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Biogenesis and fate of lipid droplets

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Editorial

Special issue “Biogenesis and Fate of Lipid Droplets”

Intracellular lipid droplets (LDs) are receiving increasing interest from the scientific community, notably because of their link with metabolic diseases (obesity, diabetes) and the production of lipid-derived biofuels in microorganisms. Understanding the biogenesis and fate of LDs upon energy mobilization is essential to monitor fat storage in adipose tissue, but also to improve lipid productivity in microalgae under various conditions of growth [1]. Intracellular LDs are today considered as individual organelles since they host specific metabolic functions such as the biosynthesis of triacylglycerols (TAGs) and phospholipids [2]. In addition to the enzymes involved in these pathways, several proteins have been identified as associated with LDs and their number has been increasing with the progress of proteomics. Some of these proteins presenting hydrophobic patches and a high amphiphilicity are involved in the structure of LDs and together with polar lipids they form the membrane surrounding the neutral lipid core. Some others are involved in the budding of LDs from lipid bilayers and the interactions of LDs with membranes and other organelles. These interactions are important for the transfer of fatty acids and lipid remodelling and homeostasis. The combination of lipidomics and proteomics has led to a better description of LD composition, while microscopy has allowed the visualisation of the specific location of proteins at the surface of LDs. Nevertheless, a better knowledge of the lipid-protein interactions that lead to the biogenesis and fate of LDs is still required. In this context, cellular biologists now adopt principles and methods from biophysics and physical chemistry of lipid emulsions and colloids [3]. Emulsions made of TAGs, polar lipids and proteins can serve as models for intracellular LDs. The biodiversity of LDs in animals, plants and microorganisms and their various functions in lipid storage and transport also allows the comparison of data and knowledge from various fields that will help build a global understanding of structure-function relationships.

The original articles and reviews of this special issue are a collection of topics presented at the 14th GERLI Lipidomics meeting, which was held at St Maximin-la-Sainte Baume, France, from September 30th to October 3rd, 2018, with the aim of gathering researchers from various areas with a common interest in LDs, their physical chemistry and metabolism, their association with diseases and various applications in biotechnology, pharmacology and nutrition.

The two first mini-reviews are related to lipid metabolism in microalgae. Lupette et al. cover the biosynthesis of fatty acids, acyl-glycero-lipids and sterols in diatoms and show how a metabolic intermediate common to these pathways, like acetyl-CoA, can play an essential role in directing the carbon flux from acyl-lipid to sterol biosynthesis and be determinant for the balance between TAGs and sterols. Prioretti et al. investigate how the target of rapamycin (TOR) signalling pathway could be modulated to enhance TAG production in microalgae. The use of TOR inhibitors increases TAG productivity in the marine diatom *Phaeodactylum tricornutum*, without stopping growth, while TAG accumulation in microalgae is usually observed under stress conditions with a low growth rate.

Yuan et al. report on the characterization of three diacylglycerol acyltransferases (DGATs) from oil palm (*Elaeis guineensis*), the main source of vegetable oil on Earth. DGATs are key enzymes for the biosynthesis of TAGs and the formation of LDs. Using the heterologous expression of these DGATs in the yeast *Saccharomyces cerevisiae*, they show that two of them are true DGATs, that could restore TAG synthesis in a yeast TAG-deficient mutant, while the third one is a wax ester synthase.

In plants, LDs from seeds have been extensively studied since they store neutral lipids as the source of energy for subsequent germination. However, LDs also accumulate in leaves during senescence and abiotic stress, but data about leaf LD biogenesis are very scarce. Coulon et al. address the role of a LD-associated protein (LDIP) in leaf LD biogenesis in *Arabidopsis thaliana*. This protein, also present in the endoplasmic reticulum, is located at specific sites on the LD surface and favors formation of new LDs.

Fat-Specific Protein 27 (FSP27) is involved in LD accumulation and fusion in the mouse, in which it is predominantly expressed in white and brown adipose tissues. No orthologs have been identified in plants. Price et al. studied its expression in stably-transformed *Arabidopsis thaliana* leaves and seeds, as well as in *Nicotiana tabacum* cell cultures. FSP27 localizes to LDs, accumulates at LD-LD contact sites, and augments the number and size of LDs. Thus, the expression of a mouse LD protein in plants could be a valuable strategy to increase oil content in oilseed crops.

