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Received: 27 February 2024 | Revised: 18 April 2024 | Accepted: 30 April 2024

DOI: 10.1002/jcb.30579

REVIEW

Journal of Cellular Biochemistry WILEY

Perilipins: A family of five fat-droplet storing proteins that play a significant role in fat homeostasis

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Funding information
Interdisciplinary Center for Clinical Research within the faculty of Medicine at the RWTH Aachen University, Grant/Award Number: PTD 1-5; Deutsche Krebshilfe, Grant/Award Number: 70115581; Deutsche Forschungsgemeinschaft, Grant/Award Numbers: WE2554/13-1, WE2554/15-1, WE2554/17-1

Abstract

Lipid droplets are organelles with unique spherical structures. They consist of a hydrophobic neutral lipid core that varies depending on the cell type and tissue. These droplets are surrounded by phospholipid monolayers, along with heterogeneous proteins responsible for neutral lipid synthesis and metabolism. Additionally, there are specialized lipid droplet-associated surface proteins. Recent evidence suggests that proteins from the perilipin family (PLIN) are associated with the surface of lipid droplets and are involved in their formation. These proteins have specific roles in hepatic lipid droplet metabolism, such as protecting the lipid droplets from lipase action and maintaining a balance between lipid storage and utilization in specific cells. Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by the accumulation of lipid droplets in more than 5% of the hepatocytes. This accumulation can progress into metabolic dysfunction-associated steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. The accumulation of hepatic lipid droplets in the liver is associated with the progression of MASLD and other diseases such as sarcopenic obesity. Therefore, it is crucial to understand the role of perilipins in this accumulation, as these proteins are key targets for developing novel therapeutic strategies. This comprehensive review aims to summarize the structure and characteristics of PLIN proteins, as well as their pathogenic role in the development of hepatic steatosis and fatty liver diseases.

KEYWORDS

fatty liver, hepatocellular carcinoma, lipid droplets, lipid homeostasis, MASLD/MASH, perilipins, steatosis

1 | INTRODUCTION

Lipid droplets play an essential role in maintaining cellular lipid homeostasis. They store cholesterol esters and contain steroid hormones and triglycerides, which are used as an energy source and precursor for membrane phospholipid synthesis.[1,2] Under normal physiological conditions, hepatic lipid droplets are small and are limited in number. However, excessive hepatic lipid accumulation leads to an increase in the number and size of cytosolic

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lipid droplets.[3] There are five proteins in the perilipin protein family, known as PLIN1 to PLIN5. These proteins are associated with lipid droplets and can serve as marker proteins for them. PLIN1 is mainly expressed in adipocytes, while PLIN2 and PLIN3 are expressed throughout the body. The major isoforms of PLIN1 (PLIN1A), PLIN2 and PLIN5 are preferentially associated with lipid droplets enriched in triglycerides, while PLIN1C and PLIN1D, and PLIN4 are associated with lipid droplets enriched in cholesterol esters. Recent studies suggest that the PLIN class of proteins plays a significant role in lipid droplet formation, and both heterogeneity and redundancy have been reported among them.[4] The increase in synthesis or secretion of lipid droplets from the endoplasmic reticulum (ER) membrane and their transfer to the cytosol lead to an increase in neutral lipid deposition. This causes several impairments involved in the pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD), including inflammation, ER stress, mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and insulin resistance due to cellular toxicity.[5] Currently, there is no FDA-approved drug in the market for the treatment of fatty liver disease. Therefore, it is essential to explore new targets such as lipid droplets and lipid-droplet-associated proteins to combat this challenge.

