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Review

Perilipin 5: Multifunctional Regulation of Lipid Droplet – Mitochondria Coupling in Glucose and Lipid Metabolism

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Abstract

Perilipin 5 (Plin5), a lipid droplet-associated protein highly expressed in oxidative tissues such as the heart and skeletal muscle, serves as a master regulator of fatty acid oxidation and glucose-lipid metabolism. Beyond its role in metabolic homeostasis, Plin5 is also essential for modulating thermogenic processes in brown adipose tissue (BAT). Plin5 facilitates the physical and functional coupling between lipid droplets (LDs) and mitochondria by maintaining lipid homeostasis, reducing lipotoxicity, and enhancing insulin sensitivity. Through signaling molecules, such as peroxisome proliferator-activated receptor alpha (PPARα), peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), and AMP-activated protein kinase (AMPK), Plin5 coordinates multiple metabolic pathways that regulate fatty acid storage and utilization in the heart, thereby supporting systemic energy balance and mitigating myocardial injury under metabolic stress. Exercise training increases Plin5 expression in skeletal muscle, promotes intramuscular fat storage, and contributes to metabolic adaptation. This narrative review examines the mechanisms underlying Plin5 function and summarizes recent findings regarding its role in regulating glucose and lipid utilization in cardiomyocytes and skeletal muscle. These insights may be helpful for the identification of strategies for managing glucose and lipid metabolism disorders.

Keywords: Perilipin 5; lipid droplets; mitochondria; glucose-lipid metabolism

1. Introduction

The energetic demand of cardiac and skeletal muscle is staggeringly high, necessitating a tightly regulated metabolic balance between carbohydrates and lipids [1,2,3]. At the heart of this process are lipid droplets (LDs), once dismissed as inert storage depots but now recognized as dynamic and essential reservoirs for neutral lipids [4]. In higher animals, where continuous, high-intensity contractile activity is physiologically required, the stability of this fuel supply becomes essential for survival [2]. However, the role of LDs extends far beyond providing a simple caloric reserve; they function as hubs for metabolic signal transduction and serve as a vital front-line defense against lipotoxic cellular damage [5]. As understanding of these organelles has expanded, attention has shifted to the proteins that coat them, with the Perilipin family emerging as central regulators of lipid organization [6].

Despite the overarching role of the Perilipin family in lipid droplet regulation, the functional contributions of individual members vary considerably across tissues. The family comprises five structural relatives (Plin1–Plin5) that share largely conserved domains, although each exhibits a distinct, tissue-specific fingerprint [7]. Specifically, Plin1 is the most extensively studied member and is predominantly expressed in white adipose tissue (WAT) and, to a lesser extent, in brown adipose tissue (BAT), where it serves as a critical gatekeeper of lipolysis by regulating the access of lipases such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) to the lipid droplet surface in a protein kinase A (PKA)-dependent manner [6,8,9,10]. Plin2 (formerly known as adipose differentiation-related protein, ADRP) is ubiquitously expressed and plays a constitutive role in lipid droplet biogenesis and stabilization across virtually all cell types [11]. Plin3 (also known as TIP47) is similarly broadly distributed and was originally implicated in intracellular vesicular trafficking [12], although a subsequent study has redirected attention to its role in lipid droplet formation and nascent lipid droplet stabilization [13]; its precise mechanistic contributions, however, remain less well defined. Plin4, the least characterized member, is expressed primarily in white adipose tis-

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sue, where it has been suggested to contribute to the coating of nascent lipid droplets, although its non-redundant functions, if any, remain to be fully elucidated [14]. While these family members collectively establish the organizational framework for lipid droplet homeostasis, none of them possesses the unique capacity to physically tether lipid droplets to mitochondria [15]. This distinctive property, combined with its preferential enrichment in tissues with the highest rates of fatty acid oxidation, positions Plin5 as a non-redundant metabolic integrator rather than a simple structural coat protein. It is for these reasons that the present review focuses specifically on Plin5 and its multifaceted roles in oxidative tissues [16].

Among them, Plin5 has emerged as a particularly important protein because of its high expression in highly oxidative tissues, namely cardiac muscle, skeletal muscle, the liver, and brown adipose tissue (BAT) [15]. This tissue distribution closely mirrors oxidative metabolic capacity, establishing the expression pattern that underlies the tissue-specific roles discussed throughout this review. Rather than functioning as a passive anchor, Plin5 acts as a metabolic bridge between lipid droplets and mitochondria, coordinating fatty acid mobilization with oxidative demand [16]. A recent study suggests that Plin5 plays roles beyond structural organization and may function as a regulator of cellular substrate utilization and modulate insulin sensitivity through a complex signaling network involving key metabolic regulators such as peroxisome proliferator-activated receptor alpha (PPARα), and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) [17].

The global health burden imposed by metabolic diseases-including diabetes, cardiomyopathy, and obesity-has become increasingly evident [18,19]. These conditions reflect a fundamental disruption in the delicate glucose-lipid equilibrium that Plin5 helps maintain, positioning this protein as a promising target for therapeutic intervention [20,21]. This narrative review examines the mechanisms by which Plin5 orchestrates metabolic harmony in the heart and skeletal muscle. By synthesizing recent advances in energy adaptation and pathological remodeling, we aim to provide a comprehensive overview of how this protein regulates metabolic homeostasis under both physiological and pathological conditions.

2. Overview of Lipid Droplets and Perilipin Proteins

LDs are specialized intracellular organelles characterized by a hydrophobic core of neutral lipids, predominantly triacylglycerols (TAGs) and cholesteryl esters (CEs), that are encapsulated within a unique monolayer phospholipid membrane densely populated with structural proteins and functional enzymes [22]. Although lipid droplets were once considered simple energy storage units, recent research indicates that they actively regulate multiple cellular pathways. As currently understood, their functional repertoire extends far beyond simple storage to include maintaining energy balance, mitigating lipotoxicity, regulating substrate flux, preserving redox homeostasis, and modulating complex stress responses [4]. This regulatory function is particularly essential in high-demand metabolic environments. In the liver, cardiac muscle, and skeletal muscle, lipid droplets serve as metabolic hubs, coordinating fatty acid supply with cellular energy demands [23] (Fig. 1).

The functional integrity of LDs depends on the assembly and regulation of their surface components, among which the Perilipin (Plin) family of proteins plays a central role [6]. Despite their diverse physiological functions, all five family members (Plin1–Plin5) share a conserved N-terminal PAT, Perilipin, ADRP, TIP47 (PAT) domain. This structural feature facilitates their stable association with the LD membrane and enables the precise modulation of lipolytic reactions that are fundamental to lipid metabolism [24]. While the tissue-specific distribution and functional specialization of Plin1–4 have been outlined in Section 1, the following discussion focuses on Plin5, which adapts this shared structural framework to meet the extreme metabolic demands of highly oxidative tissues.

In highly oxidative tissues, Plin5 adapts this regulatory framework to meet extreme metabolic demands. Plin5 (also known as oxidative tissues-enriched PAT protein (OXPAT) or lipid storage droplet protein 5 (LSDP5)) exhibits the most specialized functional characteristics within the Perilipin family [25,26]. Consistent with the tissue distribution described above (Section 1), Plin5 is most abundant in organs with the highest rates of fatty acid oxidation. Beyond its roles in membrane anchoring and structural stabilization, the C-terminal domain of Plin5 uniquely enables the formation of lipid droplet-mitochondria coupling complexes (LDMCs) [15]. These complexes serve as the primary structural and functional platform through which Plin5 channels fatty acids from LDs directly to the mitochondrial oxidation machinery, while simultaneously providing cytoprotection against lipotoxicity [27] (Fig. 2). This bridging function constitutes the defining feature of Plin5 within the Perilipin family and underpins its roles discussed throughout this review.

A recent study has organized the multifaceted roles of Plin5 within a three-tier functional framework of sensing-regulation-execution [20]. At the sensing level, Plin5 acts as a metabolic sensor whose expression is rapidly upregulated via PPARα-dependent transcriptional signaling during energy deficits such as fasting or intense exercise [25,28]. At the regulation level, Plin5 serves as a gatekeeper of the lipid reservoir, selectively suppressing non-specific lipolysis while recruiting the α/β-hydrolase domain-containing protein 5 (ABHD5)-ATGL lipolytic machinery for targeted fatty acid mobilization [29]. At the execution level, LDMCs channel liberated fatty acids toward mitochondrial β-oxidation, preventing cytoplasmic accumulation and ox-