The article by Torres Romero et al. highlights the interplay between cell division cycle in the microalga *Chlamydomonas reinhardtii* and the storage of starch and oil. A gene encoding a homolog of the Arabidopsis Cell Division Cycle 5 (CDC5) was identified in *Chlamydomonas* (CrCDC5) and the mutants deficient in CrCDC5 accumulate higher amounts of starch and oil compared to wild-type.

While much attention is paid to TAG biosynthesis to improve oil productivity in microalgae and plants, the study of TAG mobilization has lacked behind, though the control of lipolysis could be an alternative strategy to improve TAG accumulation. So far, the most advanced studies on the lipolysis of intracellular LDs are related to lipolysis in adipose tissue, where several lipases acting in synergy are well characterized and can serve as models for intracellular lipases in other organisms. Here, Kulminkaya and Oberer review the protein-protein interactions that regulate the activity of Adipose Triglyceride Lipase (ATGL). They highlight the role of various proteins that can bind at the surface of LDs and either activate (CGI-58), inhibit (G0S2, HILPDA), or regulate (fatty acid binding proteins and perilipins) lipolysis by ATGL. Still in connection with LD lipolysis, Jarc and Petan discuss the role of LDs in signalling pathways in immune cells and adipose tissue. Indeed, the lipolysis of LDs provides a highly regulated source of fatty acids as precursors of inflammatory lipid mediators.

Marze et al. review the use of microfluidic devices for generating LDs and manipulating them, including the microscopic observation of their lipolysis under various conditions. So far these approaches have been mainly developed to monitor the formation of droplets and multiple emulsions, as well as to study lipolysis of dietary emulsions by digestive lipases [4, 5]. LD degradation can be monitored in real time from changes in the size and shape of individual droplets. Other methods for studying the mode of action of lipolytic enzymes at interfaces are presented by Bourlieu et al., including monomolecular films characterized by surface tension measurements and ellipsometry, Langmuir-blodgett transfer and atomic force microscopy. The combination of these approaches allows for instance the study of the adsorption of gastric lipase onto films of polar lipids originating from human and bovine milk fat globules. It is shown how the polar lipid composition and the organization of these lipids at interfaces can modulate the adsorption of the lipase and its subsequent activity. Lipases from the digestive tract are now well characterized at the molecular level and easily available as purified enzymes, which is not the case for intracellular lipases acting on LDs. Therefore, these lipases can be used as model enzymes for studying lipolysis [6]. However, in vitro lipid digestion is often carried out with porcine pancreatic extracts (PPE), a commercially available mixture of enzymes that is used as a substitute for pancreatic juice. Salhi et al. have compared the lipolytic activities of PPE with those human pancreatic juice and they found some significant differences in phospholipase, galactolipase and cholesterol esterase activities.

Man-made dietary emulsions are often prepared using an oil phase and vegetable lecithins as emulsifiers. Robert et al. review here the impact of vegetable lecithins on lipoprotein metabolism, hepatic lipogenesis, blood cholesterol levels and their beneficial effects on metabolic disorders. Le Barz et al. depict the potential effects on lipid metabolism and cardiometabolic diseases of other polar lipids, the sphingolipids, found at various levels in lipoproteins but also in LDs. The last mini-review by Guillocheau et al. is dedicated to the nutritional impact and metabolism of trans-palmitoleic acid, a trans fatty acid naturally found in cow milk and meat.

To conclude, as exemplified from the collection of papers in this Special Issue, LDs are studied not only at a fundamental biology level (biogenesis and LD-associated metabolism), but also in several major application areas including food, medicine as well as biofuel and biomaterials. These recent studies have collectively pointed out the important physiological as well as metabolic role that LDs play in lipid synthesis, storage and homeostasis, essential for cell metabolism and fitness. Due to the complex physical properties associated with LDs, the next major advance in our understanding of LD biogenesis and biology should come from an integrated study of LDs using a combination of genetics, cell biology, biochemistry as well as biophysical techniques.

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