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Invited review

Lipid rafts, synaptic transmission and plasticity: Impact in age-related neurodegenerative diseases

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ABSTRACT

The synapse is a crowded area. In the last years, the concept that proteins can be organized in different membrane domains according to their structure has emerged. Cholesterol-rich membrane domains, or lipid rafts, form an organized portion of the membrane that is thought to concentrate signaling molecules. Accumulating evidence has shown that both the pre-synaptic and post-synaptic sites are highly enriched in lipid rafts, which are likely to organize and maintain synaptic proteins in their precise localization. Here we review recent studies highlighting the importance of lipid rafts for synaptic function and plasticity, as well as their relevance for age or disease-related cognitive impairment.

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1. Introduction

The classical Singer–Nicolson fluid mosaic model of membranes published in 1972 proposed that proteins and lipids could diffuse freely across biological membranes (Singer and Nicolson, 1972). However, ten years later, cell membranes were proposed to be organized into domains, since different phases in the lipid environment, corresponding to different levels of fluidity, were observed (Karnovsky et al., 1982). In the last three decades, there has been increasing evidence supporting the existence of such membrane microdomains, which are now termed lipid rafts (Simons and Gerl, 2010). The importance of lipid rafts in health and disease has been highlighted (Michel and Bakovic, 2007). Recent biophysical and microscopy advances have allowed a better knowledge about their function, organization and dynamics, providing a more consensual view about rafts (Simons and Gerl, 2010).

Accumulating evidence has been demonstrating that a great number of pre- and post-synaptic proteins involved in neuronal communication are localized to lipid rafts. In this review, besides summarizing lipid raft characterization and functionality, we will further discuss the localization of receptors for neurotransmitters and neuromodulators in these microdomains, as well as their importance for synaptic plasticity, ageing or disease-related cognitive impairment.

2. Lipid raft characterization

Lipid rafts are membrane microdomains enriched in cholesterol, glycosphingolipids and specific proteins (Fig. 1A). They are very small membrane domains, usually smaller than 100 nm in diameter, which greatly restrain their direct visualization by most microscopy techniques (Pike, 2006). New optical microscopy methods, which provide resolution well beyond the diffraction limit, such as the new super-resolution microscopy technique STED (stimulated emission depletion microscopy), allowed considerable advances in lipid raft detection and characterization. It is now accepted that the association of components within the raft is dynamic and that raft sizes range from small, short-lived, nanoscale assemblies to more stable membrane domains with variable size and lifetime (see Simons and Gerl, 2010).

The presence of saturated hydrocarbon chains allows cholesterol to be tightly packed inside lipid rafts, which makes them more

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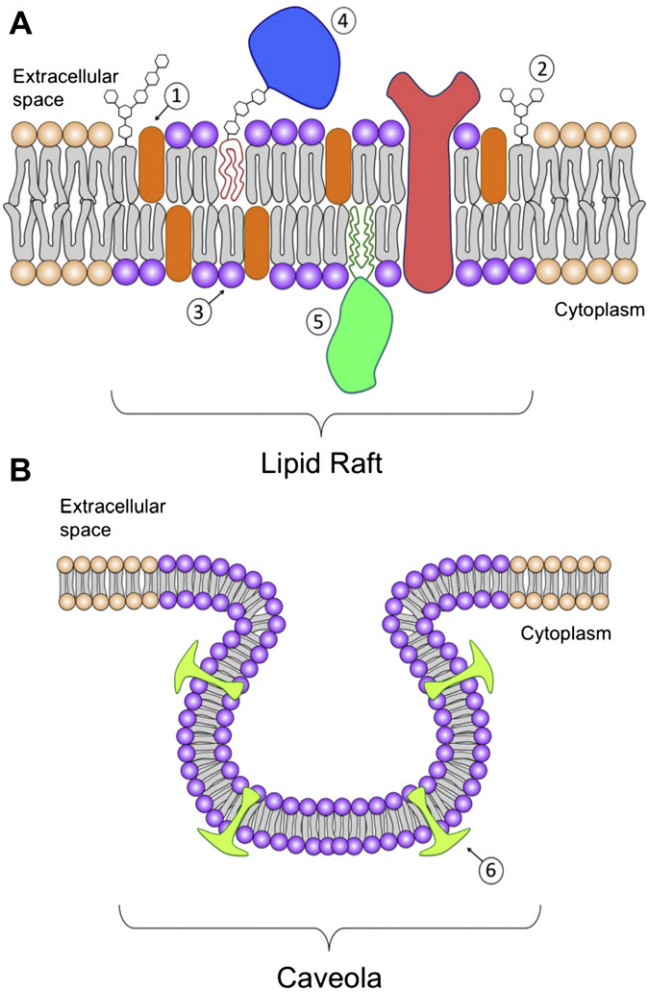