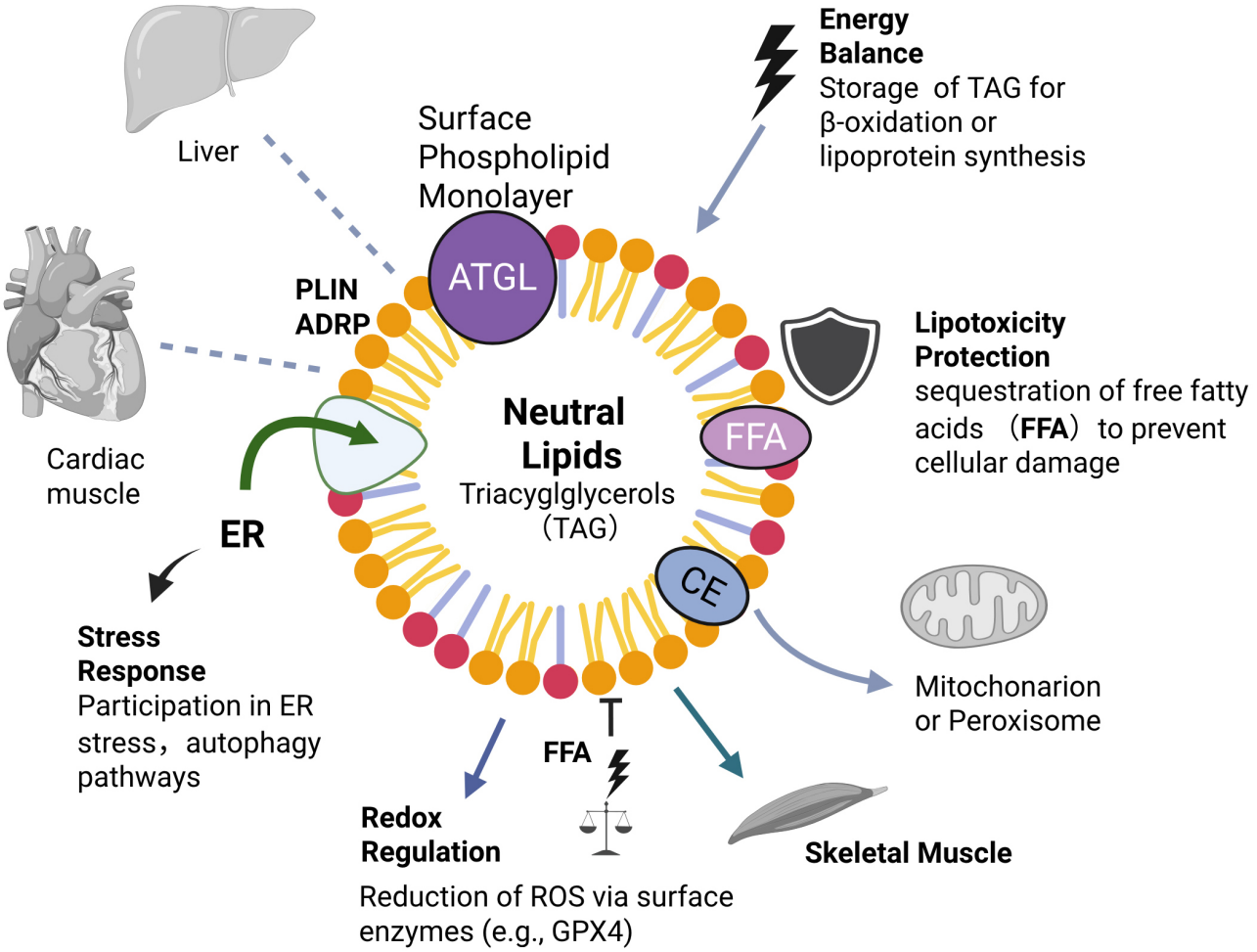


Fig. 1. Multifunctional roles of lipid droplets in cellular homeostasis. Lipid droplets regulate energy balance by storing triacylglycerol that can be used for β-oxidation or lipoprotein synthesis. They also protect cells from lipotoxicity by sequestering free fatty acids, participate in cellular stress responses through pathways such as ER stress and autophagy, and modulate redox balance by limiting ROS, partly via GPX4, which may associate with lipid droplet surfaces. Lipid droplets are widely distributed in the liver, cardiac muscle, and skeletal muscle. In these tissues, they interact with organelles such as mitochondria, peroxisomes, and the endoplasmic reticulum to coordinate lipid flux and maintain cellular metabolic homeostasis. Solid arrows indicate direct metabolic flux or activation. Dashed lines represent indirect or regulatory associations. Blunt-ended lines denote inhibitory or protective effects. These notations reflect tissue-specific roles, including oxidative coupling in cardiac and skeletal muscle, as well as lipid buffering and lipoprotein synthesis in the liver. Abbreviations: TAG, triacylglycerol; FFA, free fatty acid; CE, cholesteryl ester; Plin, Perilipin; ADRP, adipose differentiation-related protein; ATGL, Adipose triglyceride lipase; ER, Endoplasmic reticulum; ROS, Reactive oxygen species; GPX4, glutathione peroxidase 4. Created in BioRender. Wang, L. (2026) https://BioRender.com/9oilk8v.

idative damage [30]. The molecular mechanisms underpinning each tier are examined in subsequent sections: the PPARα-PGC-1α signaling network governing the sensing phase (Section 5), the phosphorylation-dependent regulatory switch (Sections 3 and 5), and tissue-specific fatty acid channeling in the heart and skeletal muscle (Sections 3 and 4). This multilayered regulatory model has received direct structural support from Miner et al. [31], who employed advanced three-dimensional electron microscopy to visualize Plin5-mediated bridging structures that physically tether lipid droplets to mitochondria.

Plin5 also integrates multiple metabolic signaling networks, including the PPARα-PGC-1α axis [17], the PKA-dependent phosphorylation cascade [32], and the Sirtuin 1 (SIRT1)-mediated transcriptional regulation pathway [21]. Collectively, these signaling networks constitute an integrated effector platform that supports lipid droplet function and mediates intracellular signal transduction. Comprehensive analyses indicate that the Perilipin family, particularly Plin5, plays an essential role in lipid droplet biology through multiple mechanisms. These include maintaining structural integrity [6,24], regulating lipolysis [29], fa-

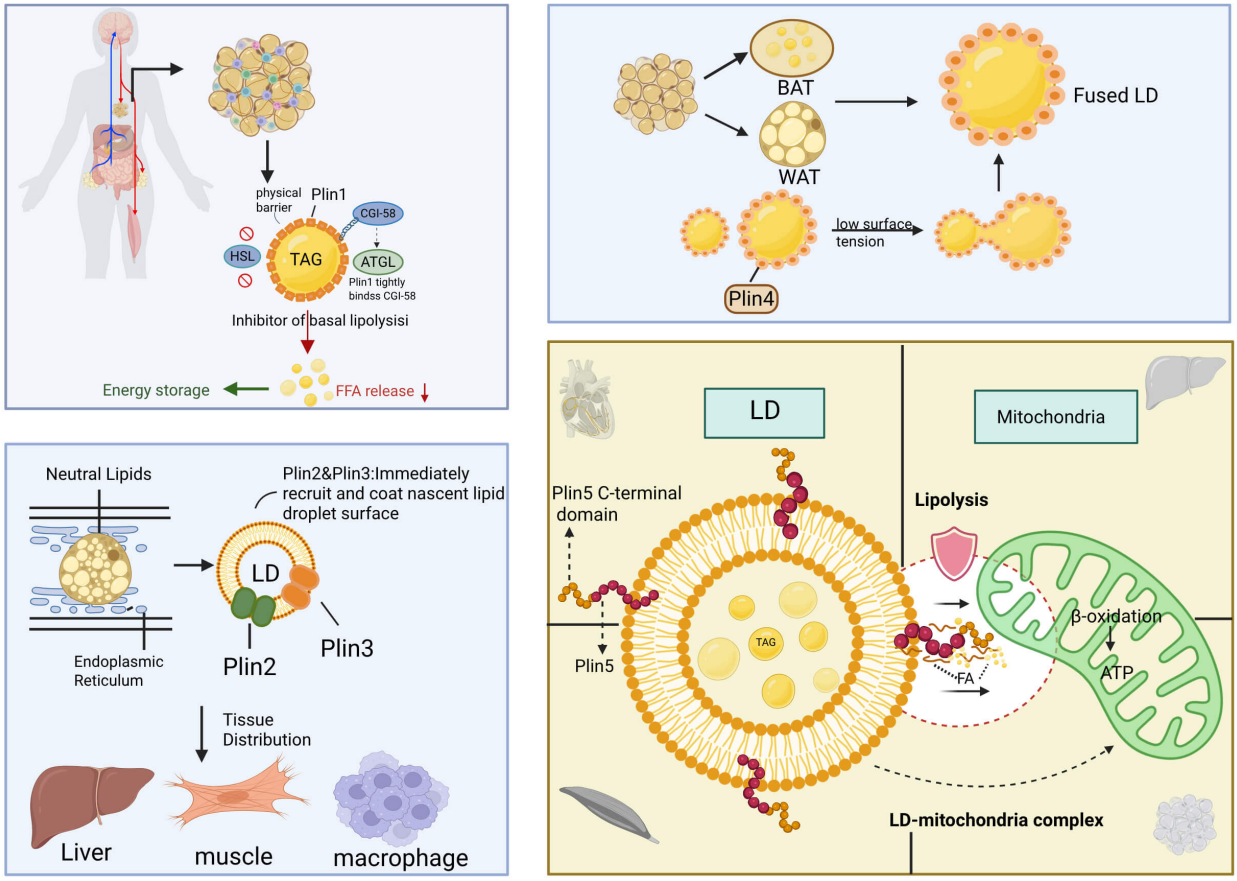


Fig. 2. Distribution and functions of perilipin family proteins. Upper left: Plin1 regulates lipolysis by controlling the access of HSL and ATGL to lipid droplets. Upper right: Plin4 mediates lipid droplet fusion in brown adipose tissue (BAT) and white adipose tissue (WAT). Lower left: Plin2 and Plin3 rapidly recruit and coat nascent lipid droplet surfaces and are widely distributed across tissues and cell types, including the liver, muscle, and macrophages. Lower right: Plin5 forms lipid droplet-mitochondria complexes to regulate fatty acid oxidation and ATP production. Abbreviations: TAG, triacylglycerol; LD, lipid droplet; FFA, free fatty acid; HSL, Hormone-sensitive lipase; ATGL, Adipose triglyceride lipase; ATP, Adenosine triphosphate. Created in BioRender. Wang, L. (2026) https://BioRender.com/mg6yqdx.

cilitating mitochondrial coupling [15], and integrating systemic metabolic signals [17].

