Lipid droplets beyond storage: Cellular metabolic modulator in the diabetic heart (Review)

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Abstract. Diabetic cardiomyopathy (DCM) is a significant complication in patients with diabetes, but its pathogenesis is not fully understood. In recent years, dynamic regulation of lipid droplets (LDs) balance has gradually become a new therapeutic direction with great potential. LDs regulate lipid storage, energy supply and interconnected drivers; for instance, oxidative damage, inflammation, autophagy, ferroptosis, affect the function and cellular homeostasis of cardiomyocytes, macrophages and fibroblasts, and thus participate in DCM. The present review discusses the multiple functions of LDs in regulating DCM by affecting cell homeostasis and summarizes the research progress of therapies targeting LDs and related metabolic pathways, which may inform novel strategies for preventing and treating DCM.

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Abbreviations: ACC1, acetyl-CoA carboxylase; ACSL, acyl-CoA synthetase long chain family member; AKT, protein kinase B; ATGL, adipose triglyceride lipase; ATP, adenosine triphosphate; CE, cholesterol esters; CIDE, cell death-inducing DNA Fragmentation Factor Alpha (DFFA)-like effector; CMA, chaperone-mediated autophagy; DCM, diabetic cardiomyopathy; DGAT, diacylglycerol acyltransferase; FA, fatty acid; HF, heart failure; HSC70, heat shock cognate protein 70; HSL, hormone-sensitive lipase; LAMP2A, lysosome-associated membrane protein 2A; LD, lipid droplet; MGL, monoacylglycerol lipase; NEFAs, non-esterified FAs; NLRP3, NOD-like receptor thermal protein domain associated protein 3; PDM, peridroplet mitochondria; Plin2/5, perilipin 2/5; PUFAs, polyunsaturated FAs

Key words: DCM, LD, cellular metabolic homeostasis, lipid metabolism, mitochondria

Contents

1. Introduction

Diabetic cardiomyopathy (DCM) is a metabolic disorder characterized by pathological features including triglyceride accumulation in cardiomyocytes, reduced glucose utilization, and structural alterations such as cardiac steatosis, myocardial fibrosis, hypertrophy and cardiomyocyte death. According to the 2024 ESC guidelines, DCM can be diagnosed in diabetic patients based on evidence of systolic or diastolic dysfunction, such as ventricular hypertrophy or diffuse myocardial fibrosis, when other cardiovascular risk factors or comorbidities are not present. DCM encompasses a spectrum of cardiac abnormalities, including coronary artery disease and heart failure (HF) (1). Its prevalence among diabetic patients reaches up to 67%, and it is a recognized precursor to HF (2).

In the diabetic heart, energy metabolism shifts toward fatty acid oxidation (FAO) as the predominant adenosine triphosphate (ATP) source. Despite elevated circulating free fatty acids (FFAs), mitochondrial efficiency in ATP production is impaired. Current therapeutic strategies remain limited, although glycemic control is traditionally emphasized, intensive glucose-lowering has not significantly reduced cardiovascular mortality in clinical trials. Intriguingly, recent studies challenge the conventional view of glucotoxicity as the

initiating factor, positioning lipotoxicity as a primordial event in DCM pathogenesis (3). Given that both lipids and glucose are the primary energy sources for maintaining cardiac energy homeostasis, targeting cellular metabolic dysregulation represents a promising therapeutic direction.

When cellular metabolic homeostasis is disrupted, excess fatty acids (FAs) cannot be efficiently oxidized, leading to further lipid accumulation and the subsequent biogenesis of lipid droplets (LDs). Typically, surplus lipids in cardiomyocytes, macrophages, fibroblasts and neurons are stored within LDs as neutral lipids that consist of triglycerides (TGs), cholesterol esters (CEs), or retinol esters. Structurally, LDs are evolutionarily conserved organelles composed of a neutral lipid core surrounded by a phospholipid (PL) monolayer, that binds specific proteins and cholesterol (4). The types and functions of LDs lead to differences in their protein and lipid composition. Nevertheless, the precise regulatory role of LD dynamics in overall lipid metabolism remains incompletely understood.

Insulin resistance exacerbates lipolysis of adipose tissue, leading to excessive systemic release of FAs. This elevated FA flux promotes the expression of LD associated protein Plin5, increases triacylglycerol (TAG) levels and enlarges LD size in insulin-sensitive tissues such as the heart (5). Plin5 enrichment at LD-mitochondria contact interface, implicates these inter-organellar contacts in governing FA trafficking and cellular metabolic balance. At this contact interface, Plin5 restricts mitochondrial respiration and lipolysis through inhibiting adipose triglyceride lipase (ATGL), as well as the decrease in lipolysis levels promotes dynamin-related protein 1 (Drp1) to mediate mitochondrial fission (6,7). Although insulin resistance impairs myocardial glucose uptake, emerging evidence indicates that LDs also regulate glucose metabolism (8). Restricting LD accumulation has been shown to ameliorate insulin resistance (9). Besides, LDs in cardiomyocytes and fibroblasts confer cytoprotective effects against lipotoxicity damage through lipase-mediated lipolysis and autophagy-dependent lipophagy, thereby attenuating energy metabolism dysregulation and structural cardiac damage. Furthermore, LD biogenesis is facilitated through LD-endoplasmic reticulum (ER) contact sites, where the conversion of non-esterified FAs (NEFAs) into neutral lipids sequestered within LDs serves to alleviate ER stress (10).

Beyond their metabolic functions, LDs serve as multifunctional organelles that orchestrate diverse cellular processes. LDs regulate substrate availability, mitigate oxidative stress, modulate inflammatory responses, and function as critical mediators in the immune signaling and cellular quality control mechanisms, including autophagy and ferroptosis. Through these pleiotropic roles, LDs facilitate energy production and alleviate ER stress under physiological conditions. However, abnormal accumulation of LDs is causally linked to mitochondrial dysfunction, ER stress, and broader metabolic perturbations (11,12). Collectively, these LD-associated alterations disrupt cardiac homeostasis and contribute to characteristic pathological features of DCM, including lipotoxic injury, plaque formation and cardiac steatosis. Therefore, the authors propose that LDs represent a pivotal therapeutic target for DCM.

In the present review, LD biology was comprehensively examined in the context of DCM, encompassing the biogenesis of LDs, lipolytic pathways and lipophagy. It was further analyzed how LD associated proteins modulate the processes of DCM. Particular emphasis is placed on cell type-specific and stage-dependent LD characteristics throughout disease progression. Finally, existing pharmacological interventions targeting LD dynamics and lipid metabolism were evaluated, proposing that targeting LDs may offer a novel avenue for DCM treatment.

Biogenesis of LDs. In cardiac tissue, the ER serves as the site of LD biogenesis, where neutral lipid synthesis precedes their assembly into nascent LDs (13). The ER harbors essential enzymes responsible for synthesizing the two major neutral lipid species: Acyl-CoA: cholesterol O-acyltransferases 1 (ACAT1, as ACAT2 is not expressed in the heart) primarily catalyzes CEs (14), and TAGs, synthesized by diacylglycerol acyltransferase (DGAT) 1 and DGAT2 (15). Whereby deficiency in specific lipid synthesis enzymes can be compensated by alternative pathways to maintain neutral lipid production and LD formation (16). DGAT1 localizes exclusively to the ER membrane, whereas DGAT2 displays dynamic subcellular distribution, localizing to ER membrane and LD interface. When intracellular FA concentrations increase, DGAT2 translocates to the LD surface, thereby facilitating TAG storage and LD expansion (15).

Beyond the canonical DGAT-mediated pathway, alternative mechanisms contribute to TAG synthesis, including transmembrane thioredoxin 1, which catalyzes storage lipid production independently of DGAT1/2, though the mechanism requires further investigation (17). LD nucleation occurs when TAG and CEs accumulate to concentrations of 5-10 mmol/l within the ER bilayer, forming lipid lenses that coalesce under the action of PL acid and diacylglycerol (DAG) (4,18-20). The subsequent LD budding is orchestrated by ER-intra TAG concentration and the scaffolding protein Seipin which localizes to nascent lipid lenses to drive LD growth and facilitate the detachment of the PL monolayer-enveloped LD through ER-to-cytoplasm (21). LD budding directionality and size are determined by the asymmetric distribution of the PL monolayer cap, which is governed by ER membrane asymmetry, lipid composition and the spatial positioning of budding site (22,23). Perturbations in neutral lipids trafficking to the ER membrane or aberrant retention on the cytoplasmic leaflet impair the clearance of misfolded proteins, thereby triggering ER stress and inflammatory responses that necessitate continuous PL supplementation to sustain budding (24). Notably, a fundamental distinction exists between mammalian and yeast LD biology; whereas mammalian LDs exist as independent cytoplasmic organelles, yeast LDs maintain persistent ER membrane continuity. This evolutionary divergence reflects species-specific adaptations in lipid storage compartmentalization and ER-LD membrane dynamics (25,26).

Dynamics of LDs: Lipophagy and lipolysis. To meet cardiac energy demands, stored LDs undergo catabolism through lipolysis and lipohagy, processes that hydrolyze TAG into FA for subsequent oxidation. Lipolysis proceeds through a sequential three-step enzymatic cascade: (i) ATGL mediates

rate-limiting TAG hydrolysis at the sn-2 position, generating DAG and FAs. (ii) Hormone-sensitive lipase (HSL) subsequently cleaves DAG into FAs and monoacylglycerol (MAG). (iii) MAG lipase (MGL) completes the process by liberating the final FAs and MAG (27,28). The specificity and efficiency of ATGL-mediated lipolysis are enhanced by its cofactor comparative gene identification 58/Alpha beta hydrolase domain-containing protein 5, which redirects ATGL activity toward the sn-1 position and cooperates with DGAT2 to generate SN1,3DAG. SN1,3DAG is a stereoisomer that bypasses protein kinase C activation but serves as the optimal HSL substrate for continued lipolytic flux (27,28). CGI 58 inhibited the lipolysis rate after interacting with Plin1, and the inhibitory effect disappeared after PKA phosphorylation of Plin1 (29,30). Similarly, Plin5 phosphorylation orchestrates a functional switch from a lipolysis barrier to a promoter of TAG breakdown, as phosphorylated PLIN5 recruits both CGI 58 and ATGL, facilitating the coordinated hydrolysis of TAG into glycerol and Fas (31,32). This phosphorylation-dependent regulation of perilipin-lipase interactions represents a critical control node integrating hormonal signals with cellular energy status to modulate cardiac lipid catabolism.

LDs are partially or completely decomposed into glycerol and FAs in a process known as lipophagy. Lipophagy mainly degrades neutral lipids such as TAGs and CEs through three autophagy modes, including molecular chaperon-mediated autophagy (CMA), macro-autophagy and micro-autophagy, each characterized by specific molecular mechanisms. In CMA, the 71 kDa heat shock cognate protein (HSC70) proteins directly recognizes Plin2, Plin3 and Plin5 via the five-peptide motif protein KFERQ like pentapeptide motifs, facilitating their selective degradation, and subsequently eliminating their protective shielding of ATGL at the LD surface (33). Following HSC70-mediated recognition, the KFERQ-bearing perilipins binds to lysosome-associated membrane protein 2A (LAMP2A), assembling into a translocation complex that delivers these cargo proteins into the lysosomal lumen for degradation. The CMA-mediated removal of Plin2 and Plin3 consequently enables ATGL accessibility to LDs, thereby promoting both ATGL-mediated lipolysis and subsequent lipophagy (34). During macro-autophagy, LDs recruit autophagy related proteins to initiate the biogenesis of autophagosomes, facilitating the selective sequestration and lysosomal degradation of lipid cargo (35). Micro-autophagy mediates direct LD engulfment by lysosomes through membrane contact site tethering mechanisms, wherein LD contents are transferred to the lysosomal lumen via direct injection or membrane transfer remains unclear, potentially regulated by membrane fusion associated small GTPases, and hydrolyzed by lysosomal acid lipase independent of cytoplasmic lipases and autophagy (36).

It should be noted that the degradation of LD through lipolysis or lipohagy is determined by the size of the LD. Lipohagy can only degrade smaller LDs in liver, while LDs exceeding the degradation capacity of lipohagy will trigger ATGL-mediated cytoplasmic neutral lipolysis under normal conditions, with starvation or cellular stress inducing acid lipolysis to release FAs for FAO. Thus, the liberation of lipids and TGs from LDs for energy production is facilitated by neutral and acidic lipolysis (37). Whether similar size-dependent and pathway-selective mechanisms operate across DCM warrants further investigation (Fig. 1).

