Published in final edited form as:
*Trends Endocrinol Metab*. 2011 June ; 22(6): 195–196. doi:10.1016/j.tem.2011.04.002.

# Expanding roles for lipid droplets

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## Hidden in plain sight – brief recent history of LDs as organelles

Previously assumed to be merely passive stores of lipid, lipid droplets have gained recognition as dynamic subcellular organelles with their own coterie of enzymes and structural proteins and a regulated metabolism that differs in different cell types. In addition to a functional life in regulating the storage and release of neutral lipids, lipid droplets are involved in functions as diverse and unexpected as autophagy and viral replication.

Although Hirsch and Rosen demonstrated that protein kinase A-mediated activation of lipolysis caused hormone-sensitive lipase to move from the cytosol to a particulate fraction [1], the identification of perilipin-1 in 1991 [2] was the first indication that specific proteins were constitutively associated with lipid droplets. After incubating adipocytes with $^{32}P$, Greenberg, Egan, and Londos found the heavily phosphorylated perilipin 1 in the fat cake [3]. Subsequent studies demonstrated that perilipin acts as a gatekeeper in controlling the storage and release of triacylglycerol (TAG) and facilitates PKA stimulated lipolysis [4–7]. Four additional proteins with sequence similarities to PLIN1 were subsequently discovered; these are termed the PAT protein and constitute a PLIN family associated with lipid droplets that is evolutionarily conserved across species, including drosophila, worms, and dictyostelium [8]. Proteomics studies have now identified dozens of additional lipid droplet-associated proteins, some of which are full-time residents on droplets and others of which, like hormone-sensitive lipase [9] are associated with droplets only under specific physiological conditions.

Lipid droplets are comprised of neutral lipids (TAG, diacylglycerol, cholesterol esters, and retinol esters) that are surrounded by a phospholipid monolayer and decorated with a diverse group of proteins and enzymes that contribute to the formation of the droplet, the synthesis and hydrolysis of its lipids, and the movement of these lipids to specific intracellular and secretory pathways.

The TAG stored in lipid droplets in adipocytes serves a vital role as the body's major stored energy supply, where-as TAG stored in other cells like liver, muscle, and heart, serves as



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both a local energy supply and as a source of materials for membrane biogenesis and repair. Hydrolysis of the TAG stored in lipid droplets releases potential fatty acid ligands for transcription factors, and cells with reduced amounts of ATGL (adipocyte triacylglycerol lipase), a TAG hydrolase associated with droplets, have defective regulation of hepatocyte PPARα [10]. Hydrolytic products of TAG, cholesteryl esters or retinyl esters also have the potential to act as mediators of signaling and inflammation, as substrates for steroid hormone biosynthesis in cells of the adrenal cortex, testes, and ovaries, and as substrates for surfactant synthesis in type II alveolar pneumocytes. Stored TAG in hepatocytes forms a pool of substrate for VLDL biogenesis as well as for β-oxidation, and droplets in mammary epithelial cells contribute to the nutritional content of breast milk.

The presence of TAG stored in lipid droplets in non-adipocytes is highly correlated with the metabolic syndrome and insulin resistance, although important exceptions have been documented, like the “athlete’s paradox,” in which highly trained athletes with elevated TAG in skeletal muscle remain insulin sensitive [11]. The term “lipotoxicity” is frequently employed, but the relationship between insulin resistance and excess TAG stores in hepatocytes, cardiomyocytes, and skeletal myocytes remains obscure, as do the purported detrimental effects of lipotoxicity on pancreatic β-cells. Hence, there is enormous interest in understanding how stored lipids contribute to mechanisms of insulin resistance and diabetes. Further, the excessive storage of cholesterol esters in foam cells is a major problem in the development of arterial plaques and atherosclerosis. The recent rapid growth of this field reflects a critical need to gain a greater understanding of the mechanisms that contribute to normal physiological processes involved in lipid droplet biology, as well as imbalances that exacerbate disease states.

In this issue of TEM we have selected several topics, first reported in a recent FASEB Summer Conference on Lipid Droplets: Metabolic Consequences of the Storage of Neutral Lipids. These topics discuss areas of lipid droplet research that have not, to our knowledge, been the focus of other review articles. The articles in this review can be grouped into into three major topic areas: 1) **Droplets and droplet proteins** (Sztalryd, Yang, McManaman) 2) **Triacylglycerol metabolism** (Lehner, Finck, Czaja), and 3) **Lipid Droplets and Disease** (Ott).

While interest in lipid droplets is growing rapidly, many unanswered questions remain. The biophysics of droplet formation and dissolution, and the specific steps involved in their formation remain poorly understood. We anticipate that important insights will be gained from proteomic studies, an improved understanding of protein trafficking between lipid droplets and other organelles, and the dissection of the relevant components and organelles that contribute to droplet assembly and regulation.

## Acknowledgments

This work was supported by grants from the American Diabetes Association, NIH RO1-DK-082574, and the U.S. Department of Agriculture, Agricultural Research Service, under agreement No. 58-1950-7-70 to ASG. This work was also supported by grants from the NIH RO1-DK59935 and RO1 DK56598 to RAC.

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