3. Plin5: A Molecular Bridge and Regulatory Switch Orchestrating Cardiac Energy Homeostasis and Metabolic Flexibility

Myocardial metabolic efficiency is closely linked to the regulatory functions of lipid droplet (LD)-coating proteins, among which Plin5 serves as a key structural and functional component [33]. As the predominant LD surface protein in the myocardium, Plin5 is positioned to coordinate the lipid mobilization, aerobic respiration, and continuous LD stabilization required for sustained cardiac FAO [15,34]. In the myocardium, the LDMC architecture mediated by Plin5 is of particular functional importance. These contact sites act as high-efficiency metabolic corridors that optimize fatty acid delivery for oxidation while shielding against lipotoxic injury [33,34] (Fig. 2).

The necessity of this structural interaction becomes most evident under metabolic stress. Although global Plin5 knockout mice often appear phenotypically normal under basal conditions, their underlying metabolic fragility can be unmasked by challenges such as acute fasting [31], strenuous exercise, or chronic high-fat diet (HFD) consumption [35]. Exposing these animals to such stressors can trigger a pathological cascade, including excessive FAO, increased oxidative stress, altered substrate metabolism, and the eventual development of myocardial hypertrophy [33,36]. This vulnerability is further demonstrated in cardiac-specific deficiency models, which highlight the indispensable role of Plin5 in myocardial homeostasis [37]. In these targeted models, although total LD volume decreases—a change that would be expected to alleviate lipid burden—uncontrolled lipolysis results in excessive accumulation of lipotoxic intermediates, notably ceramides and diacylglycerols (DAG), which cannot be effectively oxidized. This

in turn disrupts cellular architecture, manifested as reduced mitochondrial abundance and evident structural damage, ultimately impairing diastolic function [27,38]. Accumulating evidence supports an important role for Plin5 dysregulation in pathological myocardial remodeling [39]. These findings indicate that Plin5 actively regulates the mobilization and metabolic channeling of fatty acids. In contrast to the deleterious effects observed upon Plin5 deletion, the metabolic effects of Plin5 overexpression are context- and expression level-dependent, with both beneficial and potentially detrimental effects reported. A 2013 study in the Journal of Lipid Research demonstrated that cardiac-specific Plin5 overexpression restricts lipolysis by forming a lipolytic barrier that limits uncontrolled fatty acid release; however, excessive Plin5 expression also causes marked triglyceride accumulation and severe cardiac steatosis [40]. This protective effect is further reinforced by the PPARα–PGC-1α regulatory axis (see Section 5), which enhances mitochondrial respiratory capacity and protects the heart from high-fat diet-induced functional decline [33].

From a physiological perspective, this Plin5-mediated metabolic buffering represents an important adaptive response to fatty acid overload. Beyond lipid sequestration, Plin5 has been implicated in coordinating glucose-lipid metabolism. Emerging evidence indicates that Plin5 levels are positively associated with mitochondrial oxidative capacity and insulin sensitivity, suggesting a role in maintaining metabolic flexibility and substrate utilization balance [30]. Under conditions of elevated FFAs, Plin5 expression may indirectly alleviate lipid overload-induced impairment of glucose metabolism by regulating fatty acid mobilization and mitochondrial oxidative capacity, and may influence energy-sensing pathways such as AMP-activated protein kinase (AMPK), thereby contributing to the regulation of glucose metabolism [30,41]. In addition, accumulating evidence suggests that Plin5-mediated regulation of FAO may reduce mitochondrial acetyl-CoA and nicotinamide adenine dinucleotide (reduced) (NADH) accumulation, thereby alleviating the inhibitory effect of the Randle cycle on pyruvate dehydrogenase (PDH) activity and facilitating the restoration of glucose uptake and oxidative flux in the diabetic myocardium [36,42,43]. Consequently, Plin5 functions as a mediator of substrate crosstalk, integrating multiple energy sources to maintain balanced cardiac metabolism.

The functional agility of Plin5 is further exemplified by its post-translational plasticity. During acute physiological stress, PKA-mediated phosphorylation of Ser155 activates a molecular switch that releases ABHD5 and initiates ATGL-dependent lipolysis, allowing the heart to rapidly mobilize stored lipids to meet acute energy requirements (the detailed mechanism is discussed in Section 5) [29,32,44]. Rather than acting as a passive tether, these Plin5-mediated contacts undergo rapid, dynamic remodeling during acute physiological challenges, such as fasting [27], cold exposure [17,45], and exercise [46], thereby directing lipid transport toward mitochondrial β-oxidation [6]. The strong correlation between Plin5 abundance and the intrinsic oxidative capacity of tissues suggests that it plays a fundamental role in maintaining metabolic homeostasis across diverse physiological states [28]. Regarding aging, although human evidence remains limited, animal models suggest that Plin5 may influence mitochondrial function in aging tissues. For example, cardiac Plin5 interacts with SERCA2 and contributes to the regulation of myocardial calcium handling and cardiomyocyte contractility [47], suggesting a potential role for Plin5 in maintaining cardiac function during aging.

In summary, Plin5 in the myocardium has dual roles: providing static regulatory functions, such as structural protection and lipotoxicity mitigation, and facilitating dynamic metabolic responses through a phosphorylation-responsive switch and substrate coordination. Plin5 is an indispensable component of the cellular stress response owing to its roles in balancing between lipid storage and lipid utilization to safeguard mitochondrial integrity [15]. Research linking Plin5 to insulin signaling and lactate metabolism suggests that it may represent a therapeutic target for metabolic heart disease [36,48]. Future investigations into these regulatory pathways may lead to transformative applications in exercise medicine and nutritional regulation (Table 1, Ref. [15,16,17,21,25,26,27,29,30,31,32,33,34,35,36,37,40,41,43,44,45,46,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77]).

4. Plin5 in Skeletal Muscle: Fiber-Type Specificity and Exercise-Induced Metabolic Adaptation

Similar to its role in the heart, Plin5 is a cornerstone of skeletal muscle metabolism, supporting the distinct energy demands of different fiber types and mediating exercise-induced adaptation [41,50]. Predominantly localized in oxidative (Type I) fibers, Plin5 forms LDMCs that serve as the physical framework for enhancing mitochondrial respiratory capacity and metabolic flexibility, although their precise contribution to total mitochondrial fatty acid oxidation remains under investigation [41].

The physiological necessity of Plin5 is evidenced in muscle-specific models, in which its loss leads to a significant disruption of lipid homeostasis [30]. Plin5 deficiency alters intracellular lipid composition and is associated with impaired insulin sensitivity in skeletal muscle [51]. These molecular disruptions translate into significant functional deficits, as muscle-specific knockout mice exhibit a 20% reduction in maximal running capacity and reach fatigue 15% faster than their wild-type counterparts [50]. Conversely, Plin5 overexpression enhances the muscle's capacity for fatty acid oxidative utilization, particularly under conditions of activated lipolysis or increased metabolic demand [41] by engaging the PPARα-PGC-1α regulatory network

Table 1. Comparative summary of Plin5 functions, regulatory pathways, and clinical significance across tissues.

