Biochimie 96 (2014) 75–84

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Mini-review

Biogenesis and transport of membrane domains-potential implications in brain pathologies

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ARTICLE INFO

Article history:
Received 27 May 2013
Accepted 12 September 2013
Available online 27 September 2013

Keywords:
Membrane domains
Very long chain fatty acid
SNAREs

ABSTRACT

Lipids in biological membranes show astonishing chemical diversity, but they also show some key conserved structures in different organisms. In addition, some of their biophysical properties have been related to specific functions. In this review, we aim to discuss the role of sphingolipids- and cholesterol-rich micro- and nano-membrane domains (MD) and highlight their pivotal role in lipid–protein clustering processes, vesicle biogenesis and membrane fusion. We further review potential connections between human pathologies and defects in MD biosynthesis, recycling and homeostasis. Brain, which is second only to the adipose tissues in term of lipid abundance, is particularly affected by MD defects which are linked to neurodegenerative disorders. Finally we propose a potential connection between MD and several nutrient-related processes and envision how diet and autophagy could bring insights towards understanding the impact of global lipid homeostasis on human health and disease.
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1. Introduction

Pioneering studies in epithelial cells demonstrated the existence of plasma membrane components characterised by higher resistance to detergent extraction, and therefore called DRM (for the detergent resistant membrane fraction). Apical but not basolateral protein cargo were isolated in DRMs [1,2], along with sphingolipids and cholesterol. The polar localisation of these apical cargoes was revealed to be sensitive to inhibition of both sterol and sphingolipid metabolism [3,4], suggesting a particularly important role for these lipids in trafficking to the apical plasma membrane and in the lipid identity of these membranes (Fig. 1A).

Sphingolipids, compared to the more abundant glycerolipids, have acyl chains with a higher level of saturation and higher number of hydroxyl groups (OH) [5]. This structure with straighter chains results in tighter packing and better sterol intercalation, with the OH groups also greatly contributing to the strength of lipid association inside the leaflet via hydrogen bounds. Thus, sphingolipids and sterol tend to cluster together and can be demonstrated to form a liquid ordered phase (L_o) in model membrane systems *in vitro*. In contrast, glycerophospholipids generally have more unsaturated acyl side chains, which reduces packing and sterol intercalation. Hence, under physiological conditions, glycerophospholipids are generally in the liquid disordered phase (L_d) (Fig. 1B). Notably L_o and L_d phases display different biophysical characteristics including fluidity (L_o is more rigid then L_d), a key parameter which varies with temperature [6], and detergent solubility (with L_o being less soluble).

Since these initial observations, membrane domains enriched in both sphingolipids and sterols have been found in different organisms and are thought to represent key domains responsible for membrane organisation and receptor transport, internalisation and signalling [7–12]. Mass spectrometry analyses of DRMs isolated from cells has revealed the presence of a large number of associated proteins, including glycosyl-phosphatidyl-inositol (GPI)-anchored proteins [13], Gα subunits of GPCR [14], and receptors involved in cell growth regulation such as EGFR [15]. A particular enrichment of proteins associated with pathogen entry has also been observed

Abbreviations: DRM, detergent resistant membrane; GPCR, G protein coupled receptor; EGFR, epidermal growth factor receptor; GPI, glycosylphosphatidylinositol; TGN, trans Golgi network; VSVG, viral G glycoprotein of the vesicular stomatitis virus; PMA1, plasma membrane ATPase 1; VLCFA, very long chain fatty acid; GUV, giant unilamellar vesicle; MD, membrane domains; SNAREs, soluble N-ethylmaleimide sensitive factor attachment protein receptors.

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http://dx.doi.org/10.1016/j.biochi.2013.09.014

