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Review Article

Heart lipid droplets and lipid droplet-binding proteins: Biochemistry, physiology, and pathology

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1. Introduction

The heart uses fatty acids (FAs) as a preferable energy source because the large amount of energy released from FAs when oxidized in mitochondria meets the requirements for continuous myocardial contraction. Excess mitochondrial oxidation, however, would generate an increasing amount of toxic byproducts such as reactive oxygen species (ROS). Moreover, free FAs and their derivatives may cause lipotoxicity [1], by disturbing the cellular signaling network. The heart mostly obtains free FAs from plasma; FAs are either

Abbreviations: fatty acid, FA; reactive oxygen species, ROS; triacylglycerol, TAG; lipid droplet, LD; perilipin, Plin; adipose triglyceride lipase, ATGL; hormone sensitive lipase, HSL; comparative gene identification, CGI; diacylglycerol, DAG; knockout, KO; protein kinase A, PKA; neutral lipid-storage disease, NLSD; peroxisome proliferator-activated receptor, PPAR; fluorescence resonance energy transfer, FRET; cardiac muscle-specific, CM; transgenic, Tg; G0/G1 switch gene 2, G0S2; PPARγ coactivator, PGC; fatty acid binding protein, FABP; protein kinase C, PKC

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transported by albumin or produced through the action of lipoprotein lipase, which hydrolyzes triacylglycerol (TAG) contained in lipoproteins. To decrease lipotoxicity, excess free FAs entering cardiomyocytes must be converted to inert TAG and temporarily stored in lipid droplets (LDs). Due to the highly active FA consumption, the lipid turnover in the heart is particularly rapid. Thus, LDs are scarce in this organ under normal conditions. In contrast, when FA inflow is elevated upon fasting or under pathological conditions such as diabetes, numerous enlarged LDs appear in the heart, resulting from the increase in TAG. In pathological cases, heart steatosis is often associated with cardiomyopathy.

Here we review the significance of heart LDs and LD-binding proteins under both normal physiological and pathological conditions. Possible mechanisms behind the actions of these proteins are also discussed.

2. LDs and perilipin proteins

LDs are ubiquitous organelles, found in organisms from yeasts to humans, and similar structures exist even in bacteria. LDs are composed of a phospholipid monolayer that surrounds a central core mainly containing TAG and cholesteryl ester [2]. Many proteins—both specific to LDs and shared with other organelles—decorate the surface. LDs are dynamic organelles with diverse properties and functions across cell types; they contribute not only to lipid storage but also to important cellular processes such as active lipid metabolism, intracellular membrane traffic, and protein maturation and degradation [2]. In adipocytes, for example, a huge unilocular LD occupies most of the cytoplasmic space. It accumulates a large amount of TAG for long-term storage, to be used in various tissues when energy demand arises. In contrast, LDs in most other organs, such as the heart, are usually much smaller because they temporarily store only a limited amount of lipids for use by the single organ.

The diversity of LDs is likely determined by the associated proteins. About two dozen LD proteins have been confirmed in LD proteomes derived from various biological samples [3]. The perilipin (Plin) family is a group of major LD-binding proteins [4]. Plins 1–5 are named according to their order of publication by a unified nomenclature [5]. Plin1 (originally called perilipin) is abundantly expressed in white and brown adipose tissues, and at lower levels, in steroidogenic cells. Plin2 (also called ADRP, ADFP, or adipophilin) and Plin3 (also called Tip47) are expressed ubiquitously, the former being relatively more abundant in the liver. Plin4 (also called S3-12) is almost exclusively confined to white adipose tissue. The expression of Plin5 (also called MLDP, OXPAT, or LSDP5) is limited to oxidative tissues, including the heart, skeletal muscle, brown adipose tissue, and liver. This tissue distribution strongly suggests the importance of Plin5 in the regulation of heart LD functions. Hence, this minireview will primarily focus on the function and mechanism of Plin5 action.

Besides Plin4, the other 4 members share a highly conserved N-terminal domain called the PAT (perilipin, ADRP, and Tip47) domain [4]. All Plin proteins also have a conserved tandem repeat of 11-mer units, and they share considerable similarities in other regions. Plin proteins generally seem to protect LDs from the attack by lipases [6], although the efficiencies are variable. The established function of Plin1 is described in brief below. The function of Plin5 has been extensively studied recently and will be described in a later section.