Tissue/context	Main role of Plin5	Key pathways	Pathophysiological relevance	Representative references
Cardiomyocytes	Promotes LD-mitochondria coupling, fatty acid oxidation, and lipotoxic protection	PPARα-PGC-1α; AMPK-mTOR; PKA-mediated lipolytic switch	Supports cardiac energy homeostasis; dysregulation is linked to mitochondrial dysfunction and cardiometabolic injury	[15,27,29,32,33,34,36,37,40,43,44,48,70,75,76,77]
Skeletal muscle	Enhances fatty acid mobilization, oxidative metabolism, and insulin sensitivity	AMPK; PGC-1α; SIRT1; PPAR-related signaling	Supports exercise adaptation; reduced expression is associated with lipotoxicity, insulin resistance, and reduced performance	[17,30,31,41,46,49,50,51,52,53,54,55,56,57,58,59,60,73,74,76]
Liver	Stabilizes lipid droplets and regulates lipolysis	PPARα; SREBP1c and ChREBP (associated)	Maintains hepatic lipid balance, but shows context-dependent effects in NAFLD and overnutrition	[16,25,26,55,62,63,64,65,71,72]
Brown adipose tissue	Supports thermogenic lipolysis, mitochondrial function, and uncoupled respiration	β3-adrenergic signaling; cAMP-PKA; UCP1	Promotes non-shivering thermogenesis and cold adaptation; reduced Plin5 impairs BAT remodeling	[17,21,45,66]
Pancreatic β-cells	Protects against lipotoxicity and may modulate insulin secretion	Putative NAD^+/NADH- and SIRT3-related mechanisms	May preserve islet cell function, although current evidence remains limited	[67,68]
Cold or exercise stress	Rapidly increases to enhance LD-mitochondria coupling and fatty acid utilization	PKA; AMPK; β3-adrenergic signaling; PPAR-related signaling	Contributes to adaptive responses during fasting, exercise, and cold exposure	[17,25,32,45,46,55,57,58,66,69]
Aging tissues	Helps maintain mitochondrial density and oxidative function	PGC-1α; SIRT1/3	Reduced Plin5 may contribute to metabolic decline, lipid dysregulation, and impaired muscle resilience	[30,35,60,61]

Plin5, Perilipin 5; LD, lipid droplet; PPARα, Peroxisome proliferator-activated receptor alpha; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; AMPK, AMP-activated protein kinase; mTOR, Mechanistic target of rapamycin; PKA, Protein kinase A; SIRT1, Sirtuin 1; SREBP1c, Sterol regulatory element-binding protein 1c; ChREBP, Carbohydrate-responsive element-binding protein; NAFLD, Non-alcoholic fatty liver disease; cAMP, Cyclic adenosine monophosphate; UCP1, Uncoupling protein 1; BAT, Brown adipose tissue; NAD^+, Nicotinamide adenine dinucleotide (oxidized); NADH, Nicotinamide adenine dinucleotide (reduced); SIRT3, Sirtuin 3.

to upregulate fatty acid oxidation programs, notably without the impaired insulin sensitivity typically associated with high lipid loading [52]. Mechanistically, Plin5 facilitates fatty acid transport from LDs to mitochondria by interacting with fatty acid transport protein 4 (FATP4) (ACSVL4) at membrane contact sites [31]. This mechanism is reflected in clinical observations. In Type 2 Diabetes (T2D), Type II muscle fibers often contain enlarged LDs lacking Plin5 coating, whereas the Type I fibers of endurance athletes show higher levels of Plin5, which correlate with enhanced lipid turnover and improved metabolic performance [53,54]. Ultimately, Plin5 acts as a sophisticated metabolic clutch that utilizes reversible phosphorylation during energetic stress to dynamically modulate lipolysis [55]. By suppressing lipolysis under basal conditions while promoting fatty acid oxidation during contraction-induced energy demand, Plin5 prevents lipotoxicity and ensures adequate energy supply [55]. This dual role, a static structural scaffold (LDMC maintenance) and a dynamic regulatory switch (phosphorylation-dependent transport), establishes Plin5 as a primary coordinator of muscle energy metabolism [56].

Negative energy balance, triggered by fasting, caloric restriction, or intense exercise, induces an upregulation of Plin5 to facilitate fatty acid mobilization and subsequent oxidation [57]. A study in muscle and BAT consistently showed that Plin5 abundance and its proximity to mitochondria increased following nutrient deprivation or cold exposure [45]. This adaptive capacity is primarily regulated at the transcriptional level via the PPAR family. Specifically, fatty acids acting as ligands for PPARδ regulate Plin5 transcription, although the definitive role of a classical PPARα response element (PPRE) in the promoter is still under debate [58]. For immediate integration, catecholamine-stimulated lipolysis triggers PKA-mediated phosphorylation of Plin5, facilitating its nuclear translocation and the formation of a regulatory complex with Sirtuin 1 (SIRT1) and PGC-1α that promotes mitochondrial biogenesis [17]. This regulatory structural synergy is further supported by the interaction between Plin5 and acyl-CoA synthetases such as FATP4. These enzymes facilitate the transport of lipid droplet-derived fatty acids to mitochondria, where they are activated into fatty acyl-CoA and subsequently enter the β-oxidation pathway [31].

Plin5 expression in skeletal muscle reflects the organ's adaptive response to endurance exercise. Trained individuals exhibit significantly higher Plin5 protein levels than sedentary individuals, a pattern that resembles PGC-1α overexpression observed in transgenic models [30]. These findings align with the concept that exercise stimulates the PGC-1α pathway, which coordinates mitochondrial biogenesis and promotes a transition toward oxidative muscle phenotypes [59]. Although direct synergy between Plin5 and PGC-1α in promoting biogenesis remains under investigation, the correlation between elevated Plin5 and enhanced oxidative capacity in trained muscle supports a model in which Plin5 facilitates exercise-induced metabolic remodeling [30]. Collectively, current evidence identifies Plin5 as an integral component of the metabolic remodeling associated with the trained physiological state.

Aging involves substantial remodeling of skeletal muscle, in which shifts in LD dynamics and mitochondrial decline contribute to sarcopenia and metabolic inflexibility. Clinical observations in the vastus lateralis suggest that Plin5 protein levels may decrease slightly with age; however, significant reductions are primarily associated with chronic disuse rather than healthy aging itself [60]. These age-associated shifts correlate with reductions in key metabolic regulators such as PGC-1α and SIRT1 [61]. Experimental studies in rodent and cell models reinforce the functional importance of Plin5, demonstrating that its overexpression stimulates gene programs involved in fatty acid oxidation and mitochondrial maintenance [30,34,41]. Although direct evidence linking Plin5 deficiency to accelerated sarcopenia remains limited, its role in organelle communication suggests that its loss may exacerbate age-related muscle deterioration. Maintaining Plin5 expression, particularly through exercise training, is a promising strategy for sustaining muscle metabolic health throughout the lifespan.

5. Functions and Tissue-Specific Roles of Plin5 in Other Tissues

While research on Plin5 has traditionally centered on cardiac and skeletal muscle, its functional roles in the liver, BAT, and the pancreas are increasingly being recognized. In these tissues, Plin5 exhibits remarkable functional plasticity, acting as a metabolic hub that adapts its activity to meet specific bioenergetic demands [34,62]. In the liver, Plin5 helps maintain hepatocyte LD structural integrity by promoting LD-mitochondrial coupling to maintain oxidative equilibrium while also restricting deleterious, non-selective lipolysis [15,78]. During energy-demanding conditions such as fasting, hepatic PPARα expression is upregulated, which in turn induces Plin5 transcription through direct binding to the PPAR response element (PPRE) within the Plin5 promoter, via the PPARα-mediated transcriptional mechanism described in Section 5. This hepatic induction helps coordinate fatty acid uptake and oxidative utilization, and may contribute to protecting the hepatic parenchyma from lipotoxicity [63]. However, in conditions such as insulin resistance or non-alcoholic fatty liver disease (NAFLD), the role of Plin5 becomes more complex. Hepatic Plin5 overexpression has been associated with abnormal lipid droplet enlargement and increased triglyceride accumulation [65]. Although lipogenic transcription factors such as sterol regulatory element-binding protein 1c (SREBP1c) and carbohydrate-responsive element-binding protein (ChREBP) are known to be upregulated in NAFLD [64], whether Plin5 directly activates these transcription factors or whether the observed lipid accumulation represents a secondary consequence of altered lipid flux remains

to be experimentally determined. These findings suggest that hepatic Plin5 functions as a metabolic regulator whose effects depend strongly on the pathological environment.

In the thermogenic environment of BAT, direct experimental evidence demonstrates that Plin5 coordinates LD-mitochondria interactions and promotes uncoupled respiration, playing an important role in thermogenic metabolism [45]. Based on these findings, Plin5 is thought to facilitate fatty acid substrate supply for uncoupling protein 1 (UCP1)-mediated non-shivering thermogenesis, although the mechanisms by which it directly regulates UCP1 activity remain to be elucidated. Furthermore, Plin5 has been shown to activate NAD^+-dependent sirtuin signaling through lipid droplet-derived fatty acid trafficking, with direct evidence confirming its interaction with SIRT1 [17,21]. However, whether Plin5 similarly regulates SIRT3-mediated mitochondrial deacetylation and antioxidant defense in BAT remains a plausible but unconfirmed hypothesis. Consistent with these functions, Plin5-deficient animal models exhibit cold intolerance and mitochondrial dysfunction, further suggesting the importance of Plin5 in thermogenic adaptation [79]. Adaptive thermogenesis triggers a significant increase in Plin5 expression in BAT, highlighting its role in metabolic defense against thermal stress. Within hours of cold exposure, Plin5 mRNA and protein levels increase along with the thermogenic marker UCP1 and mitochondrial oxidative capacity, driven by sympathetic β-adrenergic activation of the cAMP-PKA signaling cascade [45,66]. Although PKA-dependent phosphorylation of Plin5 has been recognized as a regulator in other contexts, its specific role in mitochondrial recruitment within BAT remains a compelling research topic. Functional genetic models demonstrate that increased Plin5 expression promotes cold adaptation–associated metabolic remodeling by increasing mitochondrial cristae density and enhancing uncoupled respiration, thereby supporting thermogenic metabolism. In contrast, Plin5 deficiency impairs BAT remodeling and compromises its oxidative metabolic capacity [45]. Overall, current evidence suggests that Plin5 plays an essential role in LD-mitochondria interactions and thermogenic activity during cold stress.