LD proteome: Important factors regulating LD dynamics. The dynamic stability and regulatory function of LDs are significantly reliant on surface-binding proteins. The categorization of these LD-associated proteins remains insufficient: One perspective separates them according to the mechanism of metastasis. Class I proteins such as DGAT2, ACSL3 and GPAT4 are translocated from the ER to LDs through the ERTOLD and include hydrophobic hairpin motifs that directly engage with LDs (38).

The CYTOLD pathway mediates the direct transport of Class II proteins from the cytosol to LDs. These proteins include Plins, members of the Perilipin family that possess an amphipathic helix, as well as cell death-inducing DNA Fragmentation Factor Alpha (DFFA)-like effector (CIDE) family of proteins. Conversely, CGI58, which is associated with LDs via protein-protein interactions, engages with proteins, including histones and the small GTPase Rab18 (RAB18), which is anchored to LDs through lipid modification (39,40).

Based on their roles, these proteins can be categorized into LD structural proteins/resident proteins, lipid metabolism enzymes, and transport/signal transduction proteins. Such proteins are produced through fusion or localized lipid synthesis.

DGAT2: LD biogenesis involves functional coupling of FA transporter protein 1 on the ER membrane and DGAT2 at nascent LD surfaces, which coordinately promote TAG synthesis and lipid transfer (41). However, DGAT2 expression must be tightly controlled, as overexpression compromises ER membrane stability (42). Post-translational modification provides additional regulation, H_2S intervention enhances ubiquitin-mediated degradation of DGAT1 and DGAT2 and enhanced the expression of the E3 ligase Hrd1 to reduce LDs accumulation (43). The small GTPase RAB1B dynamically regulates DGAT2 subcellular distribution by facilitating its trafficking from ER to LDs via secretory pathways, promoting the expansion and growth of LDs (44). Collectively, these mechanisms encompassing protein interactions, expression control, proteolytic regulation and vesicular trafficking converge to fine-tune LD dynamics in response to metabolic demands.

The perilipin family represents the major LD-resident proteins in mammalian cells. In cardiac tissue, PLIN2 and PLIN5 predominate; whereas Plin1 is mainly located in adipocytes, Plin5 facilitates TAG storage. During the metabolic transition from glycolysis to β-oxidation, Plin2 upregulation activates the peroxisome proliferator-activated receptors (PPARs) signaling pathway (45,46). Plin2 regulates the shape, size and morphology of LDs, while both Plin2 and Plin5 inhibit ATGL mediated lipolysis, thereby modulating lipid accumulation (47,48).

RAB18: Plin2 harbors the RAB18 binding site within its C-terminal domain (49). Although this interaction exhibits cell type specificity. Genetic lack of RAB18 in C2C12 skeletal muscle cells does not significantly alter the expression level of Plin2, whereas RAB18 overexpression in HepG2 cells modulates

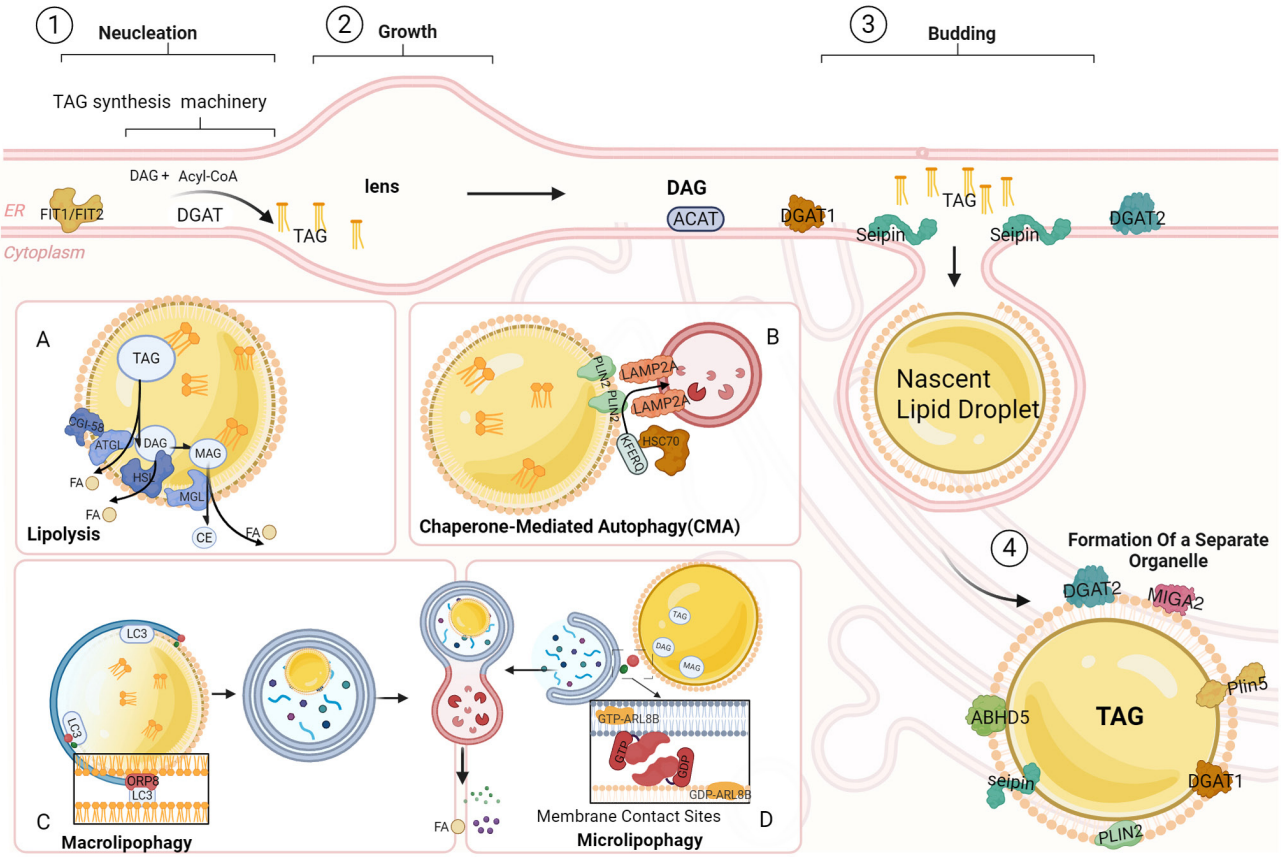

Figure 1. 1. Originating from the ER, lipid droplet formation involves a four-step procedure: It starts with nucleation, followed by growth and budding, and culminates in the creation of an independent organelle. 2. ① DGAT aggregates neutral lipids and completes the nucleation process. ② TAG and CEs reached a certain concentration during the growth process to form oily lens. ③ After being coated by phospholipids in the ER monolayer, LD separated from ER and entered the cytoplasm. ④ The assembly of surface proteins formed structurally and functionally complete organelles. The process of LD decomposition includes lipophagy and lipolysis: (A) In lipolysis, three intracellular lipases, ATGL, HSL and MGL, hydrolyze TAG to CEs and FAs. (B) In chaperone-mediated autophagy, intracellular HSC70 recognizes specific sequences such as Plin2 to translocate LD into lysosomes for degradation. (C) Macrolipophagy. LC3 binds to the PE of LD to form autophagosomes that phagocytose LD and transport it to lysosomes. In addition, the lipid transporter ORP8 anchors to the LD surface and interacts with LC3 to promote the binding of LD to autophagosomes. (D) There are relatively few studies on the mechanism of micro-lipophagy. Besides the binding of Rab7 and Rab-interacting lysosome protein to promote the occurrence of micro-lipophagy, GTP can also change the structure of amphipathic helices and promote the attachment of the complex formed by ARL8B to the LD membrane and lysosomal membrane. ER, endoplasmic reticulum; DGAT, diacylglycerol acyltransferase; TAG, triacylglycerol; CEs, cholesterol esters; LDs, lipid droplets; MAG, monoacylglycerol; MGL, MAG lipase; FAs, fatty acids; HSC70, heat shock cognate protein 70; HSL, hormone-sensitive lipase; LAMP2A, lysosome-associated membrane protein 2A.

Plin2 abundance (50). Functionally, RAB18 recruits the ER membrane-localized NAG-RINT1-ZW10 (NRZ) complex and associated SNARE proteins (Syntaxin18, USE1 and BNIP1) to form the RAB18-NRZ-SNARE multiprotein complex, which facilitates LDs' formation and mediates stable membrane contact sites (MCSs) between ER and LDs. The depletion of RAB18 does not affect early LD biogenesis but significantly impairs subsequent LD growth and maturation (50,51).

ABHD5/CGI 58: CGI 58, a highly conserved regulator, is characterized by its interaction with Plin and ATGL to function as a coactivator in ATGL-mediated lipolysis (52). PKA-mediated phosphorylation of Plin5 in the heart enhances the expression of CGI 58. By contrast, non-phosphorylated Plin5 binds CGI 58 and inhibits lipase activity. Beyond Plin regulation, cellular homeostasis also requires coordinated action of other key metabolic enzymes. Lipolysis is primarily mediated by three enzymes: ATGL, HSL and MGL. Upregulation of these key lipolysis enzymes ameliorate cardiac steatosis and myocardial fibrosis (53). Decreased expression of lipolysis enzymes aggravates mitochondrial dysfunction (54).

ATGL acts as the rate-limiting enzyme for TAG hydrolysis in LDs, ATGL deficiency reduces PPARα expression and FAO levels, resulting in human neutral lipid storage disorder and cardiomyopathy (55). Restricting lipid absorption alone fails to reverse ATGL deficiency induced cardiomyotoxicity (56). Yet ATGL overexpression ameliorates myocardial injury by enhancing lipolysis (55). This indicates that ATGL deficiency extends beyond mere lipid accumulation, as its mediated lipolysis liberates PPAR agonists that activate downstream PPARα/PGC-1α-regulated FAO and mitochondrial biogenesis (57). Although pharmacological interventions partially restore FAO, the signaling function of ATGL remains indispensable for cardiac protection.

HSL: Overexpression of Plin2 markedly reduces HSL expression, indicating that Plin2 as a functional inhibitor of HSL (53). HSL exerts a cardioprotective effect that precedes the overt development of cardiac lipotoxicity. In the context of DCM, overexpression of HSL does not influence VLDL absorption but effectively downregulates key profibrotic factors, including collagen, TGF-β and matrix metalloproteinase

(MMP) 2. This suppression alleviates the lipotoxicity and LDs accumulation driven by TAG and DAG (58).

LDs sequester excess histones, preventing histone toxicity, and supplies histones for chromatin assembly during DNA replication (59,60). Multiple proteins govern stability of LDs while concurrently engaging in membrane transport and signal transduction, thereby influencing cellular metabolic remodeling (61). Proteins of the LD proteome related to LD biogenesis in DCM are included in Table I.

Interaction between LDs and mitochondria. LDs establish contact sites with multiple organelles, most notably mitochondria; the adult heart derives ~95% of its ATP from mitochondrial oxidative phosphorylation, with FAO contributing 40-60% of reduction equivalents. Mitochondrial dysfunction generates lipotoxicity intermediates that promote intracellular lipid accumulation. LDs counteract lipotoxicity by sequestering excessive FAs and lipid intermediates. During energy stress such as fasting or β-adrenergic stimulation, increased cardiac energy demand and elevated adipocyte lipolysis lead to heightened expression of LDs, Plin5, and mitochondrial LDs contact sites in cardiac tissue. This metabolic demand promotes formation of 'peridroplet mitochondria (PDM)', a specialized mitochondrial subpopulation with unique functional, ridge-structured, and proteomically distinct mitochondrial compartment attached to LDs (5,69). Plin5 mediates these LD-mitochondria contacts (LDMCs) and preferentially targets PDMs (5). In cardiomyocytes, enhanced Plin5-dependent LDMC improve mitochondrial respiratory capacity and metabolic flexibility. Paradoxically, FAO remains independent of LDMC (70). This may relate to PDM primarily promoting FA activation and TAG synthesis with stronger oxidative phosphorylation and ATP supply capacity, which are not mainly responsible for FAO (71).

Previous studies have revealed a link between LDs and mitophagy. Mitophagy leads lysosomes to phagocytose PDM and release FAs, which aggravates intracellular lipid peroxidation and iron accumulation and eventually cause ferroptosis. Inhibiting mitophagy significantly reduces LD accumulation and FFA levels, yet DGAT1 expression remains elevated and continues to drive nascent LDs formation (72).

PLIN2 regulates LD homeostasis and mitochondrial remodeling through epigenetic mechanisms. By suppressing lipolysis, Plin2 elevates acetyl-CoA and histone acetylation levels, maintaining embryonic stem cell pluripotency (73). Loss of Plin2 shifts cellular metabolism from glycolysis to oxidative phosphorylation and accelerates pluripotency exit. Under these conditions, Plin2 is recognized by Hsc70 and degraded through CMA, promoting mobilization of LDs (74). This is similar to the metabolic transition of cardiomyocytes from embryonic to adult stages. Although short-term glucose deprivation alters Plin2 conformation, weakening its interaction with ATGL and enhancing lipolysis, though the impact on cardiac metabolism remains uncertain (75).

