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Review

Lipid droplet mobilization: The different ways to loosen the purse strings

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ABSTRACT

Cytosolic lipid droplets are dynamic lipid-storage organelles that play a crucial role as reservoirs of metabolic energy and membrane precursors. These organelles are present in virtually all cell types, from unicellular to pluricellular organisms. Despite similar structural organization, lipid droplets are heterogeneous in morphology, distribution and composition. The protein repertoire associated to lipid droplet controls the organelle dynamics. Distinct structural lipid droplet proteins are associated to specific lipolytic pathways. The role of these structural lipid droplet-associated proteins in the control of lipid droplet degradation and lipid store mobilization is discussed. The control of the strictly-regulated lipolysis in lipid-storing tissues is compared between mammals and plants. Differences in the cellular regulation of lipolysis between lipid-storing tissues and other cell types are also discussed.

1. Introduction

Fatty acids (FAs) are essential metabolites either used for energy production through β-oxidation, for membrane lipid synthesis through esterifications, or for production of lipid mediators (oxylipins) through oxidations. FAs are also cytotoxic and their cellular concentration has to stay low. To neutralize their toxicity, cells esterify FAs into neutral lipids (triacylglycerols (TAGs) and sterol esters) and package them into organelles called lipid droplets (LDs). These organelles have a unique structure composed of a core of neutral lipids surrounded by a phospholipid monolayer and coated by specific proteins. They are central hub for lipid homeostasis, managing the availability of FAs and sterols to meet cell demand for energy or membrane lipids. When cells are exposed to excess FAs, neutral lipids are synthesized in the ER, driving LD expansion and emergence from the ER membrane [refer to recent reviews on LD biogenesis [1,2]]. When cells are carbon/energy deprived, FAs are mobilized from neutral lipids stored in LDs. FAs can be released by two distinct mechanisms: lipolysis and lipophagy. Lipolysis involves lipases that gradually hydrolyze TAGs on the surface of LDs. The regulation of lipase activities allows fine-tuned release of fatty acid. The alternative route, identified more recently in mammals [3–5], yeasts [6], microalgae [7] and plants [8], involves autophagosomal engulfment of LDs and fusion with lysosome/vacuole. Autophagy of LDs, called lipophagy, is mostly activated in stress conditions and results in snap and bulk LD degradation and FA release.

Cytosolic LDs are evolutionarily conserved organelles that can be found in virtually every organisms and cell types, from bacteria to mammals [9]. LD biology in mammals has received a lot of attention in the past decade as disturbance of fat storage homeostasis is involved in the pathogenesis of human metabolic diseases such as obesity, type II diabetes and atherosclerosis [10,11]. Our knowledge also progressed in oleaginous plant, yeast and microalgae models, albeit much more modestly, as increasing production of fossil oil substitutes from renewable resources is an important biotechnological goal. To this end, research efforts in non-animal organisms have mainly focused on increasing lipid accumulation, *i.e.* on LD biogenesis. However, some recent reports in *Arabidopsis thaliana* and *Chlamydomonas reinhardtii* have demonstrated that reducing lipid degradation may also be an effective way to enhance oil content [12–14].

More than two decades ago, Londos's laboratory discovered the role of perilipin1, the major LD protein in adipocytes, in the

Abbreviations: ABHD5, α/β-hydrolase domain containing 5; ATGL, adipose triglyceride lipase; FA, fatty acid; G0S2, G_0/G_1 switch gene 2; HSL, hormone-sensitive lipase; LD, lipid droplet; MAG, monoacylglycerol; MLDP, major lipid droplet protein; NOLD, non-oleosin-based LD; OLE, oleosin; PKA, protein kinase A; PLIN, perilipin; REF, rubber elongation factor; SDP1, sugar-dependent1; TAG, triacylglycerol.

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regulation of hormone-stimulated lipolysis in adipose tissue [15]. Since this initial breakthrough, several novel LD proteins have been identified and characterized as gatekeepers controlling LD degradation. These proteins are associated to specific lipolytic pathways depending on the organism and, in pluricellular organisms, on the cell type, and depending on the function and fate of TAGs present in LDs. In animal and plant lipid-storing tissues (such as white adipose tissue in mammals and seed cotyledons in oleaginous seeds), lipolysis is strictly regulated. Failure to precisely control this process would expose the organism to carbon and energy deprivation or, conversely, to cytotoxic FA overload. In contrast to cells specialized in lipid storage, lipolysis within other cell types seems to be coordinated in a cell-autonomous manner, similarly to lipolysis regulation in unicellular organisms such as yeast and microalgae. In mammals, another lipolytic pathway occurs in cells specialized in the assembly and secretion of TAG-rich lipoproteins, e.g. in enterocytes and hepatocytes. In these cells, neutral lipids stored in cytosolic LDs can be repackaged into lipoproteins in the ER lumen for subsequent release into the blood circulation and delivery to peripheral tissues.

This review aims at comparing LD degradation pathways in several organisms – predominantly mammals and plants, – highlighting the role of some structural LD-associated proteins on the cellular control of lipolysis (transcriptional regulation of lipolysis is beyond the scope of this review). The control of lipophagy selectivity is currently unknown, thus LD degradation by autophagy is not discussed in this review.