Finally, emerging research suggests a potential role for Plin5 in pancreatic β-cells. Based on the established functions of Plin5 in hepatocytes and cardiomyocytes, it has been proposed that Plin5 may facilitate LD-endoplasmic reticulum (ER) interactions in β-cells, potentially serving as a defensive barrier against lipotoxic stress and reactive oxygen species [67,68]. However, it should be noted that direct experimental evidence for Plin5-mediated LD-ER coupling specifically in β-cells remains limited, and this model is largely extrapolated from findings in other tissues. Similarly, the hypothesis that chronic Plin5 overexpression during excessive lipid accumulation may trigger ER stress and β-cell apoptosis has been proposed by analogy with hepatic observations [80], and awaits direct experimental validation. These considerations highlight the pancreas as a compelling but largely unexplored frontier for Plin5 research.

6. Signaling Pathways and Metabolic Regulation Mediated by Plin5

Beyond its traditional role as a structural scaffold on the LD surface [81], Plin5 has emerged as an important molecular hub that integrates signals from diverse metabolic pathways involved in energy regulation [15]. By linking LD homeostasis, mitochondrial oxidative processes, and cellular energy-sensing systems, Plin5 contributes to a coordinated metabolic framework that supports cellular metabolic flexibility [34]. Among these, the involvement of Plin5 in the PPARα-PGC-1α regulatory axis is supported by existing evidence [21,82,83], whereas its relationship with AMPK-related energy-sensing pathways remains less clearly established. Additionally, its roles in lactate-responsive and redox regulatory mechanisms have been preliminarily reported, although the underlying mechanisms remain to be further elucidated [36,84]. Within the PPARα-PGC-1α regulatory network, Plin5 functions as a signal amplifier rather than a passive transcript, establishing a synergistic positive feedback loop that scales up fatty acid oxidation capacity while orchestrating mitochondrial biogenesis [17]. This regulatory system enables mitochondrial remodeling and substrate switching during exercise, converting transient metabolic signals into lasting cellular changes [17]. While these transcriptional programs regulate long-term phenotypic adaptation, the cell's immediate energetic equilibrium is controlled by the AMPK-mTOR signaling pathway. Plin5 functions to actively tune this pathway by modulating LD lipolysis rates, which shift the intracellular adenosine triphosphate (ATP)/adenosine monophosphate (AMP) ratio toward metabolic survival [17,44,85]. By modulating intracellular energy status to preferentially promote AMPK signaling while concurrently attenuating mTOR transduction, Plin5 favors mitochondrial expansion over anabolic burdens, a strategic braking and accelerating mechanism observed in both skeletal muscle training and myocardial stress remodeling [86] (Fig. 3).

The regulatory versatility of Plin5 is further highlighted in the context of lactate metabolism. Lactate acts as an endogenous ligand for G-protein-coupled receptor 81 (GPR81) and suppresses lipolysis through GPR81 activation [87]. Lactate-responsive signaling and shifts in the NAD^+/NADH ratio may further intersect with Plin5-dependent regulation of LD activity [15,88,89,90]. By regulating lipolysis rates, Plin5 helps prevent metabolic bottlenecks and optimizes the interplay between lactate and fatty acid utilization, acting as a gatekeeper for substrate selection at the glucose-lipid metabolic junction [15] (Fig. 3). This metabolic buffer may also contribute to cellular redox balance. By regulating lipolytic flux, Plin5 indirectly influences intracellular NAD^+/NADH metabolic status, which may in turn facilitate SIRT3-mediated deacetylation, en-

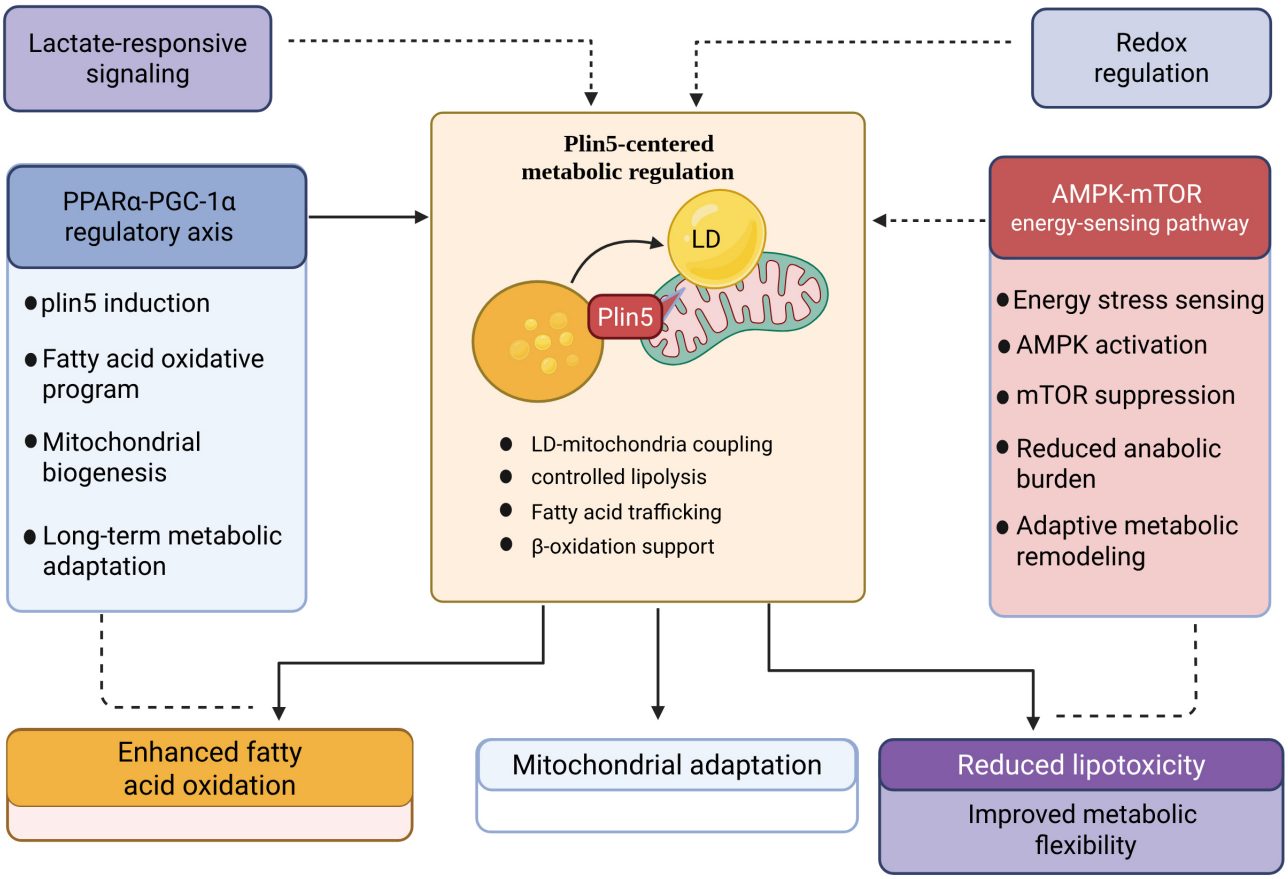


Fig. 3. Plin5-centered metabolic regulation integrating the PPARα-PGC-1α axis and the AMPK-mTOR energy-sensing pathway. The PPARα-PGC-1α axis and the AMPK-mTOR pathway converge on Plin5-centered metabolic control to promote fatty acid oxidation, mitochondrial adaptation, reduced lipotoxicity, and improved metabolic flexibility. Lactate-responsive signaling and redox regulation may also participate in this network. Solid arrows indicate established or better-supported relationships (e.g., the PPARα-PGC-1α axis), whereas dashed lines indicate indirect or putative associations (e.g., AMPK-mTOR, lactate-responsive signaling and redox regulation). Abbreviations: LD, lipid droplet; PPARα, peroxisome proliferator-activated receptor alpha; PGC-1α, PPAR gamma coactivator-1 alpha; AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin. Created in BioRender. Wang, L. (2026), https://BioRender.com/63gt5nv.

hancing antioxidant defense and mitigating mitochondrial injury under metabolic stress, although the direct causal relationship within this regulatory chain remains to be further established [51]. These diverse functions are regulated in real time through post-translational modifications, particularly phosphorylation of Ser155 by kinases such as PKA and AMPK. This modification induces a conformational change in Plin5 that weakens its association with the LD membrane, releases the co-activator ABHD5, and thereby activates ATGL to initiate lipolysis—effectively transitioning the LD from a locked storage state to an actively mobilizing organelle [40] (Fig. 3). This phosphorylation-dependent molecular switch constitutes the primary mechanism by which Plin5 rapidly adjusts lipolytic flux in response to acute energy demands.