MASLD, formerly known as nonalcoholic fatty liver disease (NAFLD), has affected one-fourth of the world population until 2010 and is characterized by the accumulation of fat in the liver, ballooning of hepatocytes, steatosis, hepatocellular fibrosis progressing to cirrhosis, and in some cases, further progression to hepatocellular carcinoma (HCC), which is one of the deadliest cancers globally.[6,7] Histologically, if more than 5% of hepatocytes are covered by lipid accumulation, it is defined as simple steatosis.[8] In the United States, one in three people is affected by metabolic dysfunction-associated steatohepatitis (MASH). Approximately 35% of individuals with fatty liver disease progress to MASH.[9] The two-hit hypothesis of MASLD suggests that hepatic lipid accumulation is the first hit, and hepatocytes' susceptibility to injuries such as oxidative stress, mitochondrial dysfunction, and proinflammatory cytokines is the second hit. Understanding the link between MASLD and new biomarkers is crucial for predicting its course and developing specific therapeutic approaches. Lipid droplets and their associated PLIN proteins play an essential role in the pathogenesis of lipid accumulation in the liver.[10] Dysfunctional lipid droplets and cellular lipid trafficking are associated with metabolic disorders, inflammation, and fatty liver.[11]

The pathogenesis of MASLD is complex and primarily involves two factors: increased de novo lipogenesis due to a deficiency of the transcription factors sterol regulatory element-binding protein 1 (SREBP1) and Carbohydrate-response element-binding protein (ChREBP), which are key regulators of lipogenesis, and impairment of fatty acid oxidation. These factors have direct and indirect effects on mitochondrial structure and function.[12,13] As a result, these pathways become dysregulated or impaired, leading to an accumulation of lipid droplets in hepatocytes and an increase in PLIN proteins. This review aims to provide firsthand information on the PLIN family of proteins and their association with fatty liver disease. By expanding our knowledge in this area, we hope to open new avenues for potential therapeutic strategies in the treatment of MASLD and MASH.

2 | LIPID DROPLET FORMATION

Lipid droplets are organelles within cells that store neutral lipids. They consist of a core primarily made up of triacylglycerols and sterol esters, surrounded by a phospholipid monolayer. These droplets are decorated with various proteins that play roles in lipid storage, release, and metabolism (Figure 1A). These organelles form by budding off the ER membrane. The driving forces in this process are fatty acids linked to glycerol-3-phosphoric acid through a process involving glycerol phosphate acyltransferase (GPAT), acylglycerol-3-phosphate O-acyltransferase (AGPAT), phosphatidic acid phosphohydrolase (also known as lipin), and diacylglycerol-O-acyltransferase (DGAT). The esterification of fatty acids into diacylglycerol (DAG) or sterols is the basis for the biosynthesis of neutral lipids in lipid droplet formation. In this process, the key enzymes involved in the formation of triacylglycerol include DGAT1 and DGAT2, while acetyl-CoA acetyltransferase (ACAT)1 and ACAT2 are involved in sterol biosynthesis. The accumulation of triglycerides in the ER drives the formation of lipid vesicles in the ER membrane and the release of lipid droplets with the lipid droplet surface consisting of a phospholipid and protein monolayer (Figure 1B).[14] Three models have been proposed for the formation of lipid droplets. The canonical model of LD formation suggests that neutral lipids form a lens within the ER bilayer and bud from the ER membrane, incorporating phospholipids from the cytosolic leaflet. The bicelle model suggests that neutral lipids accumulate within the leaflet of the ER membrane. The nascent LDs excised from the ER membrane incorporate lipids from both the cytosolic and luminal leaflets of the ER. Another model, known as the "vesicular budding" model, proposes that small bilayer vesicles are anchored to the ER membrane, forming a platform for LD formation. Neutral lipids are pumped from the ER to this bilayer,

