SnapShot: Lipid Droplets

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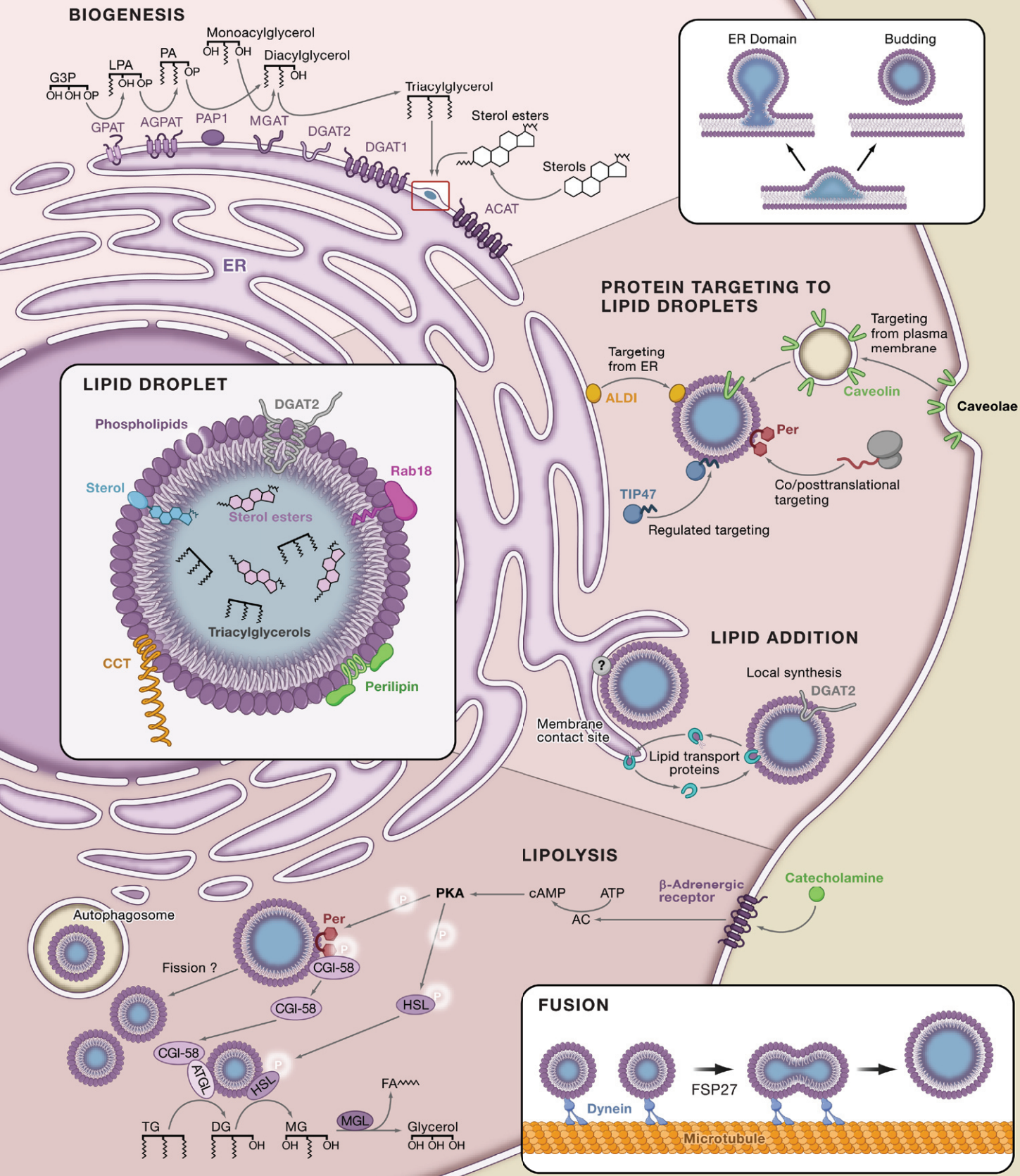

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What Are Lipid Droplets?

Lipid droplets (LDs) are universal cellular organelles that specialize in the storage of neutral lipids, such as sterol esters and triacylglycerols (see Essay by Farese and Walther, this issue). As such, they provide the main cellular reservoir for lipids of energy storage and membrane synthesis, and they protect cells from the lipotoxic effects of unesterified lipids. LDs also figure prominently in several diseases, including obesity, type 2 diabetes, liver steatosis, and atherosclerosis, which are characterized by the extensive accumulation of LDs in different cell types and tissues. Additionally, oils produced through the engineering of plant seeds and microorganisms (e.g., for production of biofuels) accumulate in LDs. LDs may also provide a cellular platform for specific proteins and processes. Intriguingly, several important intracellular pathogens, such as the hepatitis C virus and *Chlamydia trachomatis*, interact with LDs during replication.

