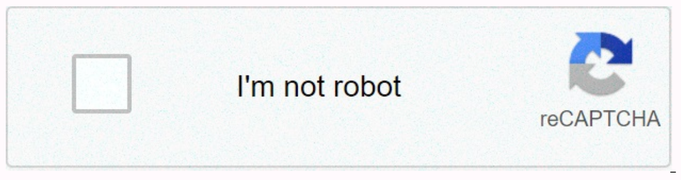


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## Lipid raft formation

D.A. Brown, in Encyclopedia of Biological Chemistry (Second Edition), 2013Lipids do not always blend evenly into membranes, but can cluster to form microdomains. A certain class of these microdomains was called lipid rafts. These are enriched in cholesterol and sphingolipids. Rafts probably exist in membranes in the liquid-ordered phase or in a phase with similar properties. Growing evidence suggests that fluid-crystalline phase domains rich in phospholipids and liquid-ordered phase domains (rafts) may exist in equilibrium in biological membranes, especially the plasma membrane. Preferential partitioning of membrane proteins into rafts can affect function. Among the proteins that are directed to rafts are those anchored in the outer leaflet of the membrane through covalent attachment to a special glucolipid, phosphaicisinasitol (GPI). Other proteins that are linked to saturated aciila chains, such as those that are directly cylatated with two or more palmitate chains, or a palmitate and a myriad chain, are also directed to rafts. The targeting of proteins anchored by GPI and other proteins for rafts plays a role in signal transduction, especially in hematopoietic cells, and possibly also in the classification in intracellular membranes and regulation of proteolysis of the cell surface in other mamherous cells. Chhanda Biswas, in Immunity and Inflammation in Health and Disease, 2018Delipid viscera are cholesterol-rich domains found on the cell surface, and normally aggregation of lipid rafts appears especially at the site of TCR-antigen ligation. This ensures the optimal immune synapse onset required for maximum T-cell activation and antigen-specific downstream signaling. However, newly isolated T cells from SLE-prone rats harbor prevented lipid rafts. Amplification of T-cell activation in lupus-prone mice can be achieved by treatment with cholera toxin, a facilitator of lipid raft aggregation, exacerbating lupus pathology and the onset of the disease can be slowed by disruption of lipid rafts by statin-based drugs that block cholesterol synthesis (Jury and Kabouridis , 2004; Deng and Tsokos, 2008). Bruno M. Castro, ... Maria F. Garcia-Parajo, in Methods in Cell Biology, 2013 Pifide beams, cell membrane domains with unique composition and properties, modulate the distribution of receptor membranes and signaling molecules facilitating the assembly of active signaling platforms. However, the underlying mechanisms linking signal transduction and lipid balsas are not fully understood, mainly due to the transient nature of these membrane sets. Several methods have been used to study the association of membrane receptors with lipid rafts. In part of this chapter, a description of how biochemical methods, such as balsa interruption by cholesterol depletion agents, are useful for qualitatively establishing the protein association with lipid rafts. The second part of this chapter is devoted to imaging techniques used to study organization and lipid rafts. We cover conventional approaches such as confocal microscopy to advanced imaging techniques such as homo-FRET microscopy and superresolution methods. For each described technique, its advantages and disadvantages are discussed. Roberto Bravo, ... Sergio Lavandero, in the International Review of Cell and Molecular Biology, 2013Balsaslipídas are cholesterol-rich plasma membrane domains that may contain caveolin. Lipid-like domains are defined as regions of cave-free plasma membrane enriched in cholesterol and members of the domain-containing protein family, such as KE04p and C8orf2. These proteins are essential for the maintenance of lipid-raft structures. Although it is known that ER has lower cholesterol and glycophingolipid levels than plasma membrane and other organelles, two homologous proteins at KE04p and C8orf2, Erlin-1 and Erlin-2 (for lipid-raft protein ER), are found in the PS, suggesting the existence of lipid-jandão domains in ps (Browman et al., 2006). Another protein involved in the maintenance of lipid-raft domains is the companion of the sigma-1 receptor (Sig-1R), a cholesterol binding protein (Hayashi and Su, 2010). Sig-1R is also involved in mitochondria-ER binding through microdomains enriched in cholesterol and ceramides (Hayashi and Fujimoto, 2010), which are part of the structure of the ER membrane