3. Major players in tissue lipolysis

Lipase-mediated hydrolysis initiates the use of LD-stored TAG. In the heart, 2 lipases, adipose triglyceride lipase (ATGL; also known as desnutrin, Ca^{2+}-independent phospholipase A_2 (iPLA$_2$) ζ, or PNPLA2) and hormone-sensitive lipase (HSL) are particularly well studied, together with a co-lipase called comparative gene identification (CGI)-58 (also known as α,β-hydrolase domain-containing (ABHD) protein 5).

ATGL was originally described in 2004 as a novel major lipase in adipose tissue [7–9] and as a member of the patatin-like domain-containing phospholipase (PNPLA) family. This enzyme actively hydrolyzes TAG but poorly hydrolyzes diacylglycerol (DAG), being almost inactive towards cholesteryl and retinyl esters. Global ATGL-knockout (KO) mice exhibit increased adipose mass and TAG accumulation in many tissues [10]. Interestingly, the heart was most severely affected among various tissues and organs, exhibiting heavy TAG accumulation and dysfunction, leading to early death. This outcome clarifies the primary role of ATGL in TAG breakdown in the heart.

HSL was formerly considered a major TAG lipase in adipose tissue. Its activation by protein kinase A (PKA)-dependent phosphorylation was thought to be responsible for catecholamine-stimulated fat mobilization. However, global HSL-KO mice were lean, which did not support a primary role of HSL in adipose tissue lipolysis [11]. HSL hydrolyzes various lipid esters but exhibits only one-tenth the specific activity of TAG hydrolysis compared with DAG hydrolysis *in vitro* [7]. HSL-KO mice exhibit DAG accumulation in various tissues, including the heart [11]. Hence, HSL is now considered a physiological DAG hydrolase.

CGI-58 was first identified as a human counterpart of a *Caenorhabditis elegans* gene and a gene responsible for Chanarin-Dorfman syndrome, a neutral lipid-storage disease (NLSD) [12] that typically displays aberrant LD development in the cells of multiple tissues and is characterized by ichthyosis (see *Human genetic NLSD* under "Physiological and pathological significance of heart LDs"). CGI-58 protein was found in a LD proteome and was shown to interact with Plin1 [13,14]. Plin1 is heavily phosphorylated by PKA upon catecholamine stimulation of adipocytes, but it binds to CGI-58 only when unphosphorylated [14]. Importantly, *in vitro* assays showed that CGI-58 was an activator of ATGL [15,16].

On the basis of these observations, a feasible model has been developed on TAG storage and mobilization in adipocytes (for review, see [17]). In a quiescent state, Plin1 docks CGI-58, prohibiting the activation of ATGL. Plin1 also blocks HSL from accessing LDs. Thus, TAG is accumulated without being hydrolyzed. In a catecholamine-stimulated state, however, CGI-58 dissociates from phosphorylated Plin1, interacting with ATGL, thereby activating it. Plin1 itself does not interact with ATGL [6], whereas phosphorylated HSL is recruited to the surface of LDs via interaction with phosphorylated Plin1. Hence, massive TAG hydrolysis occurs through sequential actions of ATGL, HSL, and a third enzyme, monoacylglycerol lipase. Thus, regulated protein interactions on the platform of Plin1 constitute a vital mechanism of TAG storage and mobilization in adipose tissue.

The importance of ATGL and HSL in heart TAG metabolism is clear from the results of KO studies, as described above. Similarly, heavy TAG accumulation and malfunction are observed in the hearts of muscle-specific CGI-58-KO mice [18]. Thus, the TAG degradation pathway involving ATGL, CGI-58, and HSL also operates in the heart, but because Plin1 is absent in this organ, the regulatory mechanism cannot be the same as that in adipose tissue.

4. Significance of Plin5 in heart LDs

4.1. Function of Plin5 in heart LDs and the underlying mechanism

Plin5 is abundantly expressed in the heart and other oxidative tissues [19–21]. Its expression is positively regulated by a nuclear