In fact, the link between LDs and mitochondria is largely established by specific molecules or pathways that serve multiple functions in both LD dynamics and mitochondrial operation. Under nutrient excess conditions, mitophagy becomes dysregulated and AMPK activity declines (76). Only part of AMPK-mediated phosphorylation of ACC1 and ACC2 fails to effectively inhibit FA synthesis, paradoxically promoting LD formation. AMPK activates PPARs γ coactivator 1 alpha (PGC1α) is blocked, disrupting the formation of complexes between PGC-1α, Plin5 and silent information regulator 1 (SIRT1), and impairing mitochondrial biosynthesis (77).

Concurrently, excessive mammalian target of rapamycin complex 1 (mTORC1) signaling stimulates lipid accumulation by activating its key downstream effector sterol regulatory element binding protein 1c (SREBP1c). Autophagy is inhibited by Akt-mediated suppression of FOXO transcription and further impaired by elevated branched-chain amino acids (BCAAs), which suppress the mTORC1/autophagy-related protein (ATG)/ULK pathway (78,79). SIRT1 mediated deacetylation activates FOXO1, whose deacetylation status regulates the expression of ATGL and PPARα (80).

Under energy-deficient conditions, FOXO1 also recruits Rab7 to sustain autophagy, a process involved in the micro-lipophagy degradation of LDs. In DCM, the inhibitory effect of FOXO on transcription factor EB (TFEB) is weakened (81). It is worth noting that PKA promotes lipolysis mediated by Plin5, CGI58 and ATGL (8). Therefore, LD metabolism is coordinately regulated by upstream kinases, for instance, PKA, mTOR, as well as AMPK and transcription factors including silent information regulator 1 (SIRT1), PGC-1α, FOXO, SREBP1, PPARs and TFEB (31).

2. Specificity of cellular LD regulation in the heart

Mechanisms of LDs and cellular metabolic homeostasis in DCM. LDs represent the principal cellular compartment specialized for neutral lipid storage, distinguished from other organelles by both structural architecture and functional capacity. The ER despite serving as the site of lipid biosynthesis, incorporates lipids within its PL bilayer rather than sequestering them in concentrated deposits, limiting its storage capacity and potentially compromising membrane function under lipid excess (4). Mitochondria maintain membrane lipids essential for bioenergetics but actively oxidize rather than store FAs, making them vulnerable to lipotoxic damage when substrate availability exceeds oxidative capacity. Peroxisomes metabolize very-long-chain and BCAAs through β-oxidation yet lack mechanisms for TAG or CEs accumulation (72). Lysosomes degrade lipids delivered via endocytosis or autophagy but function as catabolic rather than storage compartments.

By contrast, LDs possess a unique PL monolayer encompassing a hydrophobic neutral lipid core, an architecture that enables massive expansion without membrane stress or dysfunction of organelles (4). This specialized structure allows LDs to accumulate energy-dense TAGs and CEs while protecting other organelles from lipotoxic intermediates. The dynamic nature of LD expansion, lipophagy and lipolysis regulate lipid mobilization coordinated with metabolic demands, whereas lipid accumulation in other organelles typically signals pathological dysfunction rather than adaptive storage. Consequently, LDs serve as the primary defense against abnormal lipid deposition, protecting mitochondria, ER, and plasma membrane integrity from lipotoxicity-induced cellular damage.

Table I. Proteins of the LD proteome related to LD biogenesis in diabetic cardiomyopathy.

Authors, year		Expression	Cell types	Pathological mechanism	Disease	Experimental model	(Refs.)
Pham *et al*, 2023	DGAT1	Upregulated	Cardiomyocytes	Directly regulates LDs formation, reduce lipotoxicity and the mitochondrial damage	Type 2 diabetes	Db/db mice	(62)
Sun *et al*, 2021, Malis *et al*, 2024; Roe *et al*, 2018	DGAT2	Upregulated	Cardiomyocytes, Huh7 cells	Promote the synthesis and directional transport of TAG, the DGAT2 inhibitor alone has very modest effect but only inhibition of both DGAT2 and DGAT1 isoforms substantially reduced FA incorporation into TG pool in the heart. In WARBM model mice fibroblasts, DGAT2 drive the formation of new LDs at the ER-LD interface	-	Oleate, palmitate treated H9C2 cells, db/db mice were injected with NaHS, high glucose, high fat diet treated mouse, WARBM model mice	(43,44,63)
Pollak *et al*, 2013	Plin5	Upregulated	Cardiomyocytes	Alleviates lipotoxicity, regulates lipid catabolism, and increases fat acid oxidation, control of TAG hydrolysis	Type 2 diabetes	Palmitic acid treated HL-1, high glucose and oleate treated H9c2 cells, Db/db mice, oleic acid treated COS-7 cells	(64)
Najt *et al*, 2023; Akoumi *et al*, 2017; Ueno *et al*, 2017	Plin2	Downregulated	Cardiomyocytes	Regulate cardiac steatosis; Regulate LDs size, quantity, morphology and structure, partitioning toxic lipids and their metabolites in LDs	Lipotoxic cardiomyopathy	Oleate or palmitate treated H9C2 cells, mice	(47,48,53)
Deng *et al*, 2021	RAB18	Downregulated	Podocyte, myoblast cells, fibroblast cells	Participate in the growth and maturation of LDs	-	Oleic acid induced C2C12 cells	(50)
Jebessa *et al*, 2019; Inoue *et al*, 2013	ABHD5	Downregulated	Cardiomyocytes	Regulate myocardial steatosis and oxidative stress and glucose handling	-	High-sucrose/high-fat diet treated Db/ db mice, Neonatal rat ventricular myocytes and 293 cells	(8,65)
Pulinilkunnil *et al*, 2013; Haemmerle *et al*, 2011	Adipose triglyceride lipase	Downregulated	Cardiomyocytes	Hydrolyze TAG into FFA to provide metabolic substrates for the heart	Type 1 diabetes	Akita mice, STZ-treated C57BL/6J mice	(55,57)
Ueno *et al*, 2017; Ueno *et al*, 2008	Hormone-sensitive lipase	Downregulated	Cardiomyopathy	Displays cardioprotective actions before the manifestation of cardiac lipotoxicity	Type 2 diabetes	STZ-induced C57BL/6J mice	(53,58)
Holzhütter *et al*, 2019; Magré and Prieur, 2022; Guyard *et al*, 2022; Bai *et al*, 2019	Seipin	Downregulated	Cardiomyocytes	Promotes LD biogenesis within the ER, alleviates insulin resistance and heart dysfunction	Heart failure with preserved ejection fraction	Seipin knockout mice	(21,66-68)

LDs, lipid droplets; DGAT, diacylglycerol acyltransferase; TAG, triacylglycerol; WARBM, Warburg Micro syndrome; STZ, streptozotocin; ER, endoplasmic reticulum.

Beyond their canonical storage function, LDs protect cells from lipotoxicity by limiting lipid peroxidation and buffering excess FAs during metabolic dysregulation. LDs regulate diverse metabolic substrates, including BCAAs and glucose, both central to DCM pathogenesis. LDs participate in intermembrane lipid trafficking, store precursor molecules for lipids, mitigate oxidative damage, and modulate inflammatory responses. By coordinating these diverse functions, LDs protect mitochondria and other organelles while regulating cellular processes such as autophagy, ferroptosis, and cell division (11,12).

Hyperglycemia induces cardiac lipid overload and metabolic dysregulation, with insulin resistance exacerbating lipotoxic injury to cardiomyocytes, disrupts metabolic homeostasis, manifesting as mitochondrial dysfunction, ER stress and calcium overload. LDs likely play multiple roles in modulating these pathological responses through their capacity to store and mobilize lipids. Under conditions of sustained hyperglycemia, excessive FA influx overwhelms oxidative capacity, triggering abnormal lipid accumulation that compromises cellular homeostasis. Insulin resistance further impairs metabolic flexibility, preventing adaptive substrate switching and intensifying reliance on FAO despite limited mitochondrial capacity (82). The resultant accumulation of lipotoxic intermediates, including DAG, ceramides and acyl-carnitines, directly impairs mitochondrial respiration, induce calcium dysregulation and ER stress.

LDs limit FAs' incorporation into membrane PLs and reducing susceptibility to peroxidative damage. This antioxidant function preserves organellar integrity and prevents ferroptosis driven by lipid peroxidation (72). Conversely, LDs mobilize stored lipids through two pathways: Neutral lipase-mediated lipolysis and autophagy-dependent acid lipolysis. Lipolysis liberates FAs for FAO during energy demand. Insulin resistance impairs autophagy, a mechanism essential for maintaining cellular homeostasis. Lipophagy, representing a cargo-selective autophagy pathway, specifically targets LDs for lysosomal degradation. Current evidence indicates that both CMA and micro-autophagy contribute to metabolic regulation in DCM, although the role of macro-autophagy remains controversial (81). The proteins and PLs on the surface of LDs interact with specific enzymes to exert important functions. The balance between LD storage and degradation thus determines lipid flux, organelle function, and influence cellular metabolic homeostasis in DCM.

Cardiomyocytes. Cardiomyocytes mainly rely on oxidative phosphorylation for energy supply and can also generate energy through glycolysis and other ways. Nowadays, the change of FAO in DCM remains controversial (83). It may be related to the stage of DCM. A multimeric complex consisting of extended synaptotagmin 1 (ESYT1), ESYT2, VAMP Associated Protein B and C localizes to ER-LD-mitochondria contact sites. Loss of this complex reduces LD-derived FAO by 67% and promotes LDs accumulation, indicating that the complex facilitates lipid mobilization and prevents lipotoxicity (84,85). This reduced oxidation capacity appears paradoxical given previous studies of elevated FAO in DCM, suggesting compensatory mechanisms may operate under different metabolic conditions (57). These findings demonstrate that LD accumulation and the resulting imbalance in FAO are important pathogenic mechanisms in DCM.

Ca^{2+} transfer at mitochondria-ER contact sites regulates FAO. The majority of Ca^{2+} stored in the ER is transferred to the mitochondria via Inositol-requiring enzyme 1α (IRE1α) regulated inositol trisphosphate receptor (IP3R) mediates Ca^{2+} influx from the ER to mitochondria activating the IP3R-75-kDa glucose-regulated protein (Grp75) and voltage-dependent anion channel (VDAC) complex (IP3R-Grp75-VDAC) complex, promoting mitochondrial respiratory chain and ATP synthesis. This complex recruits Seipin to accelerate LDs' biosynthesis and lipid transfer in the liver. Although regulating VDAC1 and GRP75 has a protective effect on the heart, their role in cardiac LDs biosynthesis remains unclear (86,87).

Normally, acyl-CoA synthetase long chain family member 1 activates FAs to fatty acyl-CoA for subsequent β-oxidation, which directly generates acetyl-CoA for the TCA cycle. Long-chain FAs require CPT1/2-mediated mitochondrial transport before oxidation (88). In DCM, long term overload of FAO promotes electron leakage, generating reactive oxygen species (ROS) and aggravates oxidative stress. Plin5 suppresses the ROS-activated Phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway and the mitogen-activated protein kinase pathway (p38/ERK/JNK), hence preventing oxidative stress and apoptosis (89,90).

LDs protect against ferroptosis through antioxidant mechanisms. FSP1, located in LDs, and maintains antioxidant capacity by reducing Coenzyme Q10, preventing peroxidation of neutral lipids. Impairment of FSP1 function induces the peroxidation of polyunsaturated FA-LDs (PUFA-LDs), triggering ferroptosis of cardiomyocytes (91). In type 1 diabetic patients, glucolipotoxicity reduces LAMP2A, Hsc70 and Hsc90 expression, inhibits the clearance of autophagosomes and inactivates TFEB, causing autophagy disorders and rendering the myocardium vulnerable to ER stress and metabolic injury (92).

Cardiomyocytes maintain lipid homeostasis by balancing the FAO rate with LD biosynthesis. Under nutrient excess, insulin activates acetyl-CoA carboxylase (ACC) to generate malonyl-CoA, which inhibits the acetylation level of CPT1 and MPC2, thereby restricting FAO (93,94). Studies in CPT1b-deficient skeletal muscle confirm that reducing FAO alleviates mitochondrial lipid burden during energy surplus (95). Conversely, ACC2 knockdown maintains FAO and reduced cardiac hypertrophy, demonstrating that preserving oxidative capacity protects cardiac function (96).