associated with mitochondria (MAM). Hui Zheng, ... Ping-Yee Law, in Enzyme Methods, 2013 Microdomains of jangadaslipid are dynamic microdomains of plasma membrane containing high levels of cholesterol and sphingolipids (Helms & Zurzolo, 2004; Mayor & Rao, 2004). There are accumulated reports in support of the essential roles of the location of lipid balsa microdomains performed in GPCR signaling. Extracting cholesterol with methyl-β-cyclodextrin disrupts the lipid microdomains of the ferry and attenuates signaling of various GPCRs (Monastyrskaya, Hostettler, Buergi, & Draeger, 2005; Navratil et al., 2003; Zhang, Tetrault, Wang, Loh, & Law, 2006). In addition, our previous experiments demonstrated that the distribution of GPCR in the cell membrane affects biased signaling (Zheng, Chu, et al., 2008). Lipid raft microdomains are essential for inhibition of adenilic cicocyline (CA) induced by morphine or etorphine. However, morphine- but not etorphine-, eRK-induced phosphorylation is influenced by the interruption of lipid raft microdomains (Zheng, Chu, et al., 2008). Kiyotaka Toshimori, Edward M. Eddy, in Knobil and Neill's Physiology of Reproduction (Fourth Edition), 2015 Delipid beams (also known as lipid microdomains) are discrete lipid domains present in the outer leaflet of the plasma membrane. The rafts are enriched in cholesterol, glycosfingolipids, and proteins anchored by GPI glycosyl-phosphatidylinositol, and are insoluble in low nonionic detergents. Lipid rafts are present throughout the surface of mammalian spermatozoa and are not restricted to particular particular Lipid raft-related proteins detected in sperm include caveolin1 (CAV1) in the anterior acrote and main part.83 Homologous transient receptor-1 (TRPC1) was co-immunolocated with CAV1.84 Other lipid raft markers, CD59, GM1 ganglioside, and flotillin2 (FLOT2), were found in the posterior head, and FLOT2 was located mainly in the posterior head and part of the medium in human spermatozoa.85 Serine protease 21 (PRSS21) was located in the head , cytoplasmic droplet and midpiece.86 The dynamics of the sperm lipid balsa is reviewed elsewhere in relation to the sperm-zone bond and the acrosome reaction induced by the pellucida zone.87Patrick Lajoie, Ivan R. Nabi of the International Review of Cell and Molecular Biology, 2010 Pímpide beams are plasma membrane microdomains enriched in cholesterol and sphingolipids that are involved in lateral compartmentalization of molecules on the cell surface. The internalization of ligands and receptors by these domains occurs through a process defined as raft-dependent endocytosis. Caveolae are smooth invaginations enriched by caveoline-1 of the plasma membrane that form a subdomain of lipid rafts. The endocytosis of ferries, including the caveolar, but also the dynamite-dependent and dynamite-independent pathways, is characterized by its sensitivity to cholesterol and clathrin-independence. In this review we will characterize lipid rafts and caveolae, their endocytosis and their regulation by the citskeleton actin, caveolin-1, dynamite and cholesterol. Maurine E. Linder, in Manual de Signaling Celular (Second Edition), 2010Balsaslipídas were defined as small (10-200 nm), heterogeneous, highly dynamic, domains enriched with sterol and sphingolipid that compartmentalizing cellular processes. Small rafts can sometimes be stabilized to form larger platforms through protein-protein and protein-lipid interactions [42]. Raft lipids were proposed to exist in a more ordered state, similar to the liquid-ordered phase described in model membranes [2, 43]. The formation of lipid rafts in the exoplasmated plasma membrane leaflet is driven by the tight packaging of the long chains of saturated acilia of cholesterol sphingolipids. The structure of raft lipids in the cytoplasmic leaflet is less clear, but it is believed that these domains also exist in a state where the lipid chains above are well packed, highly ordered and extended. Proteins with high affinity for an ordered lipid environment are recruited for rafts. These are proteins with GPI anchors (which contain predominantly saturated fatty acids), or proteins such as kinases of the Src family that are modified with reasons of double fatty acylation. Crosslinking of proteins anchored in GPI induces the activation of family kinases Src. The domain of the lipid balsa provides a platform for of a sign of a protein anchored only to the exoplasmated