Beyond biochemical signaling, recent studies in spatial interactomics have also identified Plin5 as a main organizer at LD-mitochondrial contact sites. Under conditions of high metabolic demand, Plin5 facilitates the recruitment of mitochondria-associated proteins, including mitofusin 2 (MFN2) and voltage-dependent anion channel 1 (VDAC1), to participate in the assembly of contact site complexes, thereby coordinating metabolic communication between organelles [91]. Ultimately, the regulatory role of Plin5 extends far beyond lipid protection, as it also functions as a sensor of cellular energy status and a shaper of mitochondrial health, orchestrating the dynamic equilibrium of glucose-lipid homeostasis [34]. Understanding the spatiotemporal nuances of these regulatory pathways is essential for refining mechanistic insight and developing targeted therapeutic strategies for metabolic diseases.

7. Mechanistic Hypothesis for Plin5 Regulation of LD-ER-Mito Tripartite Structures

7.1 Tripartite Structure Formation and Functional Integration

Advances in spatial omics and super-resolution microscopy have shifted the biological perspective from viewing LDs and mitochondria as independent organelles to components of an interconnected ER-LD-mitochondria network. Within this cellular organization, membrane contact sites (MCSs) act as physical bridges that facilitate rapid lipid exchange and coordinated signaling, with mitochondria-ER and mitochondria-LD contact zones regulating lipid flux and organelle integrity [92,93]. Tripartite contact sites, where the ER, LD, and mitochondria converge, represent high-order metabolic junctions that coordinate fatty acid trafficking [94]. This relationship originates from LD biogenesis. As LDs bud from the ER, they retain structural connections that ensure ongoing communication between organelles [95]. Mitochondria-associated membranes (MAMs) further facilitate lipid and calcium exchange that is essential for maintaining mitochondrial bioenergetic capacity [96]. Under physiological stress conditions such as fasting or exercise, LDs establish simultaneous contacts with the ER and mitochondria, forming dynamic tripartite assemblies [69]. These interfaces regulate the lipid lifecycle, from synthesis and storage in the ER to mobilization and subsequent oxidation, while acting as buffering systems to help mitigate lipotoxicity and support adaptation to energetic demands [97].

7.2 Molecular Interactions, Coupling Mechanisms, and Organizational Platform Hypothesis of Plin5

At the molecular level, the LDMC function of Plin5 is mediated in part through its interaction with FATP4, which stabilizes LD-mitochondria junctions and facilitates fatty acid trafficking during metabolic stress [31]. Super-resolution microscopy has confirmed this architecture by localizing Plin5 at the LD-mitochondria interface with high spatial precision [98]. The regulation of this structural bridge is modulated by the phosphorylation-dependent mechanism described in Section 5. Notably, in the context of LD-mitochondria contacts, starvation-induced phosphorylation enhances the affinity of Plin5 for FATP4, acting as a molecular green light for accelerated fatty acid channeling toward mitochondrial β-oxidation [31]. These phosphorylation-dependent changes allow cells to rapidly recalibrate their metabolic machinery in response to shifts in bioenergetic demands. It is important to distinguish between established findings and proposed models regarding these mechanisms. The association of lipid droplets with mitochondria involving Plin5 is supported by experimental evidence [31]. Conversely, the precise role of Plin5 in regulating complex downstream metabolic pathways is frequently inferred from broader concepts of lipid metabolism. Therefore, the signaling cascades discussed herein should be considered as a proposed model, and further targeted *in vivo* studies are required to fully validate these pathways.

While a direct physical tether between Plin5 and the endoplasmic reticulum (ER) has not been clearly demonstrated, Plin5 may act as an organizer of LD-ER architecture by influencing the subcellular localization of biosynthetic enzymes such as diacylglycerol O-acyltransferase 2 (DGAT2) and Acyl-CoA synthetase long-chain family member 1 (ACSL1) [22]. Beyond enzyme recruitment, Plin5 may contribute to LD stabilization and positioning, potentially through functional crosstalk with ER-LD regulatory proteins such as Seipin and Rab18 [99,100]. During metabolic stress, Plin5 may further facilitate the formation of LD-mitochondria contact sites, potentially involving proteins associated with mitochondrial dynamics such as MFN2, which is known to participate in ER-mitochondria communication [56]. Experimental overexpression of Plin5 has been shown to enhance these contacts and streamline fatty acid trafficking, which may reduce reactive oxygen species (ROS) levels and support mitochondrial function [84]. However, the direct involvement of Plin5 at MAMs, particularly in Ca^{2+} exchange or mitophagy, remains unclear and requires further investigation. Ultimately, Plin5 may serve as a dynamic organizing platform on the LD surface that facilitates coordinated interactions between LDs, mitochondria, and potentially the ER to enhance cellular adaptation to changes in lipid fluxes.

8. Research Challenges and Controversies

8.1 Context-Dependent Dual Roles: Dose and Tissue Specificity

Plin5 plays an important regulatory role in lipid droplet (LD)-mitochondria coupling and fatty acid oxidation while contributing to a defense against oxidative stress [84]. By localizing to the LD surface, Plin5 facilitates interactions with mitochondria that are critical for high-capacity oxidative metabolism and ROS suppression [84]. However, its biological impact varies depending on its expression level, the overall metabolic state of the organism, and the tissue in which it is expressed [34]. As discussed in Sections 3 and 4, physiological expression levels support metabolic flexibility in the myocardium and skeletal muscle by facilitating LD-mitochondria coupling and sequestering lipotoxic intermediates. However, chronic or excessive expression can drive pathological lipid accumulation; specifically, transgenic overexpression of Plin5 in cardiac tissue has been shown to induce steatosis and dysregulate mitochondrial dynamics, resembling lipotoxic remodeling [70]. The precise molecular tipping point at which Plin5 transitions from protective to maladaptive, likely influenced by specific protein-interaction partners or post-translational cues, remains an unresolved topic and complicates the clinical translation of Plin5-targeted therapies.

Beyond the expression level, the functional outcome of Plin5 activity is also shaped by the tissue in which it operates. While Plin5 exhibits predominantly protective functions in the myocardium and skeletal muscle, its role in the liver appears more complex. As outlined in Section 6, although hepatic Plin5 expression increases during lipid excess, the effects of Plin5 deficiency appear to be context-dependent. Plin5 deletion has been associated with reduced hepatic fat accumulation, attenuated inflammasome activation, and reduced hepatic injury in a chronic high-fat diet model [71]. In contrast, hepatocyte-specific Plin5 deletion has been reported to impair fatty acid oxidation and lipid droplet–mitochondria interactions and to promote hepatic triglyceride accumulation and insulin resistance [72]. The central controversy lies in whether elevated hepatic Plin5 expression promotes lipid sequestration as an adaptive defense or actively contributes to disease progression; resolving this question may depend on understanding the specific lipolytic pathways and substrate fluxes present in hepatocytes. To clarify the dose-dependent and context-specific effects of Plin5, we summarize its protective and pathogenic effects in Table 2 (Ref. [15,16,25,26,27,30,37,40,41,43,45,46,49,50,51,52,60,63, 65,66,70,73,74,76,77]), illustrating its dual role across different physiological conditions.

8.2 Insulin Signaling and Perilipin Interactions

The role of Plin5 in regulating insulin signaling remains a subject of active debate. One hypothesis suggests that Plin5 protects insulin sensitivity by sequestering fatty acids within LDs, thereby limiting the accumulation of lipotoxic intermediates (see Section 3) that would otherwise activate Protein Kinase C (PKC) isoforms and impair insulin signaling cascades [73]. Although Plin5 expression in muscle has been associated with enhanced whole-body insulin sensitivity, experimental Plin5 overexpression increases intramyocellular lipid storage without compromising insulin sensitivity, suggesting that increased Plin5 abundance and lipid storage do not necessarily lead to insulin resistance [52]. Meanwhile, hepatocyte-specific Plin5 deletion has been shown to dysregulate lipid metabolism and promote hepatic insulin resistance under lipid stress conditions [72]. Ultimately, the regulatory role of Plin5 in insulin signaling appears to depend on tissue-specific factors and metabolic milieu; however, direct empirical evidence linking Plin5 to core effectors such as AKT or GLUT4 independently of lipid partitioning remains scarce.

A systematic characterization of the interplay between Plin5 and other perilipin isoforms (PLIN1–4) remains limited. While Plin2 and Plin3 are ubiquitously expressed, Plin5 exhibits the oxidative tissue–enriched distribution outlined in Section 1 [34,81]. Functional overlap between Plin2 and Plin5 has been suggested in maintaining lipid droplet stability and regulating lipase accessibility to lipid droplets [6]; however, whether they cooperate during the early stages of lipid droplet formation has not yet been confirmed *in vivo*. Similarly, although Plin3 acts as an early regulator for LD turnover [13], its mechanistic interactions with Plin5 in oxidative tissues remain incompletely understood. Determining whether other perilipins can compensate for Plin5 deficiency is a vital area for future research, as understanding these interactions can help clarify the collective impact of the perilipin family in lipid droplet biology.

8.3 Post-Translational Modification Dynamics

The functional significance of the Ser155 phosphorylation switch (described in Section 5) is corroborated by mass spectrometry studies demonstrating increased hepatic Ser155 phosphorylation during fasting [63]. However, beyond this well-characterized site, the roles of phosphatases, ubiquitination, and acetylation in modulating Plin5 stability and function remain largely unknown. Furthermore, metabolic cues also influence the physical redistribution of Plin5. Under adrenergic stimulation, Plin5 can translocate to the nucleus and form regulatory complexes with PGC-1α and SIRT1 [17]. Whether this redistribution represents a universal hallmark of metabolic cycling or a context-specific response remains under investigation. Understanding the full spectrum of post-translational modifications will be necessary to decode the mechanistic logic governing the elegant shuttle of Plin5 between cellular compartments.