2. Overview of structural LD-associated proteins

Since the first extensive report in yeast [16], LD proteomes have been described in many organisms and cell types, leading to the identification of several hundred proteins involved in various cellular functions such as lipid metabolism, membrane trafficking, signaling and protein degradation [17,18]. Despite the consistent representation of these functional groups of proteins in LDs from many organisms, the protein composition of LD depends on the species and cell types and varies with metabolic state or developmental stage. However, a distinct set of proteins predominates in some LD proteomes. These proteins are structural proteins of the perilipin family in mammals and oleosin family in plants. Besides these well-known LD markers, recent reports have identified novel structural proteins associated to LDs in plants, yeast and microalgae.

2.1. Mammalian perilipins

The major proteins associated at the surface of mammalian cytosolic LDs belong to a protein family called perilipin according to the nomenclature defined in 2010 [19]. Perilipin family is evolutionary ancient, present in vertebrates and in invertebrate species such as *Drosophila* and *Dictyostelium* but not in *Caenorhabditis* [20–22]. The five mammalian members of this family, perilipin1-5 (PLIN1-5), are encoded by single-copy genes; however *PLIN1* has several splice variants [20]. These proteins share sequence similarity and the ability to bind LDs. Highest sequence similarity locates near their N-termini, in the PAT domain and the 11-mer repeat [23,24]. The absence of hydrophobic domain in PLIN2-5 and experimental data showing that PLIN1 is translated on free ribosomes suggest that they all are, at least transiently, cytosolic [25]. Little is known about how PLINs are post-translationally targeted to LDs. Structural domains mediating LD attachment are not clearly defined. To date, the only structural information available for members of the perilipin family is the crystal structure of the carboxyl terminal region of PLIN3. This domain resembles the receptor-binding domain of apolipoprotein E, suggesting that PLIN3 C-terminus is binding hydrophobic proteins rather than phospholipid membranes [26]. The N-terminal 11-mer helical repeat, conserved in the five mammalian PLINs, is most probably involved in PLIN binding to lipid membranes. This 11-mer repeat substructure is indeed present in many other lipid-associated proteins, such as synucleins and apolipoproteins from whose it has been found to directly bind lipids [27]. Computational analysis of *Drosophila* PLIN1 hydrophobicity predicted four helices with potential lipid binding capacity, in the central region of the protein [28]. The interaction of this four helices-domain with the LD surface was recently confirmed by NMR analysis of purified PLIN1 reconstituted in LD-like particles [29]. Overall, these observations suggest that there is not one but several mechanisms for PLIN targeting to LDs and that several PLIN domains may independently contribute to the attachment.

2.2. Plant oleosins

In many angiosperm and gymnosperm plants, long-term lipid stores packed in cytosolic LDs (also called oil bodies or oleosomes) predominantly accumulate in seeds to provide carbon and energy for seedling growth after germination [30,31]. Cytosolic LDs can be found in other organs and tissues, including oleaginous fruit tissues, germ line cells and leaves [32,33]. Of all the LDs, those in seeds were the most extensively studied.

In seeds, oleosins are the predominant LD proteins, representing 75–80% of the LD protein complement [34,35]. Oleosins are small proteins exclusively associated to LDs and present in diverse plant species, from higher to primitive plants such as liverworts and mosses, as well as in some green algae species [36]. Contrary to perilipins that post-translationally attach to ER-nascent or free LDs, oleosins are co-translationally translocated into subdomains of the ER that form LDs [37]. Exclusive association of oleosins to LDs also occurs in heterologous expression systems such as yeast [38,39]. Oleosins are integral LD proteins characterized by a highly conserved central hydrophobic domain of ~70 amino acid residues – the longest hydrophobic domain described to date – flanked by hydrophilic domains of variable size and amino acid composition [40]. At the middle of the hydrophobic domain, three conserved proline residues known as the proline knot motif are essential for targeting the oleosins to LDs [41]. This hydrophobic domain forms a hairpin deeply anchored in the LD core and mainly composed of beta sheets [42,43]. In contrast, N and C-terminal hydrophilic regions are supposed to associate with phospholipids at the LD surface. Most probably because of this amphipathic tri block structure, oleosins are able to stabilize artificial emulsions [44] and to decrease the interfacial tension at oil/water interface [45]. It is interesting to note that, although mammals lack any homologs to oleosins, hydrophobic hairpins are present in some LD-associated proteins such as the mammalian caveolin and certain viral proteins.

The plant model *A. thaliana* has 16 genes encoding oleosins: five expressed in seed (called OLE1 to OLE5 according to [46]), three expressed in both seed and pollen, and eight expressed in the floral tapetum cells [47]. Tapetum-specific oleosins associate to specific LDs called tapetosomes and enable assembly and transfer of pollen coat materials to the pollen [48]. The function of the oleosins expressed both in seed and pollen is yet unknown. The role of the major seed-specific oleosins OLE1 and OLE2 has been investigated *in planta* and is discussed below.

2.3. Other plant LD proteins

Oleosin proteins are not necessarily accumulated in oil-storing tissues of plants. For example, oleosins are lacking from lipid-rich

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