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Lipid droplet–organelle interactions: emerging roles in lipid metabolism

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Cellular homeostasis depends on the precisely coordinated use of lipids as fuels for energy production, building blocks for membrane biogenesis or chemical signals for intra-cellular and inter-cellular communication. Lipid droplets (LDs) are universally conserved dynamic organelles that can store and mobilize fatty acids and other lipid species for their multiple cellular roles. Increasing evidence suggests that contact zones between LDs and other organelles play important roles in the trafficking of lipids and in the regulation of lipid metabolism. Here we review recent advances regarding the nature and functional relevance of interactions between LDs and other organelles — particularly the endoplasmic reticulum (ER), LDs, mitochondria and vacuoles — that highlight their importance for lipid metabolism.

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Introduction

Cells have the ability to store metabolic energy in the form of nonpolar or 'neutral' lipids in ubiquitous organelles, lipid droplets (LDs). Unlike other organelles, LDs exhibit a unique topology consisting of a hydrophobic core, predominantly of triacylglycerol (TAG) and steryl esters (SE), and coated by a phospholipid monolayer, which solubilizes the LD in the cytoplasm and a set of proteins involved in LD function. In response to metabolic signals, mobilized fatty acids (FAs) and other precursors derived from stored neutral lipids are used for a striking variety of functions, including energy production via β-oxidation, membrane biogenesis for cell growth, protein modification, signalling, and even secretion within lipoproteins. Growth and consumption of LDs can occur via multiple pathways but ultimately both processes depend on the regulated exchange of lipid content between LDs and other organelles within an aqueous cytoplasm. Because LDs are not directly connected to the vesicular transport pathways, the neutral lipids and phospholipids required for their biogenesis must be generated either *in situ* or arrive from other organelles through physical interactions. Here we discuss recent advances and highlight open questions on how contacts between LDs and other organelles are established and how they regulate lipid metabolism. LD biogenesis will not be discussed in detail as it has been comprehensively reviewed elsewhere [1–5].

LD–ER contact sites

While it is widely thought that LDs emerge from the ER membrane, the mechanisms responsible for the initial stages of their formation are not well understood. A popular model proposes that accumulation of neutral lipids between the leaflets of the ER bilayer forms an oil droplet or 'lens' that eventually buds towards the cytoplasm [6], although there is still little direct evidence to support it. Whether this budding process is spontaneous or assisted by ER proteins is also not clear [7]. Subsequent growth of LDs may take place by neutral lipid synthesis either on the LD surface or at the ER, or by a 'fusion' mechanism that transfers lipid during homotypic LD–LD interaction. Regardless of the pathway, neutral lipid addition to the LD core must be coupled with addition and remodelling of phospholipids, mostly phosphatidylcholine (PC), at the LD surface to enable the coordinated expansion of the organelle.

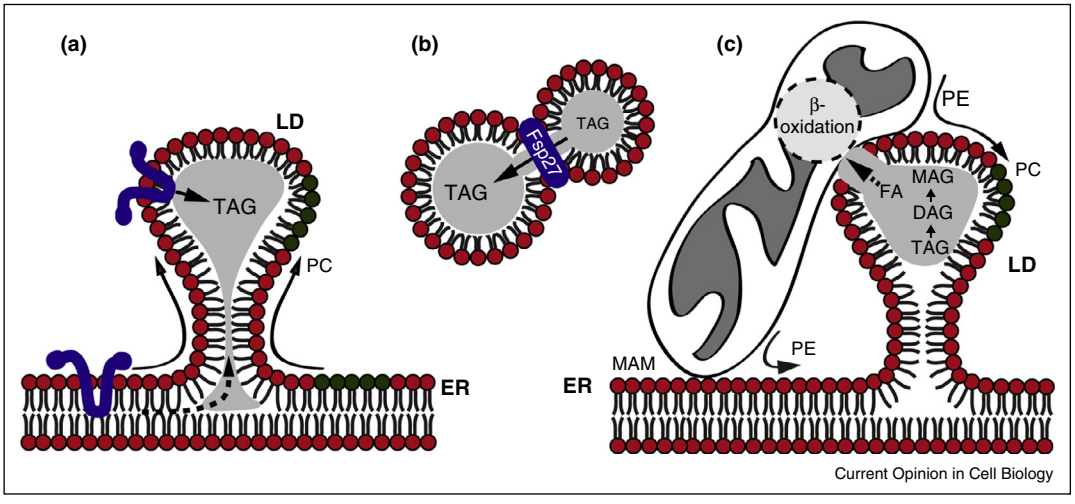
The close apposition of LDs with the ER is conserved from yeasts to mammals (Figure 2) but the exact nature of this association remains poorly defined. LDs between the two leaflets of the ER have been visualized in cells with defects in apolipoprotein B processing [8], which would be consistent with a physical continuity between the two organelles. A different arrangement was seen by freeze-fracture analysis where both leaflets of the ER bilayer were observed external to the LD and enclosed it tightly [9]. More recently, the existence of ER–LD conduits was supported by high-pressure freezing electron microscopy and tomography analyses depicting direct connections between the LD phospholipid monolayer and the adjacent