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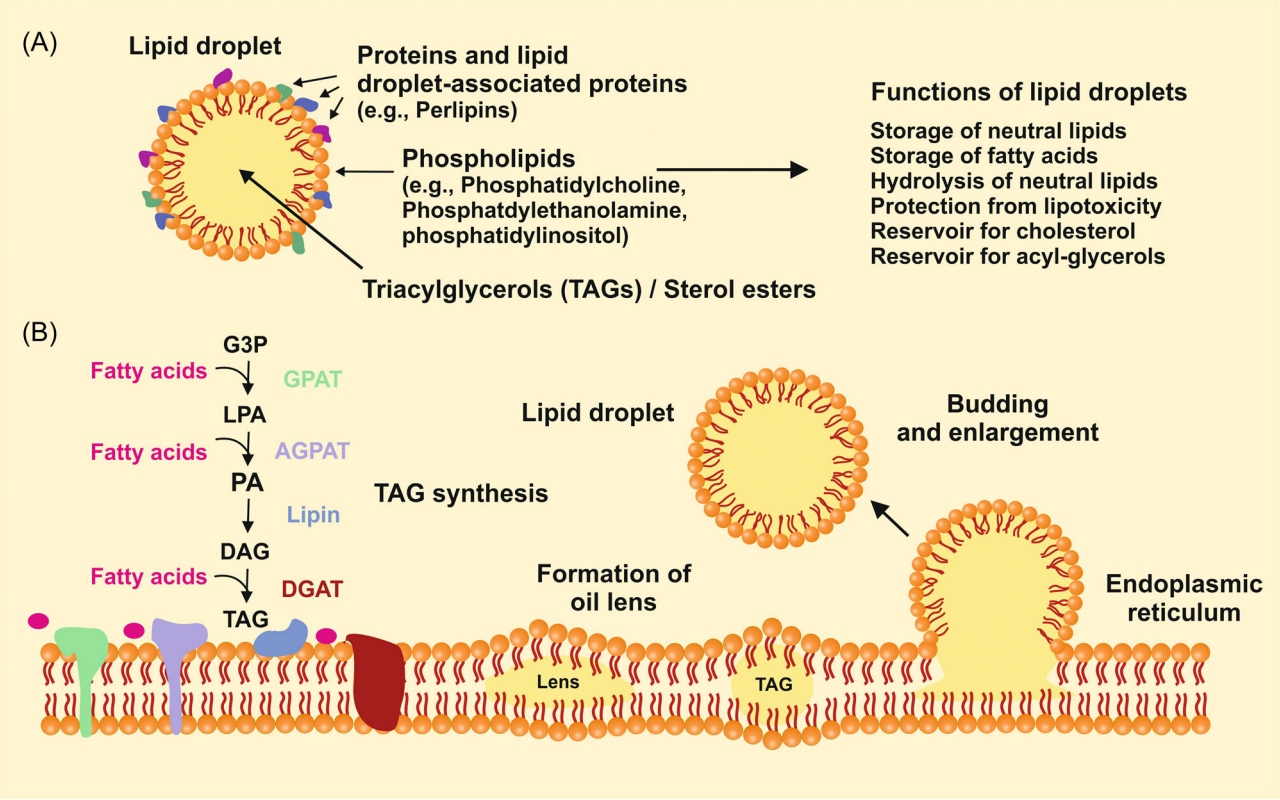


FIGURE 1 Structure, function and synthesis of lipid droplets. (A) Lipid droplets have a unique architecture consisting of a hydrophobic core of neutral lipids (triacylglycerols and sterol esters), which is enclosed by a phospholipid monolayer decorated with specific proteins. Lipid droplets regulate the storage and hydrolysis of neutral lipids and prevent cells from lipotoxicity. (B) During the biogenesis of cytoplasmic lipid droplets, triacylglycerols formed by the esterification of glycerol with three fatty acids in the endoplasmic reticulum membrane form membrane-embedded lenses that bud into the cytoplasm as droplets. Abbreviations used are: AGPAT, 1-acylglycerol-3-phosphate O-acyltransferase; DAG, diacylglycerol; DGAT, diglyceride acyltransferase; G3P, glycerol 3-phosphate; GPAT, glycerol-3-phosphate acyltransferase; LPA, lysophosphatidic acid; PA, phosphatidate; TAG, triacylglyerol. For more details refer to the main text.

eventually filling the intermembrane space, and the vesicular lumen becomes a small inclusion inside the lipid droplets.[15,16]

Although the fate of an individual lipid droplet is unclear, lipid droplets with distinct lipid and protein composition, whether targeted for lipolysis or lipid storage, are tightly regulated within the liver machinery. Dysregulation of this homeostasis ultimately leads to fatty liver or hepatic steatosis. Fat-storage protein 27 (FSP27) is abundantly expressed in white adipose tissue and brown adipose tissue and plays crucial role in LD biogenesis. The expression of FSP27 increases during adipogenesis and is responsible for lipid droplet enlargement. Furthermore, FSP27 is involved in the fusion process between lipid droplets, resulting in the formation of larger lipid droplets and increased storage and accumulation of triglycerides.[17,18]

