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Review

Phospholipids and lipid droplets ☆

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ABSTRACT

Lipid droplets are ubiquitous cellular organelles that allow cells to store large amounts of neutral lipids for membrane synthesis and energy supply in times of starvation. Compared to other cellular organelles, lipid droplets are structurally unique as they are made of a hydrophobic core of neutral lipids and are separated to the cytosol only by a surrounding phospholipid monolayer. This phospholipid monolayer consists of over a hundred different phospholipid molecular species of which phosphatidylcholine is the most abundant lipid class. However, lipid droplets lack some indispensable activities of the phosphatidylcholine biogenic pathways suggesting that they partially depend on other organelles for phosphatidylcholine synthesis.
Here, we discuss very recent data on the composition, origin, transport and function of the phospholipid monolayer with a particular emphasis on the phosphatidylcholine metabolism on and for lipid droplets. In addition, we highlight two very important quantitative aspects: (i) The amount of phospholipid required for lipid droplet monolayer expansion is remarkably small and (ii) to maintain the invariably round shape of lipid droplets, a cell must have a highly sensitive but so far unknown mechanism that regulates the ratio of phospholipid to neutral lipid in lipid droplets. This article is part of a Special Issue entitled Phospholipids and Phospholipid Metabolism.

1. Introduction

Apart from forming membrane bilayers that separate cellular compartments, phospholipids can also form a membrane monolayer thereby separating a hydrophilic from a hydrophobic environment. The prime examples for that are the surfaces of extracellular lipoprotein particles and of cytoplasmic lipid droplets. Lipid droplets are ubiquitous cellular organelles that store neutral lipids, such as triglycerides and sterol esters, in their core. The surrounding phospholipid monolayer is composed of over a hundred of different phospholipid molecular species and several dozens of specific lipid droplet proteins. The variety of the different phospholipids in this monolayer already suggests that they are not a mere border protecting the neutral lipids from the hydrophilic environment of the cell but fulfill important tasks in regulating the structure and function of this cellular organelle. As recent reviews have already excellently described and summarized the biology of lipids droplets [1–6], we would here like to emphasize on recent developments and open questions regarding composition, origin, transport and function of the lipid droplet monolayer phospholipids.

2. Phospholipid composition on lipid droplets

The lipid droplet phospholipid monolayer differs in its composition from other cellular membranes such as the endoplasmic reticulum (ER), Golgi or plasma membrane [7]. In mammalian cells and yeast, phosphatidylcholine (PC) is the most prominent phospholipid in the lipid droplet membrane ranging up to 60% of the total phospholipid content [8–10]. PC is followed in its prevalence by phosphatidylethanolamine (PE, up to 24%), phosphatidylinositol (PI, up to 8%), PS and the lyso-forms of PC and PE. In insect cells, which have more PE and less PC, PE is more abundant than PC also in the lipid droplet monolayer [11]. Generally, other phospholipids seem to be present in minor amounts but some studies have reported the presence of major amounts of sphingomyelin (SM) in lipid droplets isolated from fibroblasts [12] or 3T3-L1 adipocytes [13]. Phosphatidic acid (PA) has not been found in considerable amount on lipid droplets, consistent with its function as a transient intermediate in lipid biosynthesis. In contrast, its downstream product diacylglycerol (DG) can accumulate on lipid droplets in significant amounts [10,13,14], but its distribution between the core and the surface of lipid droplets is unknown. The same holds true for un-esterified cholesterol, which can be found in substantial amounts in adipocyte lipid droplets [15,16].

3. Origin of phospholipid on/for lipid droplets

In a current, but yet unproven, model of lipid droplet biogenesis [17], neutral lipid accumulates in between the two leaflets of the ER

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membrane, followed by evagination and budding of a nascent small lipid droplet into the cytoplasm. Accordingly, the phospholipid monolayer would originate from the cytoplasmic leaflet of the ER membrane. Once formed, lipid droplets do not exchange membrane lipids with other organelles by canonical vesicular transport pathways. Therefore, for surface expansion and remodeling they depend on other pathways such as local synthesis, protein-mediated monomeric transport or transport over contact sites or monolayer continuities (see below).

The following considerations focus on PC, since it is the most prominent and best studied lipid droplet surface lipid. In general, there are two pathways for synthesis of PC. The first is the Kennedy pathway utilizing CDP-choline and diacylglycerol, the second is the PEMT pathway methylating PE to PC. Once formed, the fatty acid composition of PC can be modified by sequential deacylation and reacylation in the Lands cycle.

Recent studies have connected several of these enzymatic activities to lipid droplets. CTP:Phosphocholine cytidylyltransferase (CCT) catalyzes the formation of CDP-choline, which is the rate-limiting step in the de novo biosynthesis of PC by the Kennedy pathway. Its presence and activity on lipid droplets were recently demonstrated [11,18], indicating a regulatory function of lipid droplets on the rate of cellular PC synthesis. However, lipid droplets lack CDP-choline:diacylglycerol phosphocholine transferase (CPT) activity [19], which localizes to the ER, where it catalyzes the actual PC synthesis. As a consequence, CCT activity on lipid droplets cannot directly provide additional phospholipids for expanding the lipid droplet surface.