ER in mammalian cells 'loaded' with excess fatty acids [10•,11•]. Generating such a connection is likely to depend upon the generation of negative membrane curvature at the ER–LD interface; the role of specific lipids or proteins has yet to be established, although a role for diacylglycerol (DAG) has been proposed [12]. In yeast where LDs predominantly appear to remain in contact with the ER [13,14•,15], protein machinery may be required to stabilize the ER–LD association.

There is increasing evidence in recent years suggesting that ER–LD contacts provide a conduit for the transport of proteins with metabolic or signalling functions on LDs (Figure 1). Such compartmentalization may increase the efficiency of metabolic inter-conversions and limit the diffusion of bioactive lipids within the ER membrane. Early biochemical studies in yeast provided evidence that enzymes involved in neutral lipid synthesis show a dual LD–ER localization [16,17]. Indeed, some of the best-studied examples include TAG biosynthetic enzymes. TAG synthesis is initiated by two sequential FA acylation reactions on glycerol-3-phosphate, catalysed by GPAT and AGPAT enzymes respectively. The resulting phosphatidate (PA) is dephosphorylated by PA phosphatase (PAP) to DAG, which is then converted by DGATs to TAG. Notably, with the exception of PAP, these enzymes are ER membrane-bound but move to LDs during conditions of increased TAG synthesis. For example, in mammalian cells DGAT2 [18,19] and acyl-CoA synthetase 3 [11•] target LDs following the addition of FAs. In yeast, re-localization of the DGAT Dga1 enzyme in response to transcriptional induction of TAG synthesis, is energy-independent and temperature-independent, supporting a diffusion-based transport mechanism through an ER–LD membrane continuity [14•]. FA loading of Drosophila cells results in the targeting of all four TAG biosynthetic enzymes onto a subpopulation of LDs that expand, while a second class of LDs lacking the enzymes remains constant in size [10•]. Other enzymes that play key roles in LD homeostasis, like the lipases Tgl1 and Tgl3 in yeast [14•,20] or the mammalian lyso-PC acytransferases LPCAT 1 and 2 that remodel PC on LDs [21], also partition between ER and LDs.

Because these enzymes behave biochemically like integral membrane proteins, their transport from the ER poses the challenge of moving from a phospholipid bilayer with an aqueous lumen (ER) to a monolayer with a hydrophobic lumen (LD). It was proposed that the presence in the enzymes of long hydrophobic domains with a kink, inserted in a hairpin fashion that does not span the entire ER membrane, would allow such a transition [22] (Figure 1). Consistently, modifying the hydrophobic domains of LD proteins to disrupt their hairpin structure blocks their translocation from the ER [10•,23,24]. This mechanism may explain the remarkable conservation of LD targeting between species despite the lack of apparent linear LD-localization signals [25,26]. However, several

Figure 1



Topology and roles of key LD–organelle contact sites in lipid metabolism. **(a)** LD–ER interaction zones. Selective partitioning of lipid metabolic enzymes (in blue) from the ER to the LD phospholipid monolayer through ER-LD membrane 'bridges' controls LD homeostasis. These include enzymes of the *de novo* TAG biosynthetic pathway, phospholipid remodelling, TAG mobilization or other. TAG may be also channeled to LDs from the ER via these LD–ER contacts though poorly characterized mechanisms (dashed arrow). Phosphatidylcholine (PC, in green) from the adjacent ER can be added during LD growth via lipid transport proteins or lateral diffusion. **(b)** LD–LD contact sites are established by CIDE–proteins (e.g. Fsp27) and mediate directional neutral lipid exchange from the smaller to the larger LD. **(c)** Mitochondrial–LD contacts are thought to channel lipolytically-derived fatty acids (FAs) destined for β-oxidation but their molecular basis remains elusive. Such contacts may also provide mitochondrial-derived phosphatidylethanolamine (PE) for the synthesis of PC destined to coat LDs. MAM, mitochondrial associated membrane.