9. Clinical Translation and Therapeutic Potential

9.1 Biomarker Development and Clinical Applications

The expression profile of Plin5 reflects a systemic metabolic status and fluctuates in response to lipid oxidative demand, exercise level, and overall energy balance. This adaptability is particularly evident in highly oxidative tissues such as the myocardium, skeletal muscle, and brown adipose tissue (BAT). Human and rodent studies have demonstrated that skeletal muscle Plin5 protein levels are markedly higher in endurance-trained individuals [41,46]. This abundance correlates strongly with increased muscular oxidative capacity and systemic insulin sensitivity, which reinforces the potential link between Plin5 expression and long-term metabolic health [73]. Interestingly, the increase in Plin5 under physiological challenges such as high-fat feeding or prolonged fasting suggests its induction reflects a proactive, adaptive recalibration of lipid utilization rather than a passive pathological byproduct [63].

Transitioning Plin5 from a molecular sentinel to a definitive clinical biosensor requires extensive validation across diverse human cohorts. Although longitudinal exercise interventions have shown that aerobic training simultaneously upregulates muscular Plin5 and enhances insulin responsiveness [74], its usefulness as a standalone biomarker of exercise-induced adaptation remains under debate. In chronic metabolic conditions such as obesity

Table 2. Summary of the context-dependent dual roles of Plin5 across different tissues.

Tissue/Organ	Expression change	Observed effect	Beneficial or detrimental	Proposed mechanism	Reference
Cardiomyocytes	Relatively high physiological expression or moderate adaptive upregulation	Promotes LD-mitochondria coupling; limits lipotoxicity; supports fatty acid oxidation	Beneficial	Sequestration of toxic lipid intermediates, maintenance of LD-mitochondria coupling, and support of controlled fatty acid oxidation	[15,27,37,43,76,77]
Cardiomyocytes	Chronic or excessive overexpression	Induces cardiac steatosis and may impair cardiac function	Detrimental	Formation of an excessive lipolytic barrier, abnormal lipid accumulation, and dysregulation of mitochondrial dynamics	[40,70]
Skeletal muscle	Increased expression (e.g., after exercise adaptation)	Enhances oxidative capacity; improves insulin sensitivity	Beneficial	Facilitates efficient fatty acid mobilization toward mitochondria during increased energy demand and supports oxidative remodeling	[41,46,49,52,73,74]
Skeletal muscle	Plin5 deficiency or reduced expression	Promotes lipotoxicity, insulin resistance, and reduced exercise performance	Detrimental	Impaired lipid droplet control, ceramide accumulation, disrupted insulin signaling, and reduced metabolic flexibility	[30,50,51,60]
Liver	Moderate or adaptive expression under metabolic demand	Supports lipid droplet stabilization and may help buffer lipotoxic stress	Beneficial	Coordinates lipid storage with oxidative demand and may reduce non-selective lipolysis under certain conditions	[16,25,26,63]
Liver	Overexpression or ectopic accumulation	Increases hepatic lipid accumulation and steatosis	Detrimental	Stabilizes lipid droplets and reduces lipolysis, thereby promoting steatosis in a context-dependent manner	[65]
Brown adipose tissue (BAT)	Normal physiological expression or cold-induced upregulation	Maintains mitochondrial function and thermogenesis	Beneficial	Regulates basal lipolysis and supports mitochondrial uncoupled respiration and thermogenic remodeling	[45,66]
Brown adipose tissue (BAT)	Reduced expression or functional loss	Impairs thermogenic adaptation and mitochondrial function	Detrimental	Disrupts BAT remodeling, reduces oxidative capacity, and weakens cold tolerance	[45]

and type 2 diabetes, the relationship between Plin5 expression and disease progression appears complex, particularly in the context of cardiac lipotoxic injury, which is closely associated with metabolic syndrome. Studies have demonstrated that Plin5 can bidirectionally regulate lipid metabolism in the heart, whereby both its deficiency and overexpression may alter the levels of lipotoxic lipids such as diacylglycerols and ceramides and affect related signaling pathways [43,48]. Furthermore, an animal model study suggests that Plin5 deficiency can lead to increased oxidative stress and impaired myocardial function [75]. Although these animal experimental findings suggest an association between Plin5 expression imbalance and cardiac pathological alterations, direct evidence that changes in

Plin5 expression in the human myocardium precede the onset of structural heart disease remains limited, and the related causal relationships await further investigation. Future high-resolution phenotyping approaches may integrate Plin5 measurements with magnetic resonance spectroscopy (MRS) or PET tracers to map fatty acid oxidation kinetics, provided these multi-modal approaches are rigorously validated [101,102].

9.2 Therapeutic Strategies and Translational Challenges

Owing to its tissue-specific expression profile and fundamental role in synchronizing lipid droplet (LD) dynamics with mitochondrial bioenergetics, Plin5 has emerged as a high-value target for therapeutic intervention [25,34,48]. Current research is increasingly shifting beyond the protein itself to focus on indirect strategies targeting its upstream regulatory network, such as the cAMP/PKA signaling axis. Within this framework, PKA-dependent phosphorylation of residues such as Ser155 acts as a molecular switch that promotes lipolysis and coordinates glucose and lipid utilization [55]. Furthermore, pharmacological activation of energy-sensing kinases such as AMPK has shown promise in preclinical studies for enhancing fatty acid oxidation and improving metabolic regulation [103]. However, whether these effects are mediated through the modulation of Plin5 remains to be further investigated.

In the context of pathological lipid storage, gene-silencing technologies such as RNA interference and antisense oligonucleotides (ASOs) have provided important insights. Experimental ablation of Plin5 has been shown to attenuate hepatic steatosis and slow the progression of non-alcoholic fatty liver disease (NAFLD) [71]. Beyond gene silencing, emerging strategies include peptide mimetics designed to stabilize protein-protein interactions at the LD-mitochondria interface and facilitate directional fatty acid trafficking. CRISPR/Cas-based activation systems aimed at selectively upregulating Plin5 expression in insulin-resistant tissues are currently being explored, although their clinical application remains a future goal. Ultimately, restoring Plin5 levels in experimental models of diabetic heart failure has been shown to improve cardiac lipid handling and contractile function, providing a compelling rationale for targeting Plin5-associated signaling pathways in the treatment of cardiometabolic disorders [104].

Despite this therapeutic promise, the translation of Plin5 research into clinical practice faces substantial hurdles. No approved pharmacologic agents currently target this protein directly. This gap reflects the broader difficulty of modulating the dynamics of lipid droplets within the complex *in vivo* environment. A formidable technical barrier is the absence of effective tissue-selective delivery systems for gene-based modulators. Although ASOs and siRNAs offer promising gene-silencing strategies, their clinical development is often limited by issues related to systemic stability and off-target effects, as highlighted in recent pharmacological reviews [105]. These challenges are further complicated by the double-edged nature of Plin5, which means that achieving surgical precision in tissue-specific targeting is necessary to prevent maladaptive lipid droplet enlargement [15].

Furthermore, the regulatory mechanisms of Plin5 have not been fully elucidated. Although phosphorylation [55] has been studied in considerable depth, how other post-translational modifications (such as ubiquitination and acetylation) regulate the stability and function of Plin5 under different pathological conditions remains to be systematically characterized. This uncertainty is exacerbated by a scarcity of large-scale human population data needed to validate Plin5 as a credible clinical biomarker [106]. Furthermore, our understanding of the genetic architecture of the PLIN5 gene remains far less characterized compared to well-studied lipid-related loci such as apolipoprotein E (APOE) [107] or lipoprotein lipase (LPL) [108], which limits our ability to predict patient-specific responses. In addition to these biological challenges, technical and regulatory constraints, such as the safety and biodistribution of targeted nanocarriers [109], also influence the translational development of Plin5-based therapies. Advancing Plin5 from a research focus to a clinically relevant target will require overcoming these technical barriers, managing development costs, and establishing clear regulatory pathways.

10. Future Research Directions and Prospects

Over the next two to three years, Plin5 research should prioritize systematic characterization in human tissues to bridge the gap between findings from murine models and clinical relevance. Establishing large-scale clinical databases that link Plin5 expression levels to metabolic indicators such as insulin sensitivity and lipid profiles will be essential for confirming the translational relevance of rodent-based findings [106]. This effort will depend on the development of standardized and high-fidelity detection methods, including non-invasive serum or plasma-based assays and clearly defined clinical reference ranges [110]. From a mechanistic perspective, it will be important to characterize the tissue-specific distribution and functional heterogeneity of Plin5 using single-cell multi-omics approaches [111], as well as to decode the broader post-translational modification landscape beyond the Ser155 residue. In this regard, validating how site-specific phosphorylation regulates LD-mitochondria interactions will be particularly important for advancing clinical translation [55]. In parallel, epigenetic mechanisms also warrant attention; the Plin5 gene may contain CpG-rich promoter regions that could be targeted by DNA methyltransferases during metabolic shifts [112], although direct evidence linking DNA methylation specifically to Plin5 regulation remains limited. Additionally, experimental validation of non-coding RNA regulation, particularly targeting miR-

378a [113] and miR-124 [114] in skeletal muscle, as well as lncRNA H19 [115] within competitive endogenous RNA (ceRNA) networks, which may coordinate lipid utilization in response to exercise and AMPK activation, will be important for understanding how tissues adapt to metabolic changes.