Although strong hydrophobicity promotes lipid droplet binding, optimal hydrophobicity is critical to enable PLINs to target specific lipid droplets of a given composition.[19] Importantly, multiple studies have emphasized that phospholipid packing and crowding of surface proteins differ between lipid droplets and membrane bilayers, which affects protein targeting to lipid droplets.[20]

3 | OVERVIEW OF PERLIPINS

Initially, PLIN1 was identified on the surface of lipid droplets and was reported to regulate the accumulation and hydrolysis of triglycerides. The sequential acylation of glycerol 3 phosphate produces phosphatidic acid, which is then dephosphorylated by Lipin. The resulting DAG is converted to triglyceride by the addition of a third fatty acyl group by DGAT, which is localized in the ER. The production of phosphatidic acid serves as a branch point for triglycerides and phospholipid synthesis. Free cholesterol, whether from extracellular sources or synthesized de novo, is acylated by ER-localized

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acyl-coenzyme A:cholesterol acyltransferase to produce cholesteryl ester. These neutral lipids, triglycerides and CE, accumulate in intracellular lipid droplets and are utilized as energy sources or as precursors for steroid hormones.[21]

Each perilipin has a defined expression pattern and function, with their precise role best understood in mouse models lacking a specific perlipin (Table 1).

The five members of the PLIN protein family, PLIN1 to PLIN5, possess an 11-mer repeat motif that forms amphipathic helices. These helices bind micelles and lipid droplets and share a conserved 4-helix bundle structure known as the PAT domain. This domain is localized in the C-terminal part of all PLINs, except for PLIN4, which has a polypeptide length three times that of the other PLIN proteins.[4] The PAT domain is known to contribute to the association of PLIN proteins with the lipid droplet surface. Additionally, the N-terminal, C-terminal, and central regions of PLIN1 and PLIN2 also contribute to LD localization.[21]

In PLIN1, a hairpin structure is formed by three sequences of hydrophobic amino acids and a carboxy terminus with central proline residues. This structure embeds into the lipid droplet core.[25] In contrast, PLIN2, PLIN3, PLIN4, and PLIN5 have a carboxy terminal hydrophobic cleft with a unique α-β domain and a 4-helix bundle.[26] It is believed that this carboxy terminal structure is responsible for binding cholesterol and

TABLE 1 Expression, function and phenotypes of mice lacking individual Perlipins.[a]

Perilipin	Expression	Function	Phenotype of knockout mouse
PLIN1	Major expression in white adipose tissue and brown adipose tissue	Stabilization of large lipid droplet, activity in hormone-induced lipolysis	Mice display resistance to diet-induced obesity and have reduced expression of lipid synthetic genes. They also show signs of adipose tissue inflammation and insulin resistance, possibly because of the recruitment of proinflammatory macrophages.
PLIN2	Ubiquitously expressed with preference in liver, premature adipocytes, macrophages, mammary gland, and epithelia	Generation of small lipid droplets, stabilization of lipid droplets, adipocyte differentiation, targeting proteins to lipid droplets, and slower rates of lipolysis	These mice exhibit reduced hepatic triacylglycerol levels and resistance to diet-induced obesity. Additionally, they exhibit increased body temperature when fed a high carbohydrate diet, they have fewer enterocyte lipid droplets in response to dietary lipids, lower lipid absorption, higher fecal lipid content, and experience alterations in the gut microbiome.
PLIN3	Ubiquitously expressed, skeletal muscle, mast cells, neutrophils, sebocytes, retinal pigment, epithelium	Formation of triacylglycerol and lipid droplets, binding to diacylglycerol, stabilization of lipid proteins, protection against endplasmic reticulum stress, required for hepatitis C virus replication, intracellular trafficking	These mice exhibit reduced lipid droplet formation, decreased steatosis, and lowered secretion of very low-density lipoprotein (VLDL) in diet-induced hepatic disease models.
PLIN4	White adipose tissue, skeletal muscle	Adipocyte differentiation, impact on mitophagy and rescue of mitochondrial damage and dysfunction	These mice display decreased levels of cardiac triacylglycerol combined with lower expression of *Plin5*.
PLIN5	Highest expression in highly oxidative tissues such as brown adipose tissue, heart, muscle and liver	Fatty acid supply to mitochondria, promotion of lipid droplet accumulation and stabilization, regulation of lipolysis	Reduced lipid droplet accumulation in various oxidative tissues, skeletal muscle insulin resistance, improved liver insulin sensitivity, protection against nonalcoholic fatty liver disease and hepatocellular carcinoma, as well as altered lipid metabolism and inflammatory responses.

