Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Cell Biology

Lipid unsaturation and organelle dynamics

Hélène Barelli and Bruno Antonny

The number of double bonds (=unsaturation) in the acyl chains of phospholipids (PL) influences the physical properties of cellular membranes. Here, we discuss disparate molecular processes, including vesicle budding, ion channel opening, and lipoprotein formation, which are greatly facilitated by PL polyunsaturation in membranes. Experimental and computer-based approaches for the structure and dynamics of PL suggest a common cause for these effects: the ability of the polyunsaturated acyl chain of PL to extend or bent along the membrane normal according to various constraints, thereby enabling a third dimension of motion in a structure that is essentially a 2D fluid.

Address
Institut de Pharmacologie Moléculaire et Cellulaire, 660 route des lucioles, 06560 Valbonne, France

Corresponding authors: Barelli, Hélène (barelli@ipmc.cnrs.fr) and Antonny, Bruno (antonny@ipmc.cnrs.fr)

Current Opinion in Cell Biology 2016, **41**:25–32

This review comes from a themed issue on **Cell Organelles**

Edited by **Pedro Carvalho** and **Davis Ng**

For a complete overview see the Issue and the Editorial

Available online 7th April 2016

http://dx.doi.org/10.1016/j.ceb.2016.03.012

Introduction

The relative abundance of major lipid species differs between cellular organelles [1–3]. In addition, some rare lipids have a restricted localization. Here, we discuss a third distinguishing trait of cellular membranes: their fatty acyl chain profile, that is, the spectrum of hydrocarbon chains at the *sn1* and *sn2* positions of glycerophospholipids (PL). These acyl chains belong to three classes: saturated (e.g. palmitate/C16:0), monounsaturated (e.g. oleate/C18:1) and polyunsaturated (e.g. arachidonate/C20:4 for the ω6 subclass, and docosahexaenoic acid/C22:6 for the ω3 subclass) (Figure 1a).

In general, the acyl chain profile of biological membranes revolves around predominant combinations and shows some trends that can be organism-dependent, cell-dependent, or even organelle-dependent [2,4,5•]. Thus, the endoplasmic reticulum (ER) is rich in monounsaturated lipids, whereas polyunsaturated lipids are extremely abundant in synaptic vesicles [1,6]. In addition, tight homeostasis mechanisms keep the acyl profile of some organelles such as the ER within narrow limits [7•,8]. Finally, the acyl chain profiles can change during cell activation, division or differentiation [9–12], show some spatial features [13,14•], or correlate with environmental changes or pathological conditions (e.g. transformation) [15,16,17•,18].

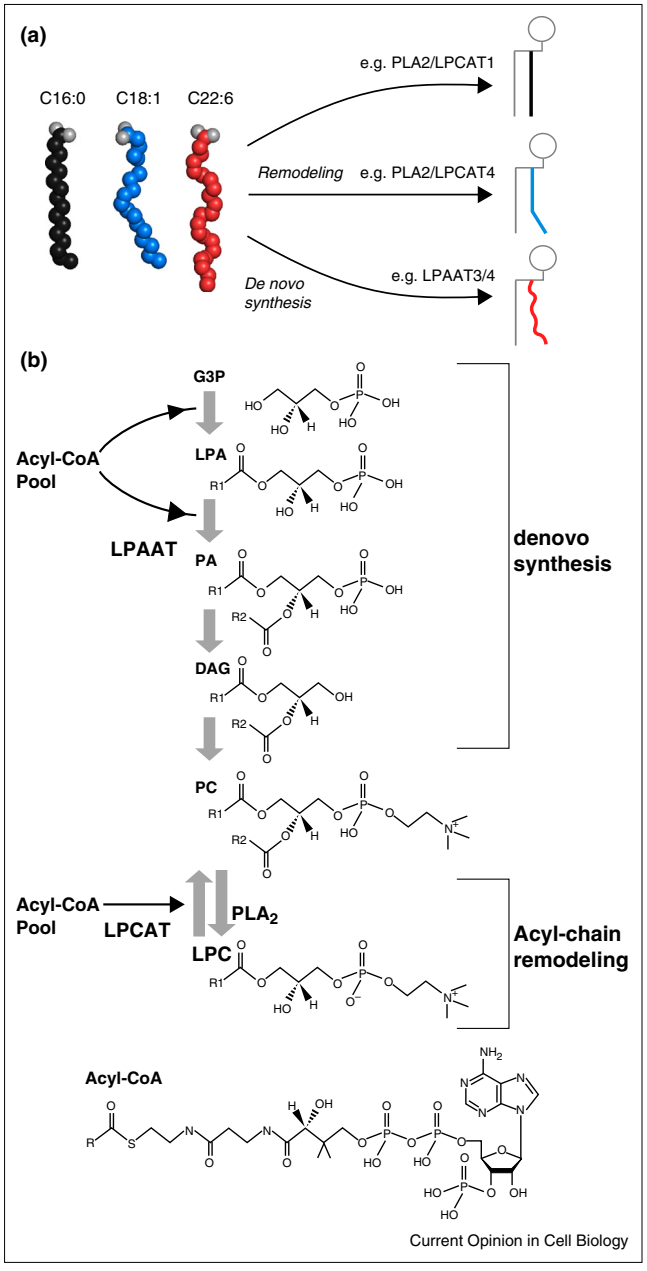
The acyl chain diversity of biological PL has been studied for decades [4]. However, our understanding of its role has remained fragmental due to some conceptual and experimental difficulties. The first are inherent of the fact that PL fatty acids form the membrane hydrophobic core. Consequently, they do not necessarily act as isolated molecules, but rather form a continuum phase with characteristic features (e.g. fluidity, water permeability, bending rigidity) [19,20]. The experimental difficulties are twofold: Firstly, manipulating the acyl chain profile; and finally, discriminating the mode of action. A classical method is to change the fatty acid diet of an organism or a cell. However, there is a long way between fatty acid transport and their incorporation into PL, leaving the possibility of other mechanisms whereby fatty acids act as free species or as precursors of eicosanoids [21].