In some cell types including hepatocytes and adipocytes, PC can be alternatively synthesized by the PEMT pathway. Hoerl et al. showed that the sequential synthesis route of PC to PS to PE (catalyzed by PS-synthetase 1 and PS-decarboxylase) and PE to PC, catalyzed by PE-methyltransferase (PEMT) localizes to ER and mitochondria in close proximity to lipid droplets [20]. Addition of fatty acids induces PEMT activity in adipocytes, and PEMT knock-out mice are resistant to high-fat diet induced obesity [21]. This demonstrates the importance of alternative pathways of PC synthesis for lipid droplet metabolism, but it remains open whether the formed PC is directly used for lipid droplet expansion and how it would reach the lipid droplet surface.

Remodeling of the fatty acids of phospholipids by the Lands cycle consists of the sequential removal of the sn-2 fatty acid by phospholipase A2 (PLA_2) followed by re-acylation by lyso-phospholipid acyltransferases (LPLAT). Moessinger et al. recently demonstrated the presence of strong LPCAT activity on lipid droplets of various cell types, mediated by the enzymes LPCAT1 and 2 [19]. In combination with soluble PLA2 activity, this would allow changing the fatty acid composition of the lipid droplet–phospholipids. Consistent with a remodeling activity of LPCAT1/2 on lipid droplets, the lipid droplet PC is enriched in monounsaturated fatty acids, and differs from PC at the ER

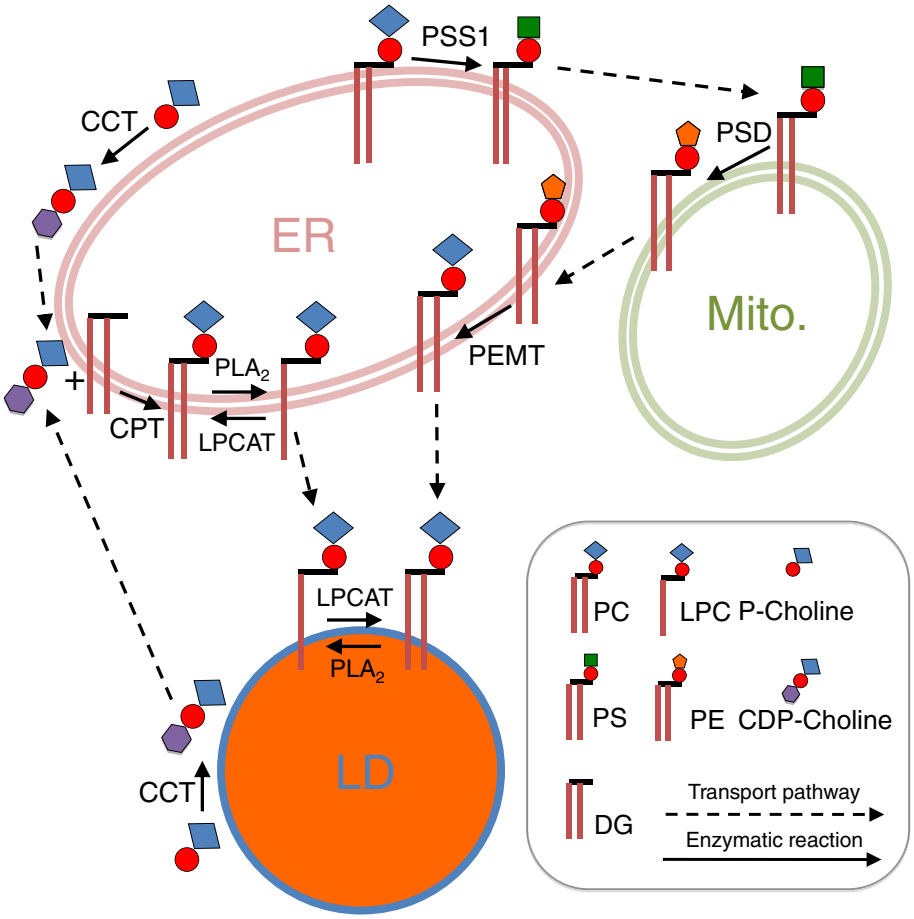

Fig. 1. Pathways of phosphatidylcholine biosynthesis. PC can be synthesized by the Kennedy pathway's sequential action of CCT (forming CDP-choline from phosphocholine) and CPT (forming PC from DG and CDP-choline). While CCT localizes both to LDs and the ER, CPT is found only in the ER. In addition to the Kennedy pathway, some cells can form PC also via the PEMT pathway. There, ER resident PSS1 produces PS (from PC), which is translocated to mitochondria (Mito.) and decarboxylated by PSD to PE. After transfer of the resulting PE back to the ER, PEMT finally methylates PE to PC. How PC is transported to LDs is so far unknown. Given the lack of a full PC biosynthesis pathway on LDs, a transport mechanism via lipid transport proteins, contact sites or membrane continuities likely exist to supply PC for LD expansion. Because of the higher solubility of LPC compared to PC, LPC could also represent the cargo transported from the ER to LDs. Enzymes of the Lands cycle, which can produce LPC and remodel the fatty acid composition at sn-2, namely LPCATs and PLA2, are found in the ER and on LDs.