The medium-term objective is to integrate Plin5 expression profiles into personalized metabolic risk prediction models and to use them to guide individual lifestyle interventions as part of precision medicine strategies. Therapeutic innovation will focus on identifying small-molecule modulators that regulate Plin5-associated signaling pathways, particularly the PPAR/PI3K-AKT axis, to optimize lipid droplet-mitochondria interactions [15,55,116]. Additional priorities include the development of tissue-specific gene therapy delivery systems [109] and the construction of multi-omics systems biology models to unmask novel protein interactors involved in cardiometabolic diseases [117]. Progress toward clinical application may be accelerated through high-resolution spatial transcriptomics, advanced metabolic imaging, and longitudinal cohort studies aimed at evaluating Plin5 as a biomarker of metabolic adaptation [118,119,120]. However, it should be noted that direct evidence linking many of the proposed regulatory mechanisms specifically to Plin5 remains limited; further targeted *in vivo* studies are therefore required to fully validate these pathways before Plin5 and its regulatory partners can be considered definitive therapeutic targets for precision interventions.

Over the next five to ten years, Plin5-based prevention strategies and early warning systems may be developed to help identify pathological changes in metabolic health through integrated lipidomic profiling. These efforts may contribute to the development of lifestyle-based medicine approaches that combine individual molecular phenotyping with personalized nutritional and exercise prescriptions to support metabolic health during aging. Achieving these strategies will require the integration of AI-driven prediction models with single-cell spatial transcriptomics to better resolve tissue-level complexity. Beyond its role in metabolic regulation, further research into the interactions between Plin5, systemic inflammation, and oxidative stress may help uncover its protective capacity in chronic disorders such as heart failure, diabetes, and liver pathologies, establishing it as a cornerstone of the cellular stress response [33,84]. By leveraging these technologies alongside multi-omics integration, the field can transition toward deciphering the regulatory networks that integrate lipid storage and lipolysis. Ultimately, realizing these long-term objectives will require initiating well-designed clinical trials, building comprehensive medical infrastructure, and integrating Plin5-related biomarkers into routine clinical practice to enhance the prevention, diagnosis, and monitoring of cardiometabolic diseases.

11. Conclusions and Future Outlook

11.1 Summary of Functional Integration of Plin5

Research on Plin5 has evolved from viewing it as a passive lipid droplet (LD)-associated protein to recognizing it as an important regulator of cellular metabolic flexibility [6]. Over the past decade, significant progress has been made to elucidate the molecular mechanisms of Plin5, its associations with metabolic diseases, and its roles within regulatory networks [121]. An early study demonstrated that Plin5 forms a critical physical and metabolic bridge between lipid droplets and mitochondria in oxidative tissues, coordinating LD dynamics with fatty acid oxidation [15]. Through the formation of LDMCs, Plin5 ensures efficient fatty acid channeling to the mitochondrial oxidation machinery, a function essential for cardiac and skeletal muscle energy homeostasis [15,31]. This unique localization is particularly important in high-energy-demand tissues such as the heart and skeletal muscle, where alterations in Plin5 expression can influence mitochondrial function, LD architecture, and oxidative gene expression [52,84]. Within the Perilipin protein family, Plin5 functions not only as a structural scaffold but also as a dynamic mediator of lipid mobilization and inter-organelle crosstalk. This perspective has been increasingly reinforced by high-resolution omics studies investigating cardiometabolic regulation [6,76].

As demonstrated in Section 3, disruption of this architectural precision is associated with adverse cardiac outcomes, including hypertrophy and heart failure under conditions of metabolic stress [34,122]. In addition, lipolytic stimulation remodels Plin5 localization and mitochondrial cristae architecture at the cardiac lipid droplet-mitochondria interface [77]. Finally, as detailed in Section 4, Plin5 contributes to exercise-related metabolic regulation in skeletal muscle. Gain- and loss-of-function studies suggest that Plin5 can influence oxidative metabolism and certain aspects of exercise performance, although it appears to be dispensable for normal substrate metabolism and skeletal muscle adaptation to exercise training [30,49,50].

11.2 Future Perspectives

The detailed research agenda outlined in Section 10 collectively aims to reposition Plin5 from a subject of fundamental inquiry to a clinically actionable target at the interface of lipid storage, mitochondrial bioenergetics, and systemic metabolic regulation [34]. Realizing this potential will require convergent advances in human-tissue validation, tissue-selective delivery technologies, and integrative computational modeling. Ultimately, Plin5 represents an important link between basic metabolic research and translational medicine, with potential relevance for developing personalized strategies to monitor and regulate metabolic homeostasis across the lifespan [30].

Abbreviations

ABHD5, α/β-Hydrolase domain-containing protein 5; ACOX1, Acyl-CoA oxidase 1; ACSL1, Acyl-CoA synthetase long-chain family member 1; ACSVL4, Acyl-CoA synthetase very long-chain 4; AI, Artificial intelligence; AMP, Adenosine monophosphate; AMPK, AMP-activated protein kinase; ASO, Antisense oligonucleotide; ATGL, Adipose triglyceride lipase; ATP, Adenosine triphosphate; BAT, Brown adipose tissue; cAMP, Cyclic adenosine monophosphate; Cas13, CRISPR-associated protein 13; CD36, Cluster of differentiation 36 (fatty acid translocase); CE, Cholesteryl esters; ceRNA, Competitive endogenous RNA; ChREBP, Carbohydrate-responsive element-binding protein; circRNA, Circular RNA; CPT1/CPT2, Carnitine palmitoyltransferase I/II; CRISPR, Clustered regularly interspaced short palindromic repeats; CVATT, Critical visceral adipose tissue threshold; DAG, Diacylglycerol; DCM, Diabetic cardiomyopathy; DGAT2, Diacylglycerol O-acyltransferase 2; DNA, Deoxyribonucleic acid; DNMT, DNA methyltransferase; ER, Endoplasmic reticulum; ERα, Estrogen receptor alpha; FABP3, Fatty acid binding protein 3; FATP, Fatty acid transport proteins; FATP4, Fatty acid transport protein 4; FFA, Free fatty acids; GLUT4, Glucose transporter type 4; GPR81, G-protein-coupled receptor 81; H3K9ac, Histone H3 lysine 9 acetylation; H3K27ac, Histone H3 lysine 27 acetylation; HDAC, Histone deacetylase; HFD, High-fat diet; HSL, Hormone-sensitive lipase; IL-6, Interleukin-6; LDs, Lipid droplets; LDMC, Lipid droplet-mitochondria coupling; lncRNA, Long non-coding RNA; LSDP5, Lipid storage droplet protein 5; MAMs, Mitochondria-associated endoplasmic reticulum membranes; MCS, Membrane contact sites; MFN2, Mitofusin 2; miRNA, MicroRNA; MR, Magnetic resonance; MS, Mass spectrometry; mTOR, Mechanistic target of rapamycin; NAFLD, Non-alcoholic fatty liver disease; NAD^+, Nicotinamide adenine dinucleotide (oxidized); NADH, Nicotinamide adenine dinucleotide (reduced); NLRP3, NOD-like receptor protein 3; OXPAT, Oxidative tissues-enriched PAT protein; PAT, Perilipin, ADRP, TIP47 domain; PDH, Pyruvate dehydrogenase; PET, Positron emission tomography; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PKA, Protein kinase A; Plin1–5, Perilipin 1–5; Plin5, Perilipin 5; PPARα, Peroxisome proliferator-activated receptor alpha; R&D, Research and development; ROS, Reactive oxygen species; SCID-X1, Severe combined immunodeficiency X-linked type 1; siRNA, Small interfering RNA; SIRT1, Sirtuin 1; SIRT3, Sirtuin 3; SREBP1c, Sterol regulatory element-binding protein 1c; T2D, Type 2 diabetes; TAG, Triacylglycerols; TNF-α, Tumor necrosis factor alpha; UCP1, Uncoupling protein 1; UTR, Untranslated region; VDAC1, Voltage-dependent anion channel 1; WAT, White adipose tissue.

Author Contributions

LXW and YPH contributed equally to this work; LXW and YPH conceptualised and designed the review and created the artwork; WDX and CXZ contributed to the conceptualization and design of the review framework and the interpretation and synthesis of the literature; they also supervised the work and critically revised the manuscript; MWK, FFZ, ZXW and YY conducted the literature review, performed the analysis and interpretation of data, and drafted the original manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

The authors declare that ChatGPT was used only to check spelling and grammar during the writing process of this manuscript. No artificial intelligence (AI) or AI-assisted technologies were used for the production of images or graphical elements, or for the collection, analysis, or interpretation of data. The authors take full responsibility for the content, accuracy, integrity, and originality of the manuscript, including any text revised with the assistance of ChatGPT.

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