Major advances have been recently made in the identification of acyltransferases responsible for the specific incorporation of fatty acids into PL [4,22,23,24••]. Thanks to these progresses, genetic strategies can now be used to modify the fatty acyl profile of biological membranes in a more directed manner. In addition, continuous advances in lipidomics, in biophysical characterization, and in atomic or quasi-atomic simulations facilitate both analysis and understanding [2,5•,25,26•,27•]. The recent examples described below illustrate how the balance between saturated, monounsaturated and polyunsaturated PL impact on membrane physicochemical properties, which, in turn, modulate various cellular processes.

Lysophospholipid acyltransferases and phosphatidylcholine diversity

Phosphatidylcholine (PC), the major PL in cellular membranes, presents a wide diversity regarding its acyl chain composition, especially at the *sn2* position. The group of Shimizu recently performed a comprehensive study of the various lysophospholipid acyltransferases responsible for this diversity [24••] (Figure 1a,b). In the *de novo* pathway, lysophosphatidic acid (LysoPA) is used as a substrate and, after incorporation of the fatty acid at position *sn2* of glycerol, the resulting PA species is further processed to give PC. In the remodeling pathway, lyso-PC is directly used as a substrate by a specific acyltransferase. This study reveals that one lysophosphatidic acyltransferase

Figure 1



PL remodeling: schematic view of the reactions leading to PL acyl chain diversity. **(a)** Atomic models of saturated (black, C16:0), monounsaturated (blue, C18:1) and polyunsaturated (red, C22:6) fatty acids. Fatty acids are incorporated into membrane PL during PL *de novo* synthesis or PL remodeling and impart membranes with different physicochemical properties. Some enzymes responsible for the incorporation of specific fatty acids into phosphatidylcholine are indicated [24••]. **(b)** LPAATs, which incorporate the *sn2* acyl chain in LysoPA, and LPCATs, which reincorporate a new acyl chain after PC synthesis and hydrolysis by phospholipases A2, are responsible for tuning the acyl chain profile of PC and other phospholipids. For example, LPCAT1 preferentially incorporates a saturated acyl chain [24••].

(LPAAT) and two lysophosphatidylcholine acyltransferases (LPCAT) contribute to the formation of some major PC species. LPCAT1, LPCAT4 and LPAAT3 promote the formation of C16:0, C18:1 and C22:6 PC molecules, respectively [24••].

The correlation between the abundance of a given PC species in a tissue and the enzymatic LPAAT or LPCAT activities is not perfect, suggesting that other factors, such as the abundance of the acyl-CoA pools, might contribute to the process of PC diversification [24••]. In addition, a recent analysis of large lipidomics data suggests variable levels of interdependency between the acyl chain esterified at positions *sn1* and *sn2*. For a few combinations, the structure of the acyl chain esterified at position *sn1* determines the acyl chain at position *sn2* and *vice versa* [5•]. In the case of cardiolipin, the four acyl chains are generally similar, suggesting a highly coordinated mechanism of incorporation [28].

Formation and transport of saturated PC for lung surfactant formation

Because LPCAT1 is very abundant in the lung where a surfactant rich in saturated C16:0-C16:0-PC contributes to pulmonary protection, a deeper analysis of lung surfactant properties was carried out in a LPCAT1 knockout mouse [24••]. Lipid analysis combined with physiological tests show that LPCAT1 contributes to the enrichment of this fluid in saturated PC, which, in turn, reduces surface tension at the alveolar surface and prevents respiratory failure [24••] (Figure 2a). Thus, a direct link is made between an enzymatic activity responsible for the synthesis of a predominant PC species, a physical effect of the resulting lipid, and a physiological function.

Like many enzymes involved in lipid metabolism, LPCAT1 resides predominantly in the ER. The mechanism by which, saturated PC in alveolar cells is transported from the ER to specialized structures (lamellar bodies), which are then released to give the pulmonary surfactant, is largely unknown. Recent studies suggest that two cytosolic lipid transfer proteins, Sec14L3 [29] and StarD10 [30], could bear this function (Figure 2a). First, they are highly enriched in alveolar type II cells. Second the expression level of Sec14L3 parallels that of LPCAT1 during development. Third, StarD10 interacts with LPCAT1 and its knockdown reduces lipid transport to lamellar bodies. However, direct transport of saturated PC was not demonstrated. Notwithstanding, lipid transfer proteins are excellent candidates for sorting lipids according to their fatty acyl chain structure because the lipid transfer reaction involves the formation of a soluble protein lipid:complex in which the fatty acyl chains directly interact with the protein [31]. A recent example is the phosphatidylserine transfer protein Osh6 for which biochemical and structural information indicates some acyl chain preferences [32••,33••]. The kinked tunnel