[a]Information of data depicted in this table was compiled from.[22–24]

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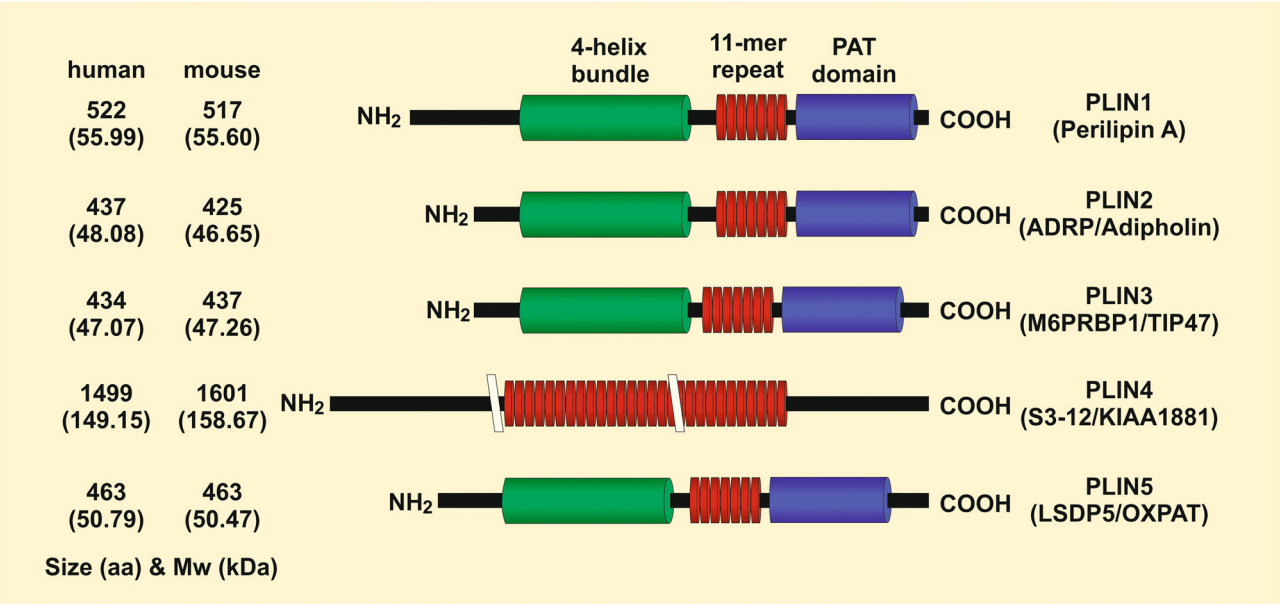


FIGURE 2 Structures of the five perilipins. The perilipin family members PLIN1 to PLIN5 are structurally related, consisting of a 4-helix bundle and variable numbers of 11-mer repeats. PLIN1, PLIN2, PLIN3 and PLIN5 also have a PAT domain, which is absent in PLIN4. The depicted sizes of proteins of human and murine perilipin proteins were obtained from the protein database of the National Library of Medicine (https://www.ncbi.nlm.nih.gov/protein/) using the following access numbers: NP_001138783.1 (hPLIN1), NP_001113.2 (hPLIN2), NP_005808.3 (hPLIN3), XP_054177885.1 (hPLIN4), NP_001013728.2 (hPLIN5), NP_783571.2 (mPLIN1), NP_001390641.1 (mPLIN2), NP_080112.1 (mPLIN3), NP_001359163 (mPLIN4), and NP_080150.2 (mPLIN5). The molecular weight (Mw) of these proteins was calculated using a Expasy online tool (https://web.expasy.org/compute_pi/).

various fatty acids. The structure of perilipins is depicted in Figure 2.