DGAT1 and GPAT4 are upregulated to enhance TAG synthesis, and the elevation of TAG levels is positively correlated with systolic dysfunction, suggesting that excessive accumulation of LDs adversely affects cardiac structure (97).

Downregulated TGR5 fails to inhibit DHHC4, which mediates the palmitoylation of CD36, consequently promoting CD36 overexpression, the abnormal FAO, and the elevated LDs' accumulation (98,99). Exceeding the LDs' buffering capacity results in surplus FAs, leading to cellular lipotoxicity and disruption of energy supply. Concurrently, the inhibitory effect of ATGL on ceramide will be weakened, resulting in increased ROS production and triggers mitochondrial dysfunction, ultimately inducing apoptosis and aggravating insulin resistance (100,101) (Figs. 2 and 3).

Macrophages. Macrophages primarily orchestrate inflammatory and immunological responses to sustain cellular metabolic

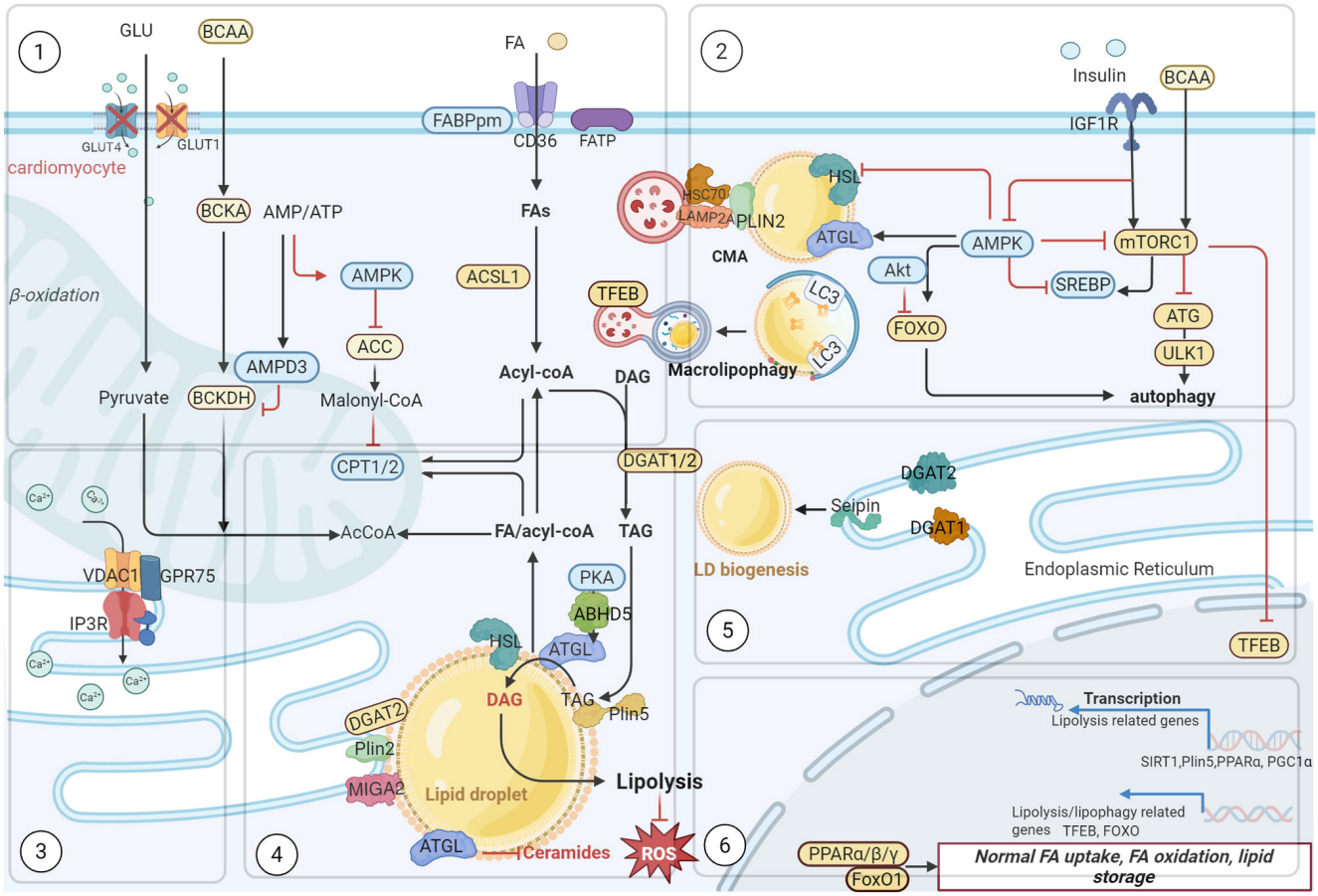

Figure 2. LDs and cellular metabolic homeostasis in cardiomyocytes. ① Metabolic pathways of glucose, BCAA and FA. ② BCAA regulates autophagy through the mTORC1/ATG/ULK1 pathway and jointly regulates SREBP with AMPK. Additionally, AMPK inhibits HSL and promotes lipolysis regulated by ATGL. In CMA, HSC70 recognizes and consumes Plin2. The degradation of LDs is initiated when its KFERQ motif is recognized by HSC70 and LAMP2A on the lysosomal surface, leading to complex formation. Under normal circumstances, the phosphorylation of TFEB in cardiomyocytes promotes macrolipophagy. ③ The flow of Ca^{2+} in mitochondria and endoplasmic reticulum depends on the VDAC1-GPR75-IP3R complex. ④ DGAT1/2 to facilitate the conversion of DAG into TAG, which is stored in LDs. Moreover, excess Acyl-CoA is also converted to TAG to protect cells from lipotoxic damage. TAG generates DAG through ATGL and CGI58, and finally lipolysis to CE and FA. The FA released in this process enters the mitochondria for FAO, and lipolysis inhibits ROS production. ATGL inhibits the accumulation of intracellular ceramides. There are membrane contact sites such as DGAT2, Plin2 and MIGA at the contact interface between LD and ER to regulate lipid metabolism. ⑤ Seipin and DGAT2 promote the biogenesis of LD. ⑥ The cell nucleus drives the transcription of lipolysis-related genes (for example, SIRT1, Plin5, PPARα and PGC-1α), along with genes such as TFEB, FOXO, and PPARβ/γ. Maintain normal levels of FA uptake, FAO and lipid storage. LDs, lipid droplets; BCAA, branched-chain amino acid; ATG, autophagy-related protein; ULK1, Unc-51 like autophagy activating kinase 1; SREBP, sterol regulatory element binding protein; HSL, hormone-sensitive lipase; HSC70, heat shock cognate protein 70; LAMP2A, lysosome-associated membrane protein 2A; TFEB, transcription factor EB; ROS, reactive oxygen species; DGAT, diacylglycerol acyltransferase; ATGL, adipose triglyceride lipase; PPAR, peroxisome proliferator-activated receptor; FA, fatty acid; ACSL, acyl-CoA synthetase long chain family member; CMA, chaperone-mediated autophagy; VDAC, voltage-dependent anion channel; GRP75, glucose-regulated protein 75; DAG, diacylglycerol; mTORC1, mammalian target of rapamycin complex 1.

homeostasis. While numerous studies have researched lipotoxicity in cardiomyocytes, studies on lipotoxicity in macrophages remain insufficient. Macrophages modulate their energy acquisition through dynamic remodeling of membrane receptors coupled with metabolic reprogramming of glucose and lipid pathways. These cells meet their lipid requirements by engulfing apoptotic cells, lipoprotein particles and LDs.

Low-density lipoprotein (LDL) is oxidized to OxLDL, which macrophages internalize via CD36-mediated endocytosis. Lysosomal hydrolysis releases FFAs and TC which are stored in LDs as CE. Reduced lipid autophagy and cholesterol efflux further lead to LDs accumulation, ultimately impairing phagocytic capacity and transforming into foam cells (102).

Macrophages form LDs under conditions of inflammation and oxidative stress. With different phenotypic switches, the expression levels of LD-related proteins are also different. Plin1 and Plin2 regulate both polarization of macrophages and LD size. Plin1 was found to promote larger LDs when overexpressed in M1 macrophages. With Plin1 overexpression promoting larger LDs in M1 macrophages, Plin1 associates with the inflammatory phenotype whereas Plin2 correlates with the anti-inflammatory phenotype and collectively governing lipid storage (103). Current investigations of LD biology in macrophage subtypes remain confined to classic M1 macrophages and M2 macrophages despite the identification of diverse macrophage phenotypes. Nevertheless, LDs serve critical functions in maintaining cellular homeostasis and macrophage function, processes fundamentally linked to atherosclerosis (104).

Advanced glycation end products in the diabetic cardiac microenvironment promote M1 macrophage polarization through the miR-471-3p/SIRT1 pathway. M1 macrophages