leaflet for proteins associated with the internal leaflet of the plasma membrane. Zhang Boyang, ... Mario Tiberi, in Advances in Pharmacology, 2014The pier rafts are regions in in. concentrated plasma membrane with cholesterol and glycosfingolipid (Allen, Halverson-Tamboli, & Rasenick, 2007; Pike, 2003). Lipid rafts may also contain cave proteins, which bind to cholesterol to form invaginations known as caveolae (Allen et al., 2007; Fra, Williamson, Simons, & Parton, 1995). As lipid rafts are enriched with GPCRs, G proteins and effect enzymes, they are believed to be platforms for efficient and fast signaling (Allen et al., 2007; Pike, 2003). It should be noted, in comparison with β1AR,

β2AR was found more localized in lipid balsas of ventricular cardiomocytes of rats, which may explain their higher constitutive activity (see Milligan review, 2003; Rybin, Xu, Lisanti, & Steinberg, 2000). To date, this property has not yet been demonstrated for the similar shared relationship between Class D1 receivers. However, in the case of hD1R, it has been reported to be predominantly found in lipid rafts of HEK293 cells (Yu et al., 2004). This was shown by most hD1Rs that cofractionated with caveoline-2 into low density membrane fractions (LDMF) — areas where lipid rafts are also segregated due to their unique cellular content (Brown & London, 2000). Within the LDMF, the basal activity of hD1R was higher when compared to high density membrane fractions (HDMF). Notably, even in HDMF regions that presented a stronger hD1R immunostaining than some regions of the LDMF, basal activity was significantly higher in the latter (Yu et al., 2004). Similarly, in COS-7 cells, the majority of the D1R population was cofractionated with caveoline-1 within the LDMF (Kong et al., 2007). However, after treatment with methyl-β-cyclodextrin to disrupt the structure and function of caveolae, the basal GTPγS binding to Gs by D1R was increased compared to the untreated condition, despite the lack of a concomitant increase in basal cAMP levels (Kong et al., 2007). This suggests that lipid rafts can negatively regulate the agonist-independent activation properties of D1R. Although this may conflict with the aforementioned study, it is important to note that both studies share a common trap: Fractionation of D1Rs in LDMF is not a direct proof of their location in lipid rafts. In addition, while both studies showed an interaction between D1R and caveolin using immunoprecipitation, this can occur through intracellular compartments (see Review Chini & Parenti, 2004; Wyse et al., 2003). Thus, much still needs to be learned about the potential role of lipid rafts in dictating the constitutive activation of class D1 receptors. Kwong Tai Cheng, ... Indu S. Ambudkar, in Current Topics in Membranes, 2013The domains of prafslipid (LRDs) that are enriched in such lipids can serve as platforms for recruiting and anchoring STIM1/channel complexes on the periphery LRDs are biochemically distinct lipid domains of the plasma membrane that are enriched in cholesterol, sphingolipids, PIP2, PIP3, and protein components of calcium signaling (e.g., Cav1, EGFRs, G proteins, PMCA, Homer and PKC pumps). SOCE SOCE was proposed to occur within LRDs, because the interruption of these domains attenuates the SOCE. Dependence on TRPC1 channel function in intact LRDs has been shown in many cell types, such as HSG cells, C2C12 skeletal myoblasts, polymorphonuclear neutrophils, endothelial cells, and human platelets (Ong & Ambudkar, 2012). Other evidence for the involvement of LRD in the assembly of functional TRPC1 channels was provided by data demonstrating an increase in the partition of TRPC1 in lipid rafts after cell stimulation and the exhaustion of the Ca2 + store (Lockwich et al., 2000; Pani et al., 2008). Consistent with the suggestion that STIM1 can be anchored to the plasma membrane through interaction with LRDs, the partition of STIM1 in LRD is increased during SOCE activation. More importantly, trpc1 + STIM1 co-immunity is achieved in lrd, but not in non-LRD fractions. When these domains are interrupted, the partitioning and coimmunoprecipitation of TRPC1 and STIM1, as well as SOCE, are attenuated. The polybasic tail of STIM1 contains a consensus sequence that can potentially mediate its binding to PIP2 in the plasma membrane (Liou, Fivaz, Inoue, & Meyer, 2007). This was confirmed in experiments showing that the exclusion of the