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Review

Lipid droplet functions beyond energy storage☆

Michael A. Welte[a,*], Alex P. Gould[b,*]

[a] Department of Biology, University of Rochester, Rochester, NY, United States
[b] The Francis Crick Institute, London, UK

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ABSTRACT

Lipid droplets are cytoplasmic organelles that store neutral lipids and are critically important for energy metabolism. Their function in energy storage is firmly established and increasingly well characterized. However, emerging evidence indicates that lipid droplets also play important and diverse roles in the cellular handling of lipids and proteins that may not be directly related to energy homeostasis. Lipid handling roles of droplets include the storage of hydrophobic vitamin and signaling precursors, and the management of endoplasmic reticulum and oxidative stress. Roles of lipid droplets in protein handling encompass functions in the maturation, storage, and turnover of cellular and viral polypeptides. Other potential roles of lipid droplets may be connected with their intracellular motility and, in some cases, their nuclear localization. This diversity highlights that lipid droplets are very adaptable organelles, performing different functions in different biological contexts. This article is part of a Special Issue entitled: Recent Advances in Lipid Droplet Biology edited by Rosalind Coleman and Matthijs Hesselink.

1. Introduction

Lipid droplets (LDs) are intracellular organelles specialized for the storage of energy in the form of neutral lipids such as triglycerides and sterol esters. They are ubiquitous organelles, present in animals, plants, fungi, and even bacteria [1,2]. LDs comprise a core of neutral lipids surrounded by a polar lipid monolayer containing many different proteins, some of which are involved in lipid metabolism [1–4]. Synthesis of neutral lipids in the endoplasmic reticulum (ER) membrane by enzymes such as diglyceride acyltransferase 1 (DGAT1) leads to the formation of nascent LDs, which emerge as organelles partially or completely distinct from the ER [5,6]. After formation, LDs can continue to grow by local synthesis of neutral lipids or – in certain specialized tissues like adipocytes – via fusion [5,7]. In times of need, the neutral lipids stored in LDs can be broken down by either of two pathways, lipolysis or lipophagy [8]. Lipolysis is mediated via lipid droplet-associated lipases such as adipose triglyceride lipase (ATGL) whereas lipophagy involves lysosomal acid lipase (LAL) acting upon LDs delivered to autolysosomes via autophagy. Fatty acids (FA) liberated from neutral lipid breakdown can then be used for energy production via mitochondrial or peroxisomal beta-oxidation [9,10]. LDs therefore respond to the cellular balance of lipogenesis and lipolysis and so play a key role in energy homeostasis. This homeostatic role is critical for normal cellular and organismal function and becomes impaired in many human pathologies including obesity, diabetes, cardiovascular disease and fatty liver disease [11].

The unique cell-biological properties of LDs and their important physiological roles have resulted in an explosion of research in recent years. This has led to a better understanding of the basic mechanisms by which LDs form, grow, and are turned over to regulate energy homeostasis. These aspects of LDs have been reviewed extensively (*e.g.*, [1–7,11–21]; see also the reviews in this issue by Bersuker and Olzmann, Schulze et al., and Wang et al.). Yet the importance of LDs is not restricted to energy storage. Emerging evidence suggests that LDs also function in the storage of a wide range of lipids with diverse functions as well as protecting against some forms of cellular stress. In addition, LDs have important roles in protein homeostasis, assisting the maturation, storage, and turn-over of many different proteins. Here we review these non-energy storage roles of LDs and identify important recent developments in this emerging field.

2. Lipid droplets and lipid handling

Lipidomics reveals that the core of an LD can contain over 100 different species of neutral lipids [22–26]. This repertoire is sure to expand over the next few years with the development of increasingly sophisticated lipidomics methods as well as imaging techniques based on Raman and mass spectrometry [27–34]. In many cell types,

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* Corresponding authors.
E-mail addresses: michael.welte@rochester.edu (M.A. Welte), alex.gould@crick.ac.uk (A.P. Gould).

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including adipocytes and hepatocytes, the majority of lipids in the droplet core correspond to triglycerides and sterol esters with a range of different FA side chains. These play important functions in energy storage and also as a major source of phospholipid precursors and cholesterol for cell membranes. Such precursors can be released from LDs for use in maintaining the homeostasis of the ER and other membranes, particularly during nutrient stress [35–38]. LDs are also part of the machinery that allows cells to adjust the balance of lipid flux that goes to membranes (for growth) or to storage (for starvation/stress survival). A key metabolic branchpoint here involves regulating how much phosphatidic acid (PA) in the ER membrane is used to synthesize membrane phospholipids versus LD triglycerides. In yeast, phosphatidate phosphatase (Pah1) converts PA into diglycerides, the precursors of triglycerides [39]. Nutrient depletion leads to relocalization of Pah1 from the cytoplasm to the nuclear envelope, which is contiguous with the ER, at a subdomain that contacts growing LDs. Lack of nutrients in yeast leads to cytoplasmic acidification and this is thought to activate Pah1, via the Nem1-Spo7 complex [39]. Hence, activation of the Pah1 pathway during starvation may be an important part of the cellular survival response that diverts fatty acyl chains from PA away from membrane biogenesis and into storage in LDs.

2.1. What's inside a lipid droplet?

LDs can store more unusual cargo than triglycerides and sterol esters. These lipophilic molecules play diverse functions not directly related to energy storage. Neutral ether lipids of the monoalk(en)yl diacylglycerol (MADAG or MDG) family account for ~20% of the droplet lipids isolated from mammalian cell lines grown in the presence of oleate [22]. MADAG is also present in droplets isolated from liver but not from white or brown fat, indicating that it is a cell-type specific component of the droplet core [22]. As with other ether lipids, the first steps of MADAG biosynthesis occur in peroxisomes and, correspondingly, it is absent in cells from Zellweger patients defective in peroxisomal biosynthesis [22]. It has therefore been proposed that MADAG precursors are transferred from peroxisomes to LDs via the direct contacts that have been observed between these two organelles ([40,41]; see also review in this issue by Schuldiner and Bohnert). MADAG in droplets may then function primarily as a precursor supply depot for the synthesis of ether phospholipids contributing to the phospholipid monolayer surrounding LDs and also to the bilayer of other cell membranes [22,41].