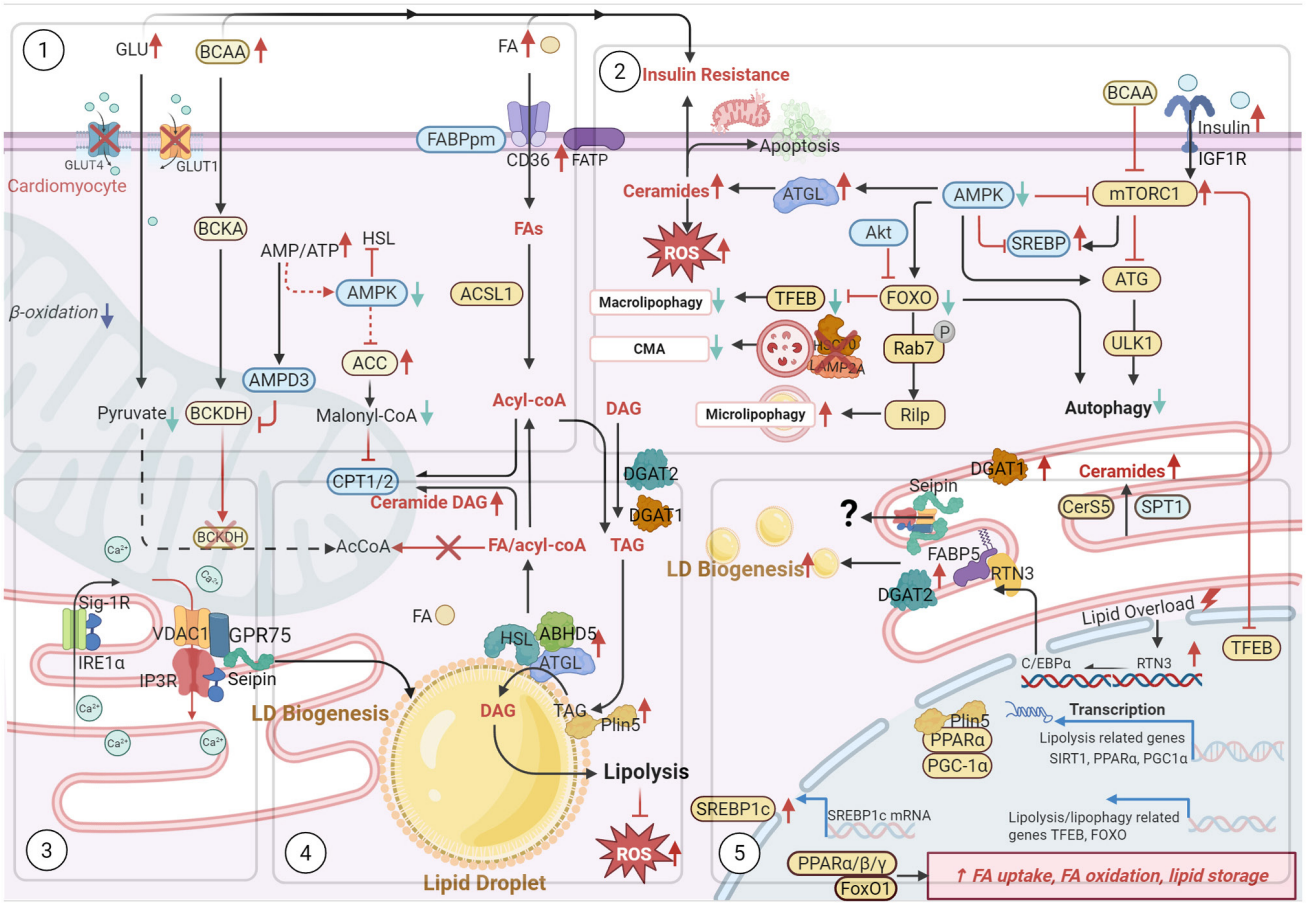

Figure 3. LDs and imbalance of cellular metabolic homeostasis in cardiomyocytes. ① In insulin resistance, the lipolysis of adipose tissue is enhanced, increasing the concentration of FAs. Cardiomyocytes upregulate the expression of receptors such as CD36, increasing the rate of FA uptake. Along with the reduction of glucose uptake by cells through GLUT1/4, the concentration of BCAA increases, and the effect of AMPD3 on BCKDH is enhanced. ② Decreased FOXO and increased BCAA reduced the level of autophagy through the mTORC1/ATG/ULK1 pathway, and FOXO and mTORC1 reduced TFEB and its regulated macrolipophagy; Glucolipotoxicity damaged heat shock cognate protein 70 and LAMP2A, and inhibited CMA. When FOXO was decreased, Rab7 enhanced mitochondrial Ca^{2+} overload through Rilp. ③ Similar to the liver, in diabetic hearts the effect of IP3R-Grp75-VDAC complex may be weakened, which reduced Ca^{2+} transport to the ER, aggravated FA accumulation, and mitochondrial dysfunction. ④ ER stress and mitochondrial dysfunction lead to massive ROS production, which increase the expression of Pin5, ABHD5 and HSL. Enhanced lipolysis and increased expression of DGAT1 and DGAT2 accelerate the turnover of TAG and DAG within cells. In the meantime, FA-CoA cannot be converted to AcCoA, and with the increase of ceramide DAG, also aggravated the lipolysis to a certain extent. ⑤ Lipid overload activates reticulon 3-FABP5 to regulate FA transport and increase LD biosynthesis. IP3R-Grp75-VDAC complex increases LD production through Seipin in the liver, but it is not clear in the heart. Insulin inhibits AMPK and mTORC-mediated lipid degradation through the IGF1 pathway to promote LD biosynthesis. LDs, lipid droplets; FAs, fatty acids; BCAA, branched-chain amino acid; mTORC1, mammalian target of rapamycin complex 1; ATG, autophagy-related protein; ULK1, Unc-51 like autophagy activating kinase 1; TFEB, transcription factor EB; LAMP2A, lysosome-associated membrane protein 2A; CMA, chaperone-mediated autophagy; VDAC, voltage-dependent anion channel; GRP75, glucose-regulated protein 75; ER, endoplasmic reticulum; HSL, hormone-sensitive lipase; DGAT, diacylglycerol acyltransferase; ATGL, adipose triglyceride lipase; TAG, triacylglycerol; DAG, diacylglycerol; MGL, monoacylglycerol lipase; Rilp, Rab-interacting lysosome protein.

enhance glycolysis while suppressing FAO, thereby activating the pentose phosphate pathway to generate pro-inflammatory and bactericidal mediators (105). M2 macrophages, by contrast, exhibit greater LD accumulation and elevated FAO levels, maintaining their anti-inflammatory phenotype through PPARγ (101). TGF-β promotes LDs synthesis via the ERK1/2 pathway and attenuates STAT1 to inhibit M1 polarization (106). Activation of the PPAR pathway upregulates CD36 and Plin2, thereby promoting LD formation, and influences immunophenotypic switching (107,108). CX3CR1 signaling appears to inhibit M1 polarization while promoting foam cell formation (109). The expanding lipid core subsequently elevates the levels of MMP, nitric oxide and endothelin, and eventually causes plaque rupture (110).

Macrophage-derived LD-associated hydrolase upregulates Abca1 and Abcg1 expression through an LXR dependent mechanism, thereby attenuating the inflammatory response induced by SE accumulation (111). Although conventional perspective considers that accumulation of LDs fosters insulin resistance or inflammation, protective regulatory mechanisms exist. Forkhead box protein C2 (foxc2) suppresses the angiopoietin-like 2 (angptl2)/NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome pathway, reducing the expression of NLRP3, ASC and caspase-1. Foxc2 also modulates Bcl-2/Bax to diminish apoptosis, oxidative stress and LDs' accumulation in macrophages (112,113).

Foam cell formation is regulated by lipophagy factors including HSPA5, UBE2G2 and AUP1. Upon autophagy activation, LDs initiate lipophagy by recruiting LC3 and adaptor protein Sequestosome 1 (SQSTM1). Sirt6-dependent chromatin remodeling factor SNF2H inhibits Wnt family member 1/β-catenin pathway to accelerate lipophagy and

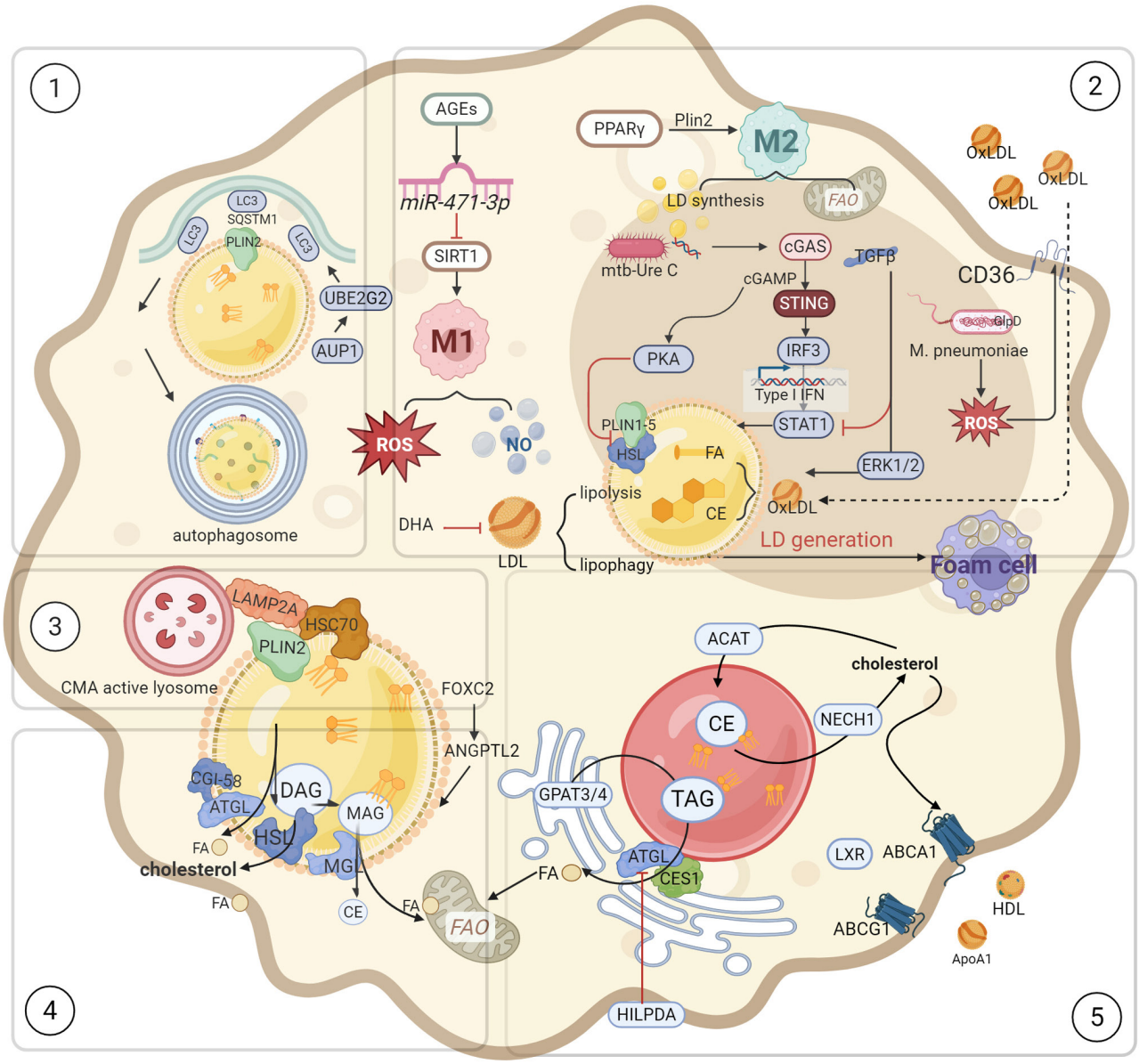

Figure 4. LDs in macrophages. ① The recruitment of lipophagy factors such as UBE2G2 and AUP1 activates LC3 and Sequestosome 1-mediated autophagy, promoting the foaming process of macrophages. ② AGEs promote M1 polarization through the mir-471-3p/SIRT1 pathway, generating a large amount of ROS and NO. The long-term maintenance of the M2 phenotype depends on PPARγ. M2-type macrophages exhibit low levels of glycolysis and high levels of oxidative phosphorylation, as well as more LD accumulation. TGFβ can reduce LD accumulation. Multiple pathogens promote the foaming of macrophages. Mtb enables macrophages to switch from the glycolysis pathway to ketone body synthesis. It also regulates the cGAS/STING pathway to accelerate the formation of foam cells, and pneumococcus accelerates the foaming process through ROS. ③ Before lipolysis, Plin2 on the LD surface was recognized by heat shock cognate protein 70 at the KFERQ motif and degraded by lysosomes after interacting with LAMP2A. ④ ABHD5 and ATGL promote the conversion of TAG to DAG, and continue to hydrolyze CE and FA through MGL, and HSL continue to hydrolyze CE to free cholesterol and FA, and FA enters mitochondria for FAO. FOXC2/Angptl2 promotes LD accumulation. ⑤ The regulation process of TAG and CE levels in macrophages. GPAT3 and GPAT4 help FA synthesize TAG, CES1 and ATGL hydrolyze CE to FA, and HILDPA inhibits ATGL-regulated lipolysis. It catalyzes the synthesis of cholesterol to CE at ACAT, which is then decomposed to cholesterol by neutral cholesterol ester hydrolase 1 (NECH1). ABCA1 and ABCG1 contribute to cholesterol efflux when excess cholesterol accumulates. LDs, lipid droplets; AGEs, advanced glycation end products; ROS, reactive oxygen species; NO, nitric oxide; PPAR, peroxisome proliferator-activated receptor; ATGL, adipose triglyceride lipase; LAMP2A, lysosome-associated membrane protein 2A; TAG, triacylglycerol; DAG, diacylglycerol; HSL, hormone-sensitive lipase; CMA, chaperone-mediated autophagy; oxLDL, oxidized low-density lipoprotein; FA, fatty acid; FFA, free FA; DHA, docosahexaenoic acid; HDL, high-density lipoprotein.

autophagosome lysosome mediated lipolysis and accelerating autophagosome-lysosome-mediated lipolysis and FA transfer to mitochondria for FAO. A key unresolved question concerns the specific mechanism through which sirtuin6 regulates this transfer (114). In vascular smooth muscle cells, Plin2 similarly facilitates lipophagy through elevated LC3II levels and enhanced autophagosomes biogenesis, which impedes foam cell formation (115). Targeting lipophagy may represent a promising strategy for stabilizing vulnerable plaques (Fig. 4).

Fibroblasts. Cardiac fibroblasts exhibit region-specific distribution patterns and undergo distinct phenotypic transitions during pathological remodeling. Following acute myocardial infarction (MI) and HF, F9 (FAP/POSTN^{+}) fibroblasts

differentiate into the POSTN lineage through PI3K-Akt and AGE-RAGE signaling rather than adopting an ACTA2$^+$ myofibroblasts phenotype (116). The transition of CD34$^+$ cells to FABP4$^+$ fibroblasts represents a critical fibrotic process, enhancing lipid storage via the PPARγ/Akt/Gsk3β pathway activation (117). Therapeutically targeting the NF-κB and Wnt/β-catenin/GSK3β pathways may mitigate pathological cardiac remodeling, including cardiac hypertrophy and fibrosis (118), underscoring how inflammatory signals govern fibroblast activation and differentiation. Lipotoxic intermediates, for instance, long-chain acyl-CoA, ceramide, acylcarnitine and DAG, can directly induce myocardial fibrosis (119). Hypoxia and cellular stress stimulate intracellular LD accumulation in fibroblasts. During early stage of myocardial fibrosis, cardiac fibroblasts proliferate excessively and excessive secretion of α-smooth muscle actin and alongside extracellular matrix (ECM) proteins generated in large quantities (116).

Fibroblasts-derived kinesin-like protein 23 (Kif23) activates the Ras homolog family member a pathway to enhance proliferation while suppressing LD hydrolase carboxylesterase 1d through ROCK1, thereby impairing FAO and promoting lipid accumulation in fibroblasts, and facilitating myofibroblast transformation (120). Thus, targeting Kif23 may represent a new direction for attenuating myocardial fibrosis. Nevertheless, additional investigation is required to define how LDs in fibroblasts contribute to myocardial fibrosis. Fully exploring the effects of cellular stress, inflammation, and LD accumulation on cardiac lipotoxicity represents a novel target for fibroblasts in DCM.