Fig. 1. Schematic representations of a lipid raft (A) and Caveola (B) within the plasma membrane. A) Lipid rafts are tightly packed membrane microdomains mainly due to the presence of cholesterol (1), glycosphingolipids (2) and phospholipids with saturated hydrocarbon chain (3). Glycosylphosphatidylinositol-proteins (4) and proteins with post-translational modifications, such as palmitoylation and myristoylation, are widely anchored to these domains (5). B) Caveolae represent a subset of lipid rafts that form an inward curvature, induced by Caveolin proteins (6).

insoluble than the remaining membrane (Simons and Toomre, 2000). So, most of the biochemical and functional studies on lipid rafts, rely on their insolubility in non-ionic detergents at low temperatures (Brown and London, 1998). The detergent-resistant membranes (DRMs) float after differential centrifugation in density gradients and can therefore be isolated from the soluble lipid and proteins. The obtained fraction is rich in cholesterol and sphingolipids, and this technique has been widely used to study protein and lipid dynamics in biological preparations (Simons and Toomre, 2000). Triton X-100, NP-40, CHAPS and Brij 98 are some of the most common detergents that can be used to extract lipid rafts. The need to select a proper lipid raft extraction method was highlighted recently (Williamson et al., 2010) in showing that the lipid and the protein contents of the extracts may change according to the detergent used. Alternatively, several detergent-free lipid raft isolation approaches can also be used; cell lysis can then be achieved, for example, by sonication in a pH 11 buffer or by using an isotonic buffer with calcium and magnesium. Subsequently, lipid raft isolation can be done by fractioning in sucrose or Percoll gradients (Smart et al., 1995; Song et al., 1996; Macdonald and Pike, 2005; Persaud-Sawin et al., 2009).

Along with the chosen extraction method, the most common experimental approach to assess lipid raft involvement in cellular mechanisms makes use of molecules that promote lipid raft disruption. Since cholesterol is essential to lipid raft integrity, the usual procedure is to add molecules that promote cholesterol depletion from the cell membrane. Such molecules can be cholesterol-sequestering agents (*e.g.*, filipin), cholesterol-chelating agents (*e.g.*, methyl-β-cyclodextrin) or inhibitors of cholesterol synthesis (*e.g.*, statins). If cholesterol depletion leads to loss-of-function one may suggest a dependency on lipid rafts (Allen et al., 2007; Korade and Kenworthy, 2008). However, because cholesterol depletion can lead to several pleiotropic effects, cholesterol reloading protocols can be used to further confirm the relevance of lipid rafts for a given function (Allen et al., 2007). It should, however, be kept in mind that changes in membrane fluidity (either increases or decreases) may affect membrane signaling properties. Furthermore, disassembly of lipid rafts has been shown to occur upon both cholesterol depletion and cholesterol enrichment (Meyer dos Santos et al., 2007).

In most cell types, the presence of caveolin, a protein present in a specific subset of lipid rafts, leads to the formation of invaginated structures called caveolae (Fig. 1B). Because of their unique morphology, caveolae were visualized in the 1950s and their existence is now generally accepted (Yamada, 1955; Parat, 2009). Interestingly, neurons seem to be an exception, where expression of caveolin is very low and formation of caveolae could not be directly visualized yet (Masserini et al., 1999). Nevertheless, the presence of caveolin-1 can be detected in neurons, where it seems to be involved in compartmentalization and internalization of signaling complexes, neuronal differentiation and arborization of primary neurons and also in neuroprotection, since it provides a healthy neuronal ageing (Gaudreault et al., 2005; Hibbert et al., 2006; Head et al., 2010, 2011). Indeed, young caveolin-1 knock-out mice feature decreased levels of synaptic markers and a reduced number of hippocampal synapses that resemble those found in aged hippocampi (Head et al., 2010). These findings are in keeping with the notion that proper synapse function and spine density depends upon lipid rafts (Hering et al., 2003).

3. Lipid raft functions

3.1. Clustering

Lipid rafts can bind to proteins and, despite the fact that no specific amino acid sequence has yet been identified as targeting proteins to lipid rafts, it has been demonstrated that post-translational modifications, such as the addition of glycosylphosphatidylinositol (GPI) anchors, palmitoylation and/or myristoylation, might localize proteins to rafts (Lucero and Robbins, 2004).

Convincing proteomic data have reinforced the role of lipid rafts as coordinators of signal transduction. From the proteins identified to be located in lipid rafts, many of them are tyrosine and serine/threonine kinases, phosphatases, and heterotrimeric G-proteins (Foster et al., 2003). It is very important to note that localization of different proteins within lipid rafts seems to be dependent on the cell type and receptor levels. This observation is in agreement with the large variability of membrane domains and raft abundance observed in different cell types, where cholesterol content, caveolin expression and other factors dictate raft abundance and function, which generates a cell-specific organization of receptors and effectors (Simons and Toomre, 2000).

During signaling processes, lipid rafts are thought of as platforms that co-localize and therefore facilitate the interaction of the necessary molecules for the activation of a specific signaling pathway. As a consequence of ligand binding, a rapid and efficient