polybasic tail results in the loss of SOCE, as well as in the formation of STIM1 puncta in the junctional regions of the ER-plasma membrane (PM). The exact interactions between stim1 and plasma membrane proteins or lipids have not yet been resolved. It is also unclear whether other scaffolding proteins are involved in directing STIM1 clusters to specific regions of the plasma membrane. It is likely that these regions have specific biochemical, structural and spatial characteristics, since ion channels and possibly other effector proteins regulated by SOCE, such as CAM and calcineurin, are recruited and regulated within this domain. Thus, the rate and specificity of these processes need to be strictly controlled. Cav1, a cholesterol binding protein that is located within and organizes lRD, has been proposed to be involved in regulating SOCE through Orai1 and TRPC1, and serve as a scaffold for the recruitment of various proteins in LRDs. In Xenopus oocytes, Orai1 actively recycles between the endomal compartment and the plasma membrane. After cell stimulation, Orai1 is actively trafficked to the plasma membrane from the endorsement compartments. A putative cav1 binding site is present in the N-terminus of Orai1 and Cav1 has been shown to play a role in orai's endocytosis1 during meiose (Yu, Sun, & Machaca, 2010). While further studies are needed to define the role of LRDs in modulating orai channel function1, a series of published studies have demonstrated a role for cav1 in the regulation of TRPC1 (Ong & Ambudkar, 2012; Pani & Singh, 2009). TRPC channels have retained Cav1 connection domains inside the N-e C-termini. The pin1 connection motif of terminal N (aa 322 and TRPC 349) connects to the scaffolding domain in Cav1 (aa 82 82 101). TRPC1 coimmunoprecipitates with Cav1 in HSG (Lockwich et al., 2000) and pulmonary artery endothelial cells (Kwiatek et al., 2006). In addition, the N-TRPC1/Cav1 interaction serves for TRPC1 scaffolding in the plasma membrane region and determines its subsequent activation by store exhaustion. A concerted role for Cav1 and STIM1 has been demonstrated in the regulation of TRPC1. The suggested mode of regulation for TRPC1 is that in resting cells, it is present in the recycling of endomosis. Cav1 interacts with and scaffolding TRPC1 vesicles near the plasma membrane. This scaffolding probably represents a brief retention of the channel in this location. From here, either it recycles back to the traffic route or if the store depletion is initiated, the channel is recruited to the plasma membrane, interacts with STIM1 and is activated. Following the exhaustion of the ER-Ca2+ store, STIM1 transallocates to the periphery of cells, interacts and activates Orai1, and Ca2 + orai-mediated influx 1 boosts the insertion of TRPC1 into the plasma membrane. After insertion, STIM1 and TRPC1 gates. The linking of STIM1 to TRPC1 also induces the dissociation of the TRPC1/Cav1 complex (Pani et al., 2009). Current data suggest that STIM1/TRPC1 forms a stable complex that helps retain active TRPC1 channels in the plasma membrane. The replenishment of ER-Ca2+ stores leads to channel inactivation, due to the dissociation of STIM1 from TRPC1. At this point, TRPC1 can be associated with cav1 (Pani et al., 2009) or, alternatively, it can be endocited by a different route. Further studies are needed to further delineate the protein-protein interactions involved in the progress of TRPC1 through the different steps involved in its activation (trafficking, insertion in the plasma membrane, scaffolding and activation by STIM1). Interestingly, it was reported that Homer-1 links the TRPC1 channel and facilitates the rapid reassembly of the TRPC1/Homer/IP3R complex, after the restocking of ER-Ca2+ stores (Worley et al., 2007). How exactly Homer-1, Cav1, STIM1 and IP3R regulate the trafficking and function of TRPC1 in a single cell has not yet been elucidated. Another interesting hypothesis that needs to be further analyzed is the proposal that the recruitment of Orai/TRPC/STIM1 complexes for LRDs is necessary for store-dependent regulation, but that the same complexes can function as channels operated by receivers when located outside lipid rafts (Liao et al., 2009). Thus, several proteins have the ability to critically affect the functions of TRPC. Whether these are ubiquitous in all cell types or if the TRPC1 -SOCE is regulated specifically cells needs to be established. Established.