3. Effect of LDs on the pathogenesis of DCM

Regulation of metabolic substrates

Glucose. Elevated glucose levels promote the production of LDs, while excessive glucose and FFAs can damage peripheral neurons, disrupting the sympathetic nervous system's control over the heart (121). The conventional viewpoint points out that lipotoxicity is considered a key driver of metabolic heart disease. Nevertheless, certain investigations indicate that cardiac dysfunction in neutral lipid storage disorders resulting from genetic mutations in CGI58 and ATGL is predominantly influenced by CGI58 rather than ATGL. This indicates that LDs may have a possible correlation with glucose metabolism. CGI58, serving as a serine protease, responds to phosphorylation by PKA and subsequently cleaves the epigenetic regulator histone deacetylase 4 (HDAC4), producing the N-terminal polypeptide of HDAC4 (HDAC4-NT), HDAC4-NT transcriptionally repress Nr4a1 expression, which interacts with myocyte enhancer factor 2 (MEF2). Nr4a1 prevents CaMKII from driving HDAC4 to activate MEF2. This blocks MEF2 from subsequently activating the hexosamine biosynthesis pathway, a metabolism linked to protein O-GlcNAcylation. Consequently, the calcium-handling protein Stim1 avoids undergoing O-GlcNAcylation, thereby protecting cardiac function (8,31,57,122). ATGL is blocked by Plin5; however, the ablation of Plin5 does not affect gene expression involved in glucose metabolism, FAO, along with glycogen metabolism (123).

Glucose deprivation activates P38 to phosphorylate glycolytic enzyme phosphofructokinase, liver type (PFKL) at Thr331, converting it from a tetramer to a monomer. PFKL then acts as a protein kinase, phosphorylating Plin2 to enhance its interaction with CPT1A, therefore facilitating FA transfer, FAO and lipolysis. PFKL, which inhibits glycolysis during low glucose availability, is posited to promote the anchoring of PLIN2 to LDs' phosphorylation and mitochondria to modulate lipolysis. This direct transfer of FAs from glucose to LDs may prevent lipid accumulation and mitigate cellular lipotoxic damage (75).

BCAA. Clinical studies report elevated plasma concentrations of fibroblast growth factor 21 (FGF21) in patients with DCM. Animal experiments show that inhibiting FGF21 reduces PGC1α expression and upregulates CD36, leading to LD accumulation and cardiac dysfunction. PGC1α is a downstream factor of FGF21, effectively reduces blood glucose as well as lipid levels while enhancing insulin sensitivity. Under dual intervention of knocking down FGF21 and fasting, glucose production and ketone body synthesis are damaged, suggesting that FGF21 holds promise as a potent therapeutic target for DCM management (124,125). Alterations in BCAA and FGF21 signaling establish metabolic links between the heart and the liver.

BCAAs inhibit the PPARα-FGF21 axis in the liver and reduce FGF21 secretion in the liver, thereby upregulating the content of BCAA in the heart and the expression levels of zinc-finger and BTB domain-containing 7B and Lat1, activating mTOR signaling and inducing mitochondrial damage and cardiomyocyte apoptosis, ultimately accelerating myocardial fibrosis in mice with type 1 diabetes (126). Knockout of PPARα in mice induced a metabolic shift towards glycolysis, HIF1α, as well as augmented glucose metabolism alongside ECM remodeling, finally decreasing FAO (127). PGC1α is also involved in regulating the rate of glycolysis BRM-associated factor 60c facilitates the transition of oxidative muscle fibers to glycolytic muscle fibers via the PGC1α-PPARα-mTOR pathway, thereby preserving oxidative metabolism/glycolysis balance and enhancing mitochondrial function in rats with HF (128). The metabolic disorder of BCAA in cardiomyocytes results into an abnormal rise in the biosynthesis of LD as well as a reduction in FAO rate, which coincides with suppression of branched-chain alpha-ketoacid dehydrogenase (BCKDH) located in the ER and the excessive expression of AMPD3. Interestingly, there is a mutual repulsion between BCAA oxidation and glucose metabolism (83). In the DCM state, BCKDH cannot restrict the upregulation of AMPD3. Subsequently, the uncoupling of AMPD3 activation induces excessive adenine nucleotide degradation and ROS production. After knocking out BCKDH-E1α in cardiomyocytes, the expression levels of PPARα, CD36 and ATGL significantly increase, making the utilization of cardiac substrates more inclined towards FA, which is similar to the rat model of obese type 2 diabetes state (129).

FFAs. FFAs derived from food are transported to cardiomyocytes, with excess lipids stored in LDs and VLDL. VLDL and LDL transfer lipids to the heart and adipose tissue. As TAG reserve, LDs maintain the supply of circulating FAs and maintain cardiac lipid homeostasis and energy demand (130). Most of the TAGs constituting LDs come from lipoproteins

and NEFAs, and a small amount of FA is provided by the heart via *de novo* lipogenesis (DNL) pathway. This process activates transcription factors such as insulin-responsive SREBP1 and Farnesoid X Receptor (FXR), enhancing adipogenic gene expression to drive FA trafficking into the ER for neutral lipid synthesis (TAG and CE). Increased expression of DGAT2, which regulates TAG synthesis in prediabetes and type II diabetes, leads to abnormal nerve lipid signaling (131). In the presence of electronegative LDL (-), the intracellular levels of NEFA, TAG and ROS in cardiomyocytes lacking plin5 are substantially increased (132). Acetylcholine may reduce cardiomyocyte apoptosis through PLIN5, activating the interaction between LDL and mitochondria (133).

Management of oxidative damage in cells. The biogenesis and degradation of LDs finely regulate lipid homeostasis. Prolonged lipid excess in diabetic heart triggers the dysfunction in cardiomyocytes, macrophages, along with vascular endothelial cells, with lipotoxic injury being the primary cause. The response of cardiomyocytes to different kinds of FAs remains incompletely understood. Evidence suggests that lipotoxicity is closely tied to FA saturation levels, saturated FAs (SFAs), such as palmitate, hinder LD formation and inflict significant cellular damage. The activation of the ULK1 autophagy signaling cascade may be linked to the ROS-dependent NLRP3, driving IL-1β/IL-18 production, leading to subsequent insulin signaling disruption. Conversely, unsaturated FAs such as oleic acid encourage the accumulation of TAG in LDs and store excess palmitic acid in the TAG pool, thereby preventing palmitic acid from triggering apoptosis and consequently reducing lipotoxic cellular damage (134). The previously mentioned investigations have overlooked the potential excess of FAs, while an appropriate amount of palmitic acid can actually promote the formation of LDs.

The accumulation of TAG and stearoyl-CoA desaturase 1 in LDs enables endothelial cells to sequester palmitic acid and prevent the palmitoylation of ciliary proteins, which would otherwise lead to lipotoxic injury. Upon reinstating the supply of PA, ciliary homeostasis is restored, subsequently delaying AS (135). PA also activates the Toll-like receptor (TLR) 4/MyD88 pathway in macrophages, triggering expression of TNF-α and intercellular adhesion molecule-1 (136,137).

Impaired TAG synthesis within cells can trigger lipotoxicity, which is associated with the synthesis of lipotoxic intermediates. Elevated DGAT2 expression in type 2 diabetic mice promotes TAG synthesis (131). Myocardial-specific knockout of DGAT1 significantly reduces LD formation, leading to DAG and ceramide accumulation, which activate PKCα and induce cardiac dysfunction (138); conversely, overexpression of DGAT1 promotes TAG storage in LDs without harming the heart (139). Lipid overload upregulates CCAAT/enhancer-binding protein α (C/EBPα), increasing the transcription of reticulon 3 (RTN3), subsequently driving LD accumulation and cardiac dysfunction through the DGAT2-dependent RTN3-FABP5 pathway (140). Therefore, isolating TAG and promoting LD formation represent potential strategies to alleviate lipotoxicity.

Lipotoxicity is closely associated with ROS; ROS induces post-translational modifications of a-kinase anchor protein 121 (AKAP121), DRP1 as well as optic atrophy 1, enhancing mitochondrial fission and leading to mitochondrial dysfunction (141). Increased ceramide DAG levels activate NADPH oxidase to damage mtDNA and reduce ATP synthesis (142), ultimately impairing left ventricular compensatory function (143). Targeting Sirt5 to mediate CPT2 dessuccinylation and C1q/tumor necrosis factor (TNF)-related protein 3 to inhibit mitochondrial apoptosis can reduce lipotoxicity (144,145). CPT2 is a regulator of FA uptake, and further studies have confirmed the relationship between CD36 and lipotoxicity and ER stress. Endogenous H_2S stimulates Hrd1 to mediate S-sulfation to regulate VAMP3 ubiquitination and inhibit CD36 membrane translocation to reduce FA uptake. Exogenous H_2S can reduce ER stress and lipotoxicity (146,147).

SREBP1c represents another potential target for reducing lipotoxicity, p21-activated kinase 3 in the myocardium promotes SREBP1c expression to induce lipid peroxidation deposition through the mTOR/S6 kinase 1 pathway (148,149). SREBP1c activation linked to myocardial injury in patients with aortic stenosis and metabolic syndrome, and statins can trigger lipotoxic injury through the DNL pathway (149,150).

Inflammation and immune response

Participants in the process of inflammation. LDs first convert stored constituent lipids into active lipid mediator precursors, which then generate active lipid mediators that interact with cells to interact with cells and participate in inflammatory responses. FAs stored in LDs include SFAs, monounsaturated FAs and PUFAs, of which PUFAs are precursors of two key lipid mediators-pro-inflammatory eicosanoid compounds are mainly derived from ω6-PUFAs, while specific pro-resolved mediators (SPMs) are derived from ω3-PUFAs (151).

Active lipid precursors on the monolayer PL shells of LDs rely on cytosolic phospholipase A2α to produce lysoPLs and PUFAs such as arachidonic acid, eicosapentaenoic acid (EPA), along with docosahexaenoic acid. TAG releases PUFAs through the lipolytic pathway mediated by ATGL and HSL. During ATGL-regulated lipolysis, released FFAs act as agonists for FFA receptor 4 (FFA4), which in turn inhibits adenylate cyclase via G_i/o protein and reduces high levels of cyclic adenosine monophosphate (cAMP) in LDs and ER regions, thus balancing energy mobilization and storage. FFA4 thus regulates the lipolysis process at LDs through cellular endocrine signaling (152).

EPA inhibits TGFβ-mediated myocardial fibrosis via FFA4, possibly through its ability to activate PKC and induce phosphorylation of endothelial nitric oxide synthase (eNOS) (153). Cyclooxygenase (COX) co-localizes with 5-lipoxygenase on the LDs' surface, cooperatively regulating the generation of lipid mediators (154). Although eicosanoids and SPMs produced by COX and LOX have partial anti-inflammatory properties, immune and inflammatory responses can also be stimulated by these mediators via their interactions with receptors such as PPARs and TLRs (155). However, hypoxia-induced overexpression of the LD-associated protein (HILPDA) inhibits ATGL-mediated lipolysis and obstructs the generation of prostaglandin E2 as well as interleukin-6 (156). Similarly, the removal of HILPDA in adipose tissue reduced LDs' accumulation and lipid excess, although did not ameliorate inflammation, possibly due to tissue specificity (157).

As mediators of immune response. Research shows that viruses and bacteria can target and interact with LDs. The integration of ORF6 into the LD monolayer is mediated by its two amphipathic helices. ORF6 inhibits UBXD8-Plin2 binding in LD-mitochondrial interactions to enhance lipolysis, and it also promotes lipid synthesis by binding to DGAT1/2 at LD-ER contact sites. Finally, accelerated FAO provides energy for virus replication (84). It has been recently indicated that LDs are not just energy storage units but also help regulate immune responses in cells like macrophages. *Pneumococcus* accelerates LDs' accumulation in macrophages by producing ROS through glycerol-3-phosphate oxidase (158), *Mycobacterium tuberculosis* protein (Mtb) Ure C inhibits DNA repair in macrophages, genomic instability and intracellular micronucleus stimulation activate the cGAS-STING pathway, phosphorylating TBK1 and IRF3 to induce IFN-β to upregulate the scavenger receptor SR-A1 as well as promote the formation of LDs that provides energy for pathogen survival (114). Subsequently, Mtb activates the anti-glycolysis G protein-coupled receptor 109a, shifting macrophages from glycolysis to the ketone body synthesis pathway and accelerating foamy transformation (159). Thus, targeting the composition and formation of LDs may be a new direction for immunotherapy.

Avoiding organelle damage

Promotion of energy production. ROS are generated by the cytosolic nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) as well as mitochondrial ETC complexes I/II/III. Large amounts of ROS damage mitochondria and affect cellular homeostasis. Therefore, the presence of LDs makes it possible for cells to store excess FFAs and also relieves oxidative stress and reduces the accumulation of lipotoxic intermediates; storage of FAs occurs through their incorporation into neutral lipids' pools. In times of energy demand such as starvation and cellular nutrient deprivation, it is supplied to mitochondria to maintain energy production.