Numerous plants, insects and microbes synthesize substantial quantities of hydrocarbons such as alkanes, alkenes, and isoprenoids [42–45]. These neutral lipids are likely to partition into the droplet core, although this has only been shown thus far in a few cases [42,46]. For the hydrocarbon precursor of cholesterol, squalene, it has been shown in yeast that its sequestration in LDs is essential for preventing toxicity [47]. Natural rubber (*cis*-1,4-polyisoprene) is a commercially important hydrocarbon produced by laticifer cells of the rubber tree *Hevea brasiliensis*, but also made in varying amounts by thousands of other plant species. It is stored in specialized LDs called rubber particles, which lack structural proteins of the oleosin family common on other types of plant LDs [42]. Rubber is synthesized by the sequential condensation of isopentenyl diphosphate subunits [48]. The enzyme responsible, rubber transferase, likely corresponds to one or more *cis*-prenyltransferases localized to the ER and/or to the phospholipid monolayer of the rubber particle [42,48]. The polyisoprene latex cargo of rubber particle LDs plays important roles in the protection and defense of plants against wounding, insect herbivory, and environmental stresses [49].

Another emerging function for LDs is in the cellular detoxification of endogenous or exogenous lipophilic molecules. A fungus residing asymptomatically inside lichens, *Phaeosphaeria*, can kill competing fungal species by producing toxic perylenequinones (PQs) [50]. PQs are toxic because light irradiation stimulates them to generate lethal levels of reactive oxygen species (ROS). PQ resistance of the producer fungus and also that of the intended target species requires triglyceride and LD biosynthesis genes such as a diglyceride acyltransferase (DGAT). Storage of PQs in LDs is thought to provide a “safe haven” by somehow decreasing the ability of PQs to generate ROS. This and related detoxification functions for LDs may also have therapeutic implications. For example, some antifungal agents are more potent against yeast strains with defective LD biosynthesis [50]. Moreover, several drugs and prodrugs are known to accumulate in LDs [51,52]. The hydrophobic anticancer prodrug CHR2863 localizes to LDs before being converted by esterase(s) into its active hydrophilic form, a cytotoxic aminopeptidase inhibitor [52]. Interestingly, myelomonocytic cell sublines selected for resistance to CHR2863 display increased LD abundance [52]. This raises the possibility that sequestration in LDs could be a therapeutically important mode of drug resistance and that inhibitors of droplet biogenesis might therefore be useful adjuncts for improving drug efficacy.

Many man-made environmental toxicants partition selectively into triglycerides rather than phospholipids and so would be expected to be concentrated in LDs [53]. Confirmed LD-associated toxicants include polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and dioxins [54–57]. Hence, the ability of LDs to accumulate selectively several types of toxicants makes them a sensitive indicator of exposure to environmental pollutants. In the case of plants, it has even been proposed that detoxification of hydrophobic pollutants by LDs could be developed as a “biomimetic” strategy for environmental remediation [57].

2.2. Storage of vitamins and signaling precursors

For some fat-soluble vitamins and their metabolites, the LD core is known to provide a physiologically relevant storage site, but for others this is less clear. Vitamin E (tocopherol) is an antioxidant that accumulates in the LDs of plant chloroplasts and cyanobacteria [58,59]. It is also present in the LDs of human adipocytes [60], although the functions of tocopherol storage here are not yet clear. More is known about vitamin A (retinol), a precursor of the nuclear receptor ligand retinoic acid. Vitamin A is esterified with FAs and accumulates in the core of LDs as retinyl esters [61–64]. The LDs of hepatic stellate cells are a major storage site for 70–80% of vitamin A in the body. These hepatic droplet stores ensure that there is a constant supply of vitamin A during periods of dietary insufficiency. Smaller quantities of retinyl esters are also stored in the LDs of extrahepatic stellate cells in the intestine, lung, and kidney as well as in hepatocytes and adipocytes [61,62,64–66]. Retinol is released from retinyl esters by the action of retinyl-ester hydrolases [63,67]. This enzymatic reaction is broadly analogous to FA mobilization from TAG by adipocyte triglyceride lipase (ATGL). There appears to be no consensus yet on which enzymes are the most physiologically relevant hydrolases for retinyl esters but it may be that ATGL itself contributes to this function in hepatic stellate cells, with hormone sensitive lipase (HSL) performing it in adipocytes [63,68,69]. It is also not yet clear how retinol is transferred from its retinyl-ester storage site in the LDs of hepatic stellate cells to its major site of release, complexed with retinol-binding protein 4, in hepatocytes. What is clear, however, is that hepatic LDs are an important source of vitamin A and they are critical for its homeostatic regulation.

The LD core can accumulate the precursors of molecules important for intercellular communication, such as steroid hormones and FA signals [70,71]. In specialized endocrine cells of the gonads and adrenals, cholesteryl esters stored in LDs provide an important source of cholesterol for the mitochondrial biosynthesis of several different steroid hormones [72]. Proteomic analyses of LDs from several types of steroid-producing cells indicate that they copurify with some steroidogenic enzymes [71,73]. This has led to the idea that, in addition to cholesterol storage, LDs may also function as a site for steroidogenic enzymes and/or the transfer of steroid intermediates [71,73].