The diameter of LDs varies tremendously (from 50 nm to 200 μm) depending on the cell type. However, their structure appears to be fairly consistent, comprising a neutral lipid core surrounded by a phospholipid monolayer that harbors small amounts of free cholesterol (see center inset). Multiple proteins apparently interact with the LD surface through different structural features. These include lipid anchors (e.g., Rab18), amphipathic α helices (e.g., those of perilipin and other PAT proteins), and long hydrophobic helices that integrate into the phospholipid monolayer (e.g., those of DGAT2 and caveolin). PAT proteins associate with LDs co- or posttranslationally without a requirement for other factors. In contrast, the targeting of caveolin from the plasma membrane to LDs is dependent on vesicle budding. There may also be a mechanism for transporting proteins from the endoplasmic reticulum (ER) to LDs.

How Are Lipid Droplets Formed?

The mechanism of LD formation is uncertain. The prevailing model posits that LDs form at the ER, where the enzymes that catalyze neutral lipid synthesis are located. The final step of triacylglycerol synthesis, the transfer of a fatty acid from fatty acyl CoA to diacylglycerol (DG), is catalyzed by diacylglycerol acyltransferases (DGATs). Diacylglycerol, the precursor of triacylglycerol, is synthesized either by PAP1 from phosphatidic acid (PA) or by monoacylglycerol acyltransferases (MGATs) from monoacylglycerol. Similarly, sterol esters are synthesized by acyl CoA:cholesterol acyltransferases (ACATs), which transfer fatty acyl chains to free cholesterol. Newly synthesized triacylglycerols and sterol esters are thought to accumulate between the two leaflets of the ER membrane. Eventually, the growing oil lens buds from the ER membrane, forming a detached cytosolic LD (budding model), or stays in contact with the ER membrane and forms a specialized LD and ER domain (ER domain model) (top inset).

How Do Lipid Droplets Grow?

Under certain conditions, LDs may grow to enormous sizes. At least three mechanisms could contribute to LD growth: localized synthesis of lipids, transport of lipids to LDs, and coalescence of LDs. Localized synthesis of lipids is likely to occur (e.g., DGAT2 localizes to LDs). The transport of lipids to LDs, in contrast, has not been reported, although membrane contact sites with the ER and mitochondria might be involved. In adipocytes, FSP27 regulates the fusion and size of LDs (bottom inset).

How Are Lipids Mobilized from Lipid Droplets?

Mobilization of neutral lipids in the LD core requires their access to surface lipases that hydrolyze them and release their components (lipolysis). A prominent example is the mobilization of energy reserves (triacylglycerols) in adipocytes, which is triggered by catecholamine hormones binding to G protein-coupled receptors. This results in activation of protein kinase A (PKA), which in turn phosphorylates several proteins involved in lipolysis. Phosphorylation of LD-associated perilipin results in the release of CGI-58, which then binds and activates adipose triacylglycerol lipase (ATGL), which removes the first acyl chain from triacylglycerol. Subsequently, PKA-activated hormone-sensitive lipase (HSL) removes a second acyl chain. Finally, monoacylglycerol lipase (MGL) hydrolyzes the remaining acyl chain, ultimately liberating glycerol and free fatty acids. The hydrolysis of sterol esters involves analogous processes that yield sterols and fatty acids. The transport of ATGL to LD surfaces appears to require ARF1/COPI machinery. Recent studies suggest that LDs may also be degraded through autophagy.

Abbreviations

AC, adenylate cyclase; ACAT, Acyl CoA:cholesterol acyltransferase; AGPAT, *sn*-1-acylglycerol-3-phosphate acyltransferase; ALDI, associated with lipid droplet protein 1; ATGL, adipose tissue triglyceride lipase; ATP, adenosine triphosphate; CGI-58, comparative genome identification-58; cAMP, cyclic adenosine monophosphate; DG, diacylglycerol; DGAT, acyl CoA:diacylglycerol acyltransferase; ER, endoplasmic reticulum; FA, fatty acid; FSP27, fat-specific protein 27; G3P, glycerol 3-phosphate; GPAT, glycerol-3-phosphate acyltransferase; HSL, hormone-sensitive lipase; LPA, lysophosphatidic acid; MGAT, acyl CoA:monoacylglycerol acyltransferase; MG, monoacylglycerol; MGL, monacylglycerol lipase; PA, phosphatidic acid; PAP1, phosphatidic acid phosphohydrolase; PAT, protein family including perilipin, adipophilin, S3-12, and TIP47; PKA, protein kinase A; TIP47, tail-interacting protein of 47 kDa.

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