During energy stress, PDM facilitates targeted transfer of FA from LDs to mitochondria, rapidly replenishing energy deficits while mitigating lipotoxicity damage caused by FA accumulation (75). Besides PDM, LDs can transport FAs to lysosomes via an autophagy-dependent pathway for cytoplasmic release and mitochondrial energy supply. This mechanism appears better suited for energy-deficient states such as starvation (160,161).

Mitofusin 2 (Mfn2) enrichment after aerobic exercise reduces LD accumulation and increases FAO levels in PDM. Mfn2 acts as a mitochondrial outer membrane protein that enables mitochondria to link both LD and ER (162,163). It is hypothesized that PDM may promote FAO through a special pattern related to Mfn2 (164). After the interaction between Mfn2 and ATGL, the lipolysis of liver LDs, FA transport and the formation of more PDM are enhanced, and the ATP synthesis capacity and high FAO level of PDM are maintained (165). Mfn2 as well as LD-localized Hsc70 assemble into a complex to promote FA transfer in myocardial LDMC. Upregulation of Mfn2 after lipid overload may restore the coupling between LDs and mitochondria and reduce lipotoxicity-induced myocardial damage via the ubiquitin-proteasome degradation pathway (166).

However, the mechanisms of lipids' transfer from LDs to mitochondria remain uncertain. Investigations show that mitochondria and ER contact sites enlist seipin to accelerate LDs' biosynthesis and lipid transfer, mitigating neutral lipid accumulation. Mutations in the seipin protein can result in irregularities at the LD-ER contact interface, suggesting its potential role in regulating the construction of membrane bridges by stabilizing this contact interface (167). Seipin keeps the level of phosphatidic acid in the ER under control and achieves protein transport through LD-ER contact, transferring TAG to nascent LDs and counteracting the shrinkage of small LDs induced by LD maturation (168,169).

Seipin forms a complex with Oxysterol binding protein-related protein 5 (ORP5) and ORP8 within the PA-enriched mitochondrial-associated membrane subdomain. ORP8 enhances interaction with ORP5 via a coiled-coil domain, maintaining lipid transport across the mitochondrial ER-LD tri-interface and promoting LD biogenesis (67). This mechanism is widely conserved in mammals. Additionally, there are two necessary factors for Plin5 transferring FAs from LDs to mitochondria: Plin5 requires PKA-mediated phosphorylation at serine 155 and an intact C-terminal domain (31). Its interaction with the chaperone ACSL4 at the MCS enables the conversion of FA into acyl-CoA for FAO, completing the lipid movement from LDs to mitochondria (170,171).

Release of ER stress. ER stress, featured by insufficient protein folding capacity, calcium ion imbalance as well as lipid metabolism disorder, is a key metabolic feature of DCM (172). Increased intracellular lipid accumulation induces ER stress and LD formation. It has been suggested that ER stress can degrade Plin2 and inhibit the generation of LDs (48), therefore it can be concluded that LDs and ER stress influence each other. Researchers point out that ROS-triggered ER stress in DCM induces cardiomyocyte apoptosis mainly through protein kinase RNA-like ER kinase (PERK) pathway, but not IRE1 or activating transcription factor (ATF) 6 signaling pathways (173). At this time, G protein-coupled receptor 78 (GPR78) dissociates from PERK, and PERK activates the eukaryotic translation initiation factor 2 subunit α/ATF4 pathway to enhance cardiac autophagy and alter normal myocardial morphology (174).

LDs likely represent a common therapeutic for mitigating ER stress and preserving lipid homeostasis. Patients with HF with preserved ejection fraction exhibit decreased LDs and PDMs, abnormal LD dynamics, lipid overload, and downregulation of X-box binding protein 1 (XBP1), which affects the ER degradation enhancing alpha mannosidase-like protein 2 (EDEM2), which regulates protein glycosylation, endoplasmic reticulum-associated degradation, and maintains ER stability (175). The absence of XBP1 or EDEM2 in cardiomyocytes leads to decreased cardiac systolic function and exacerbates LD formation and lipid disorders. Under excessive FFA stimulation, EDEM2 interacts with SEC23A in an ATGL-dependent manner to efficiently alleviate lipotoxic damage, including myocardial LDs' accumulation and elevated TAG and DAG levels (176). These data suggest that enhancing cellular lipid oxidation and accumulating comparatively 'non-toxic' lipids to partially regulate lipid flow may be a viable approach to reduce lipotoxicity (177).

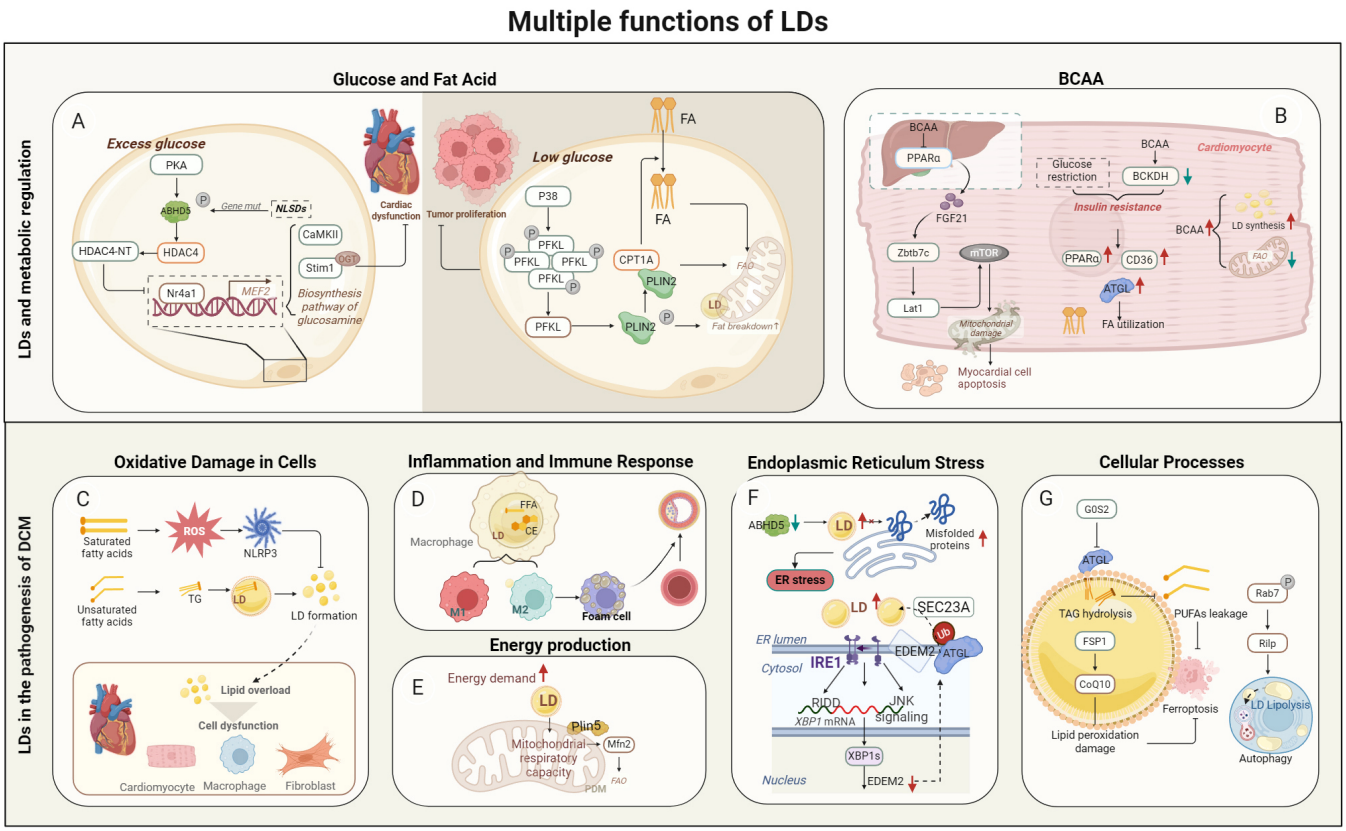

Figure 5. Multiple functions of LDs. (A) Excessive glucose stimulation of ABHD5 inhibits MEF2-triggered hexosamine synthesis pathway and Stim1 protein expression through HDAC4 to protect the heart. During glucose deprivation, PFKL enhances the binding of Plin2 to CPT1A to promote FAO and lipolysis. (B) BCAA and FGF21 achieve the metabolic link between heart and liver. When cardiac BCAA metabolism is impaired, BCKDH is decreased and AMPD3 is increased, resulting in increased LD biosynthesis and decreased FAO rate. (C) Difference in lipotoxic damage caused by the formation of LD by saturated fatty acids and unsaturated fatty acids. (D) LD affects macrophage polarization, foam cell formation, and accelerates the formation of atherosclerotic plaques. (E) Plin5 promotes PDM to enhance FAO. (F) Downregulation of ABHD5 leads to blocked lipolysis and increased LD accumulation, which is caused by abnormal LD biosynthesis and increased accumulation of unfolded protein inducing ER stress. By upregulating EDEM2, XBP1s promotes the SEC23A-dependent translocation of ATGL and prevents its degradation, thereby alleviating myocardial lipotoxicity. (G) LD regulates normal cell division, autophagy, and ferroptosis. LD accumulation increased in the cell cycle arrest state, and G0S2 inhibited ATGL-regulated lipolysis. Impairment of FSP1 significantly induces peroxidation of PUFA-LDs leading to ferroptosis of cardiomyocytes. Rab7 and Rilp mediate macrolipophagy of LD. LDs, lipid droplets; HDAC4, histone deacetylase 4; PFKL, phosphofructokinase, liver type; FAO, fatty acid oxidation; BCAA, branched-chain amino acid; ER, endoplasmic reticulum; ROS, reactive oxygen species; TG, triglyceride; NLRP3, NLRP3, NOD-like receptor thermal protein domain associated protein 3; ATGL, adipose triglyceride lipase; PUFA, polyunsaturated fatty acid-rich; XBP1, X-box binding protein 1; Rilp, Rab-interacting lysosome protein; Mfn2, mitofusin 2; Coq10, coenzyme Q10; PPAR, peroxisome proliferator-activated receptor; G0S2, G0/G1 switch 2 gene.

Regulation of cellular processes. LDs participate in the regulation of normal cell division, ferroptosis, autophagy as well as other cellular processes and indirectly affect the progression of DCM. LD regulates normal cell division and induces DGAT-dependent LD biosynthesis during cell cycle arrest. The G0/G1 switch 2 gene (G0S2) inhibits ATGL-mediated TAG hydrolysis and prevents excessive leakage of PUFAs within TAG, which is essential for LDs to protect cells against ferroptosis (178). During iron depletion, cells enhance LD biosynthesis through the DGAT1-dependent pathway to regulate mitophagy and maintain cellular homeostasis (179).

During the process of DCM micro-autophagy, Rab7 is phosphorylated at the 183 site of tyrosine and interacts with Rab-interacting lysosome protein (Rilp) to accelerate the lipolysis of LDs via the lysosomal pathway (81). Additionally, RAB18 may regulate the process of autophagy by downregulating adipogenic genes' expression and reducing TC and TAG levels. RAB18 knockout did not affect lipolysis gene expression, but the liver lipophagy was weakened and LD accumulation was observed in mice (180). While RNA is mainly involved in the transmission of genetic information, it was recently revealed that RNA regulates lipid metabolism (181). Previous experiments have shown that overexpression of LIPTER can alleviate cardiac dysfunction and ameliorate cardiomyopathy in mice, and that LIPTER in cardiomyocytes connects long non-coding RNAs to strengthen the connection between LDs and actin by binding PA/Phosphatidylinositol-4-phosphate and interacting with myosin heavy chain 10 protein, facilitating LD transfer (182) (Fig. 5).

4. Role of LDs in the pathological progression of DCM

Lipid steatosis. Abnormal cardiac LD accumulation constitutes a key feature of cardiac steatosis in diabetic patients. It is associated with a large accumulation of TAG and an enhanced lipolytic barrier in the heart after overexpression of Plin5 (64,183). This imbalance in LD dynamics accelerates ventricular remodeling and cardiac dysfunction. Studies in

PPARα knockout mice have shown reduced TAG accumulation after fasting, while normal mice fasting for 16-48 h exhibit an upregulation of Plin2 expression and a concurrent increase in accumulation of LDs (184), suggesting that LDs can provide energy supply. Cardiac lipid accumulation is independent of systemic metabolism, and PPARα downregulation itself does not induce cardiac pathology (185).