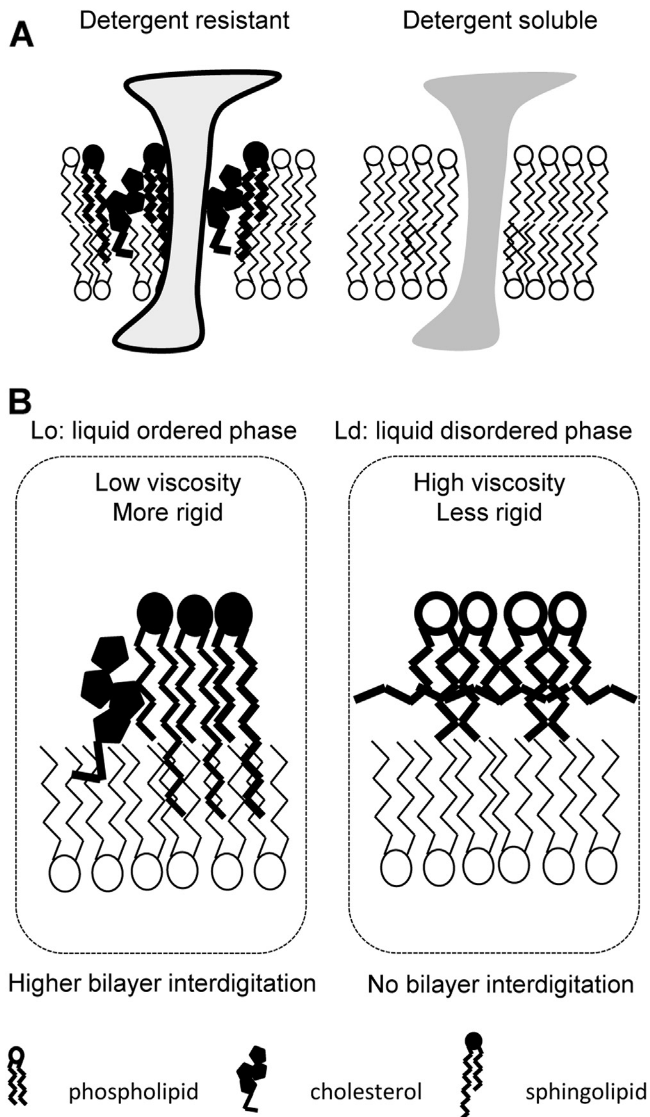

Fig. 1. Membrane organisation. A) Schematic representation of detergent resistant and detergent soluble. Proteins resistant to detergent solubilisation are considered to reside in cholesterol–sphingolipid microenvironments, here represented in black. B) Lo (liquid ordered) and Ld (liquid disordered) membranes. Lo and Ld phase bilayer rigidity and interdigitation are emphasised in relationships with lipid structure.

[1,16–18]. Hence a number of human diseases may be linked to defects in cholesterol and sphinogolipid-enriched MD, as we discuss below. Since these seminal papers, the physiological significance of DRMs obtained with cold detergent procedure has been criticised and it would be of interest reinvestigate all DRMs data with new and more reliable microscopy and spectroscopy approaches. To avoid any confusion we will clearly refer either to DRM (for *in vitro* membrane obtained with cold detergent procedure from cells) or membrane domains (MD) to refer to sphingolipids- and cholesterol-rich membrane nano- and micro-domains. Several resident proteins of MD have been visualised by microscopy both *in vitro* and in cells, providing information on their organisation. GPI-anchored proteins have been visualised in artificial membranes by three-dimensional atomic force microscopy [19]. Transient expression of Remorin-GFP in tobacco cells revealed a dynamic patchy fluorescent pattern on the membrane surface [20]. Stimulated emission depletion far-field fluorescence nanoscopy (STED) was used to track a fluorescent GPI-anchor in the plasma membrane of living cells, enabling the direct observation of the dynamic assembly of domains containing this marker, and allowing determining that the clusters can be of the order of nanometres [21]. Fluorescence correlation spectroscopy [22] as well as fluorescence lifetime imaging microscopy-Förster resonance energy transfer [23] were recently successfully used to track partition in MD and diffusion rate of fluorescently-tagged proteins or lipids by fluorescent ligands in both artificial membranes and cell cultures. High-resolution secondary ion mass spectrometry also allowed to detect the enrichment and distribution of specific lipids in MD [24].

2. Membrane domains form by spontaneous lateral segregation

Membranes of the secretory and endocytic systems of eukaryotes (ER-Golgi and endosomes-PM-degradative compartments) are composed of three main lipid classes: glycerophospholipids, sphingolipids and sterols. These lipids present a different stoichiometry in different organelles. In the ER, sphingolipids and sterols are synthesised, but do not accumulate while glycerophospholipids make up the bulk of ER-membrane lipids: PC (phosphatidylcholine) accounts for 60% of total lipids; PE (phosphatidylethanolamine) for 20–30%; PI (Phosphatidylinositol) for 10–15% and PS (phosphatidylserine) up to 5%. In contrast, at the plasma membrane sphingolipids and sterol may account for 10–30% of total lipids each, followed by PC representing 30%, and PS representing 10%, as reviewed by van Meer [25].

The pathways by which sphingolipids and cholesterol domains form and are sorted preferentially to the PM are still not fully understood. Caveolae, which are stable flask shaped cholesterol–sphingolipid rich domains, have been proposed to first assemble at the Golgi apparatus and quickly leave this compartment to reach the PM [26]. MD associated with glycosphingolipid receptors have been shown to form via a ligand induced clustering process directly at PM [27]. Whether sphingolipids follow a specific secretory pathway and cholesterol a different one and they finally meet at PM, or if they travel together in vesicles remains an open question. It is also unclear if they are transported exclusively in vesicles, or whether they can arise by the action of lipid transfer proteins at membrane contact sites [28].

A gradient of sterols and sphingolipids along the secretory pathway has been described since the 1980s in several organisms [11,29–33]. These gradients may result from vesicular transport as well as Golgi cisternal maturation. The latter model postulates that cargoes arriving at the Golgi from the ER are confined to the cis Golgi, undergo processing, and then upon modification migrate, while cisternae mature, to the distal part of the Golgi (Trans Golgi Network) for exit. Patterson et al. [34] measured the kinetics of Golgi transit of several different cargoes and found that there were different lag periods for different proteins transiting through the Golgi. The temperature inducible VSVG-GFP, was shown to distribute into Golgi domains containing the Golgi resident galactosyl-transferase (GalT), after induction at permissive temperature, then move into a different region, close to putative export sites. Several other PM-targeted proteins could pass or not through GalT domains to then reach export domains. This work suggested that at least 2 Golgi subdomains exist and that partitioning of cargos may occur within Golgi cisternae. This model called the "rapid partitioning model" would imply that an intra-cisternal lipid sorting could occur at the Golgi and cause partitioning of proteins on the basis of their inclusion in specific domains [34]. In yeast, the exogenous chimera Fus-Mid-GFP known to be associated with MD [35] was used to assess if sphingolipids and cholesterol arise together in vesicles from the Golgi. The immuno-isolation of TGN-derived vesicles containing Fus-Mid-GFP was achieved and vesicle-

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