compartment they reside in (Bretscher and Munro, 1993). The thickness of the bilayers is probably mostly dependent on cholesterol content and phospholipid composition, but is likely also influenced to some degree by proteins (Mitra et al., 2004).

In experiments where the length of transmembrane helices in proteins have been systematically altered it has been observed that proteins with transmembrane helices that are too short, are not transported to the plasma membrane, but stay in the Golgi, while proteins with sufficiently long helices reach the plasma membrane (Munro, 1995; Rayner and Pelham, 1997; Ronchi et al., 2008). It is thought that the proteins with longer transmembrane helices are co-sorted together with the plasma membrane lipids, and that prior to leaving the Golgi, these lipids and proteins segregate into lateral domains. In line with this, it has been observed that the hydrophobic length of model peptides determines to what degree the peptides partition into cholesterol-rich bilayers (Kaiser et al., 2011), and it has been observed that the efficiency with which systematically mutated model transmembrane proteins are transported to the plasma membrane correlates with their association with ordered lateral domains in GPMVs (Diaz-Rohrer et al., 2014b). A common view is that hydrophobic matching between the transmembrane segments and the lipid bilayer is a major force in the co-sorting of lipids and proteins into lateral domains prior to the formation of transport vesicles. The mechanisms governing this process are not known, but it may be driven by lipid self-organization (alternative 1 in Fig. 1) or protein segregation (alternative 2 in Fig. 1), or a combination of both of these.

Besides their hydrophobic length, also the shapes of the transmembrane domains of plasma membrane proteins and e.g., Golgi proteins differ (Sharpe et al., 2010; Quiroga et al., 2013). In plasma membrane proteins the exoplasmic half of the transmembrane helix has a lower volume than in Golgi proteins. Supposedly the more dense helix is a response to the higher order in the outer leaflet of the plasma membrane (Sharpe et al., 2010). Results from a recent study where both the hydrophobic length and the volume of the exoplasmic half of the transmembrane helix were altered, suggests that also the shape of the segment can determine whether or not a protein is transported to the plasma membrane (Quiroga et al., 2013).

Further support for the existence of lateral structure in biomembranes comes from lipidomics studies of virus membranes, which have shown to accumulate especially sphingolipids and sterols (Gerl et al., 2012; Brugger et al., 2006). The fact that the virus membranes have a higher content of these lipids than the plasma membrane on average, which seems to be the case at least for the influenza virus, suggests that the lipids are incorporated into lateral domains together with the virus proteins prior to virus budding. Whether the virus proteins induce the formation of such domains or partition into already existing domains is not known.

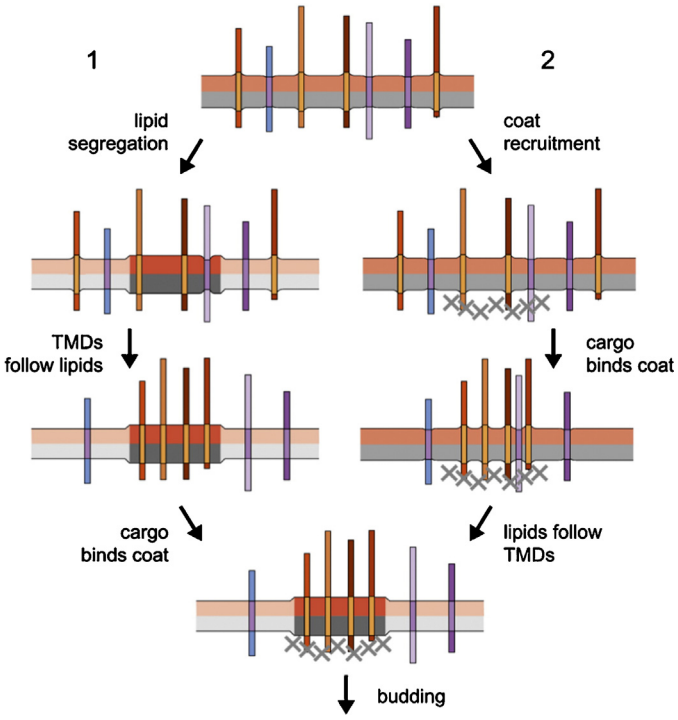

Fig. 1. Sorting of membrane lipids and proteins. Sorting of membrane components in Golgi membranes could be driven both by lipid self-organization (alternative 1) after which the more ordered lipid would attract proteins with longer transmembrane segments. Alternatively, proteins with e.g., longer than average transmembrane segment lengths could be collected into lateral domains that would attract suitable lipids (alternative 2). Modified from (Sharpe et al., 2010).