During starvation, vacuolar protein sorting-associated protein 13D (VPS13D), endosomal sorting complex required for transport protein tumor susceptibility 101, along with adaptor-binding domain of VPS13, facilitate FAs transport at the LDMC site to achieve high-efficiency oxidation (186). This pathway may become dysregulated in diabetic hearts due to chronic energy excess.

LD-associated proteins form a complex regulatory network in the heart. Reduced expression levels of ATGL and CGI58 jointly impair lipolysis, which instead increases TG synthesis, promotes cardiac steatosis, and raises oxidative stress levels (65). Plin2 is involved in regulating LDL hydrolysis, and the increased TAG accumulation following Plin2 knockout may be associated with lipophagy. Overexpression of Plin2 reduces HSL levels, suggesting that energy stress during metabolic remodeling stimulates Plin2 to enhance lipase affinity for LDs, consequently exacerbating cardiac steatosis and dysfunction (53,187).

Plin5 inhibits lipolysis to preserve TAG storage within LDs, thereby limiting the rate of FAO and reducing excessive oxidative stress in heart. Upon Plin5 knockout, the upregulation of PPARα as well as PGC-1α induces mitochondrial proliferation, resulting in higher FAO and lipolysis, which can worsen cardiac hypertrophy potentially leading to HF (188). The deletion of Plin5 exerted no notable impact on heart function. During fasting, Plin5 associates with Rab8a in skeletal muscle and collaborates with ATGL, this process couples LCFAs transfer from LDs to mitochondria, indicating that Plin5 may have a cardioprotective effect through preserving mitochondrial integrity (64,189).

Myocardial fibrosis. Myocardial steatosis and fibrosis are the basis of ventricular remodeling in DCM. Computed tomography scans of patients with MI have revealed substantial lipid deposition (190). Reduced expression of eNOS at the infarct site exacerbates abnormal myocardial lipid accumulation. This in turn promotes LD formation, increases oxidative stress, and activates the TGFβ/TβRII pathway, phosphorylating Smad2/3, inducing Smad4 to modulate transcription of ECM genes and hindering myocardial repair (190,191).

Macrophages also help regulate fibroblast activation through IL-1β and its downstream target mesenchyme homeobox 1 (116). In fact, the process of macrophage-to-myofibroblast transition (MMT) may involve LD regulation. In chronic pancreatitis, high expression of mitochondrial uncoupling protein 2 (UCP2) regulates ACSL3 to promote acinar cell release of LDs. Stimulation of SIRT1 and activation of downstream TGF-β/Smad3 signal transduction affect MMT and fibrosis process, while whether UCP2 has a similar regulatory effect still needs to be explored (192).

In this process, ATGL-dependent lipolysis promotes FA accumulation and inhibits ECM remodeling in fibroblasts (193). Low levels of CGI58 in the heart decrease the lipolysis rate and aggravate oxidative stress and myocardial steatosis (65). This indicates that the regulation of lipolysis is particular to cell type.

In addition to lipid metabolic disorders, alterations in cardiomyocyte energy metabolism are also considered to indirectly affect fibrosis progression (194). Wilms' tumor 1-associating protein promotes AR methylation in a YTHDF2-dependent way, subsequently promoting FAO proliferation, along with cardiac fibroblasts migration (195).

Direct investigations of cardiac fibroblasts and LDs are limited; however, alternative cellular models offer insights. In mouse embryonic fibroblasts, FAs generated by non-specific autophagy can be directed to LDs. This process is considered a protective regulatory technique, as LDs sequester excess FFAs to mitigate lipotoxicity (196). DGAT1 can channel FFAs generated during mTORC1-regulated autophagy to TAG-rich LDs, which then hold onto the FAs and reduce mitochondrial damage caused by acylcarnitine accumulation (160). TANGO2 is associated with LDs and the ER to modulate acyl-CoA metabolism. The cardiomyopathy and arrhythmia caused by the TANGO2 mutation may result in disturbance of LDs' morphology, function, and neutral lipid metabolism homeostasis. Consequently, lipid peroxide levels in TanGO2-deficient fibroblasts were raised metabolized, and LDs increased (197). Patients with neutral lipid storage disease with myopathy exhibit muscular, cardiac and hepatic impairment due to defective LD functions, similar to cells deficient in ATGL or CGI58, therefore providing a suitable model for investigating LD function (198). Collectively, these findings suggest that LDs may influence cardiac steatosis and myocardial fibrosis.

5. Main effects of different drugs on lipid metabolism and LDs on DCM

Cardiac lipid-lowering therapeutics have gained substantial research attention over recent decades. Emerging strategies now target multiple approaches of cellular lipid homeostasis, including biosynthesis, uptake, trafficking and catabolism, with the dynamic regulation of LDs representing a critical target. Currently, pharmacological approaches targeting LDs encompass three principal mechanisms: Modulating lipid metabolism to prevent excessive accumulation, indirectly suppressing LD biogenesis, and promoting LD degradation through enhanced lipophagy or lipolysis pathways (197,199).

Statins lower blood lipids by blocking the mevalonate pathway, inhibiting Rho/Ras/Rac, and activating PPARα/β, resulting in anti-inflammatory pleiotropic effects (200,201). They also downregulate the expression of Plin5 in hepatocytes (202). However, long-term usage of activated cardiac SREBP1 to speed up the process of DCM may make myocardial lipid deposition and lipid peroxidation worse (149). Niacin reduces the progression of atherosclerosis by diminishing the synthesis of proinflammatory cytokines by macrophages (203). It also facilitates reverse cholesterol transport through adipocyte lipolysis via the cAMP/PKA and 15d-PGJ2/PPARγ pathways, inhibits the expression of Plin4 in neuroblastoma to prevent the formation of LDs and promotes macrophage polarization to the anti-inflammatory M2 type (204,205). However, the regulating mechanism of cardiac LDs remains ambiguous. CL2-57, an ABCA1 inducer that targets cholesterol transport, promotes cholesterol efflux

from macrophages, reduces inflammation, and prevents lipid abnormalities caused by LXR agonists (206,207). The MEK1/2 inhibitor (U0126) in conjunction with the LXR ligand (T0901317) modulates lipid metabolism through lipolysis and FAO to reduce LXR-associated adverse effects (208). IL4 via the STAT6/PPARγ axis, boosts ABCA1/ABCG1 expression, decreases lipid overload and foam cell formation, and stimulates M2 polarization to control late adipogenic phase suppression, which prevents inflammation and formation of LDs (199). Notably, IL4 did not influence C/EBPβ and PPARγ in lipogenesis and lipid metabolism during the first phase of lipid synthesis, nor did it affect HSL. Moreover, ezetimibe impedes cholesterol absorption (209,210). In addition, ezetimibe can accelerate LDs synthesis through LD-mitochondrial membrane contact sites, store excess FAs in LDs, reduce lipotoxic damage, and at the same time, LDs degradation may also be accelerated, thus alleviates podocyte apoptosis (211). It indicates that LD-organelle interaction may serve as an effective target for intervention. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors enhance LDL-LDLR binding by preventing LDLR degradation and promoting lipophagy to eliminate lipids (212), with PCSK9 mediating lipid degradation independently of LDLR (213). Inclisiran, a small interfering RNA targeting PCSK9, significantly reduces LDL-C levels in patients with cardiovascular risk (214). This effect may be associated with the suppression of AKT activation, affecting downstream mTOR and the facilitation of ULK1 kinase complex formation, which regulates Beclin1 and enhances the degradation of intracellular lipids via lipophagy (215).

Short-term continuous and excessive administration of prednisolone substantially elevates the mRNA levels of CGI-58, CEIDE-C and CEIDE-A in serum FA and adipose tissue and reduce the expression of G0S2 mRNA. CIDE proteins block ATGL-mediated lipolysis and promote lipid storage (216,217), indicating that prednisolone is involved in both lipolysis and lipid storage through complex pathways and alleviates insulin resistance by inhibiting insulin receptor phosphorylation and Akt activation (218,219).

Fibrates, such as fenofibrate, activate PPARα to reduce blood glucose and lipid levels, modulate insulin resistance, markedly enhance cardiac function, and maintain glucose metabolism via the downstream Nr4a1/hexokinase 2 pathway. They also enhance the sirtuin 3/superoxide dismutase 2 pathway to achieve anti-oxidative stress (122,220). Furthermore, the elevation of LC3 and SQSTM1 in a diabetic condition hinders the heart's autophagic capacity, potentially linked to the formation of LD and macrophage foam cells. Fenofibrate restores autophagy ability through FGF21/SIRT1 to alleviate macrophage foam cell formation and myocardial fibrosis caused by LD accumulation (221).

Pemafibrate, a novel PPARα agonist, also improves cardiac diastolic function in diabetic patients (222). Thiazolidinediones, such as troglitazone, reduce lipotoxicity through AMPK activation, but full-acting PPARγ agonists are associated with obesity and cardiac risk (223,224). However, the incomplete agonist dihydrosanguinarine is safer, reducing LD accumulation and enhancing glucose uptake (225). SGLT2i inhibitors exhibit multidimensional cardioprotection: Empagliflozin regulates autophagy balance through AMPK/GS3Kβ and mTOR/ULK1 pathways (79). *In vitro* models of SGLT2i inhibitors all increase LD biosynthesis in a DGAT1-dependent manner, but the specific pathways differ. Canagliflozin does not reduce LD formation in vascular endothelium via an AMPK-dependent pathway, while empagliflozin may reduce lipogenesis through the SREBP1/PPARγ pathway (226,227). In the meantime, empagliflozin also reprograms energy metabolism in podocytes, inhibiting glucose utilization and switching to FAs for energy, enhancing lipolysis and ketone body formation, providing additional fuel for the heart, and alleviating ER stress and lipotoxicity, which is extremely similar to metabolism shift observed in the diabetic heart (228-230). In summary, as the intersection of metabolism and inflammation, the formation and decomposition of LDs and the targeted intervention of cellular homeostasis constitute an emerging therapeutic frontier in DCM.

Despite gaining substantial progress, investigations of LD biology in DCM exhibit critical knowledge gaps. Studies on LDs in cardiac fibroblasts and vascular endothelial cells remain markedly underdeveloped, while the existing studies on macrophages have predominantly focused on M1 and M2 polarization states, neglecting other types related to DCM pathogenesis. The present review predominantly explores the role of LDs in DCM and does not comprehensively address their involvement in other heart diseases, such as atherosclerosis and HF. Exploring dynamic functions of LD across diverse cardiovascular diseases would provide comprehensive insights into their regulatory mechanisms and therapeutic potential in the heart.

6. Conclusions and prospects

Contemporary understanding of LD evolved beyond their classical role as inert lipid reservoirs to recognize their multiple regulatory functions in metabolic substrates, oxidative stress responses, inflammation, immunity, and cellular processes such as autophagy and ferroptosis, ER stress.

LDs sequester excess lipids through diverse mechanisms, effectively mitigating the accumulation of lipotoxic intermediates that trigger cellular oxidative damage. In addition, LDs catabolize stored lipids to supply FAs for oxidation and delay cardiac energy depletion. Under pathological conditions, lipophagy attenuates myocardial injury induced by glucotoxicity and lipotoxicity while delaying myocardial fibrosis remodeling and macrophage foam cell formation. LDs participate extensively in cell proliferation, development and signal transduction, with LD-associated proteins maintaining cellular metabolic homeostasis through protein-protein interactions that modulate signaling cascades. However, research on macrophages and fibroblasts remains in its infancy. As central hubs of lipid metabolism, LDs critically influence metabolic homeostasis, and their dysregulation drives metabolic imbalance in DCM. Therapeutic strategies targeting LD accumulation include modulating lipid metabolism, interfering with Plin2 or DGAT1 to inhibit biogenesis, and promoting lipophagy and lipolysis to accelerate degradation. PDM localize at LD surfaces and establish functional coupling that facilitates metabolic exchange, suggesting that mitochondrial-directed interventions, including regulation of FAO rate or antioxidant treatment, may alleviate LDs accumulation. However, the safety profiles and off-target effects of these approaches remain incompletely characterized,

and existing pharmacological agents exhibit significant adverse effects that necessitate mechanistic clarification for rational drug development. Understanding of the regulation of heart function by LDs remains limited. The mechanism of action of LDs in each stage of DCM still needs to be studied, and the impact of the cellular heterogeneity of LDs on the occurrence of DCM remains unclear. The development of related drugs targeting LD to reduce lipid deposition holds great promise for the treatment of DCM.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YL was responsible for conceptualization of the review, literature search, drafting of the manuscript, and visualization of table and graphs. XF conceived the study, wrote the original manuscript and prepared the figures. XG, YJ, WS, XSu, JG and GY curated data and collected references. BZ, ZZ, YK and XSh organized the table, JZ acquired funding and contributed to writing review and editing. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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