3.1 | PLIN1

PLIN1, which was originally discovered in white adipose tissue, is abundantly expressed in mature adipocytes and phosphorylated in a cAMP-dependent manner. It is localized to the surface of lipid droplets during the differentiation into lipid-accumulated mature adipocytes. Interestingly, PLIN2 in immature adipocytes is replaced by PLIN1 in lipid droplet particles enriched with lipids during this differentiation process. This clearly demonstrates the involvement of PLIN1 in the formation of large lipid droplets, which is a characteristic feature of white adipose tissue. PLIN1 is also expressed in brown adipose tissue and cardiac muscle, but to a lesser extent than in white adipose tissue.[27] In white adipose tissue, the hormonal stimulation activates lipogenesis, followed by the hydrolysis of three ester bonds by adipose triglyceride lipase (ATGL). ATGL hydrolyzes triglycerides to generate diacyclglycerol (DG). Hormone-sensitive lipase (HSL) then converts DG to monoacylglycerol (MG), and MG lipase hydrolyzes MG. The phosphorylation of PLIN1 and HSL by protein kinase A (PKA) occurs after activation by adrenaline and interaction with G-protein β receptors. Catecholamines initiate lipolysis through β-adrenergic receptors, which activate PKA in a phosphorylated manner. This signaling cascade in turn phosphorylates PLIN1 and recruits' lipases and other enzymatic proteins to initiate lipolysis.[28]

To summarize, under basal conditions, PLIN1 stabilizes lipid droplets, inhibits lipolysis, decreases triglyceride hydrolytic activity and ATGL, and decreases fatty acid and direct cellular lipotoxicity. In contrast, when there is dysregulation in lipid homeostasis, activation of PKA leads to phosphorylation of PLIN1, activating ATGL and causing lipotoxicity.

Strikingly, when PLIN1 and ATGL localize on the surface of lipid droplets, under unstimulated conditions, lipid droplet-associated protein comparative gene identification-58 (CGI-58) forms a complex with PLIN1. CGI-58 is released after PLIN1 phosphorylation, followed by ATGL activation. It is noteworthy that changes in lipid droplet size of the hormone stimulated adipocytes are driven by PLIN1, which acts as a regulator of triglyceride hydrolysis by controlling CGI-58, the activator of ATGL.[29,30]

Although PLIN1 is not expressed in normal hepatocytes, it is upregulated in steatohepatitis, particularly surrounding large lipid droplets.[31] PLIN1 overexpression

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is associated with hepatocyte ballooning due to its interaction with FSP27, which facilitates fusion between two lipid droplets and the formation of a large lipid droplet that stores neutral lipids.[14] An interesting study demonstrated that, contrary to its anti-lipolytic effects, PLIN1 may actually aid in the synthesis of lipid droplets by enhancing the uptake of fatty acids. This is achieved through its interaction with Caveolin 1, which coordinates the incorporation of exogenous fatty acids into triacylglycerols stored within lipid droplets.[32]

Despite studies showing that PLIN1 ablation reduces lipid synthesis and makes mice resistant to obesity, PLIN1 null mice still experience inflammation in their adipose tissue and insulin resistance due to the recruitment of proinflammatory macrophages.[33] Furthermore, when PLIN1 is overexpressed specifically in adipose tissue, it improves glucose tolerance and insulin sensitivity, indicating that PLIN1 plays a crucial role in balancing lipid homeostasis and insulin sensitivity in adipose tissue.[34]

3.2 | PLIN2

PLIN2 is the major protein found in hepatic lipid droplets and is expressed in various cell types such as macrophage-derived foam cells, sebocytes, and epithelial cells. During the differentiation of adipocytes, PLIN2 is present in premature adipocytes but is replaced by PLIN1 in mature adipocytes.[35] PLIN2 is known to be the most abundant protein in the phospholipid monolayer of hepatic lipid droplets, and it plays a crucial role in their formation and stability. Several studies have shown that PLIN2 promotes the formation of lipid droplets and protects triglycerides from being broken down (lipolysis). In fact, one study found that mice lacking PLIN2 are resistant to obesity, fatty liver disease, and hepatic steatosis caused by a high-fat diet.[36] The expression of PLIN2 in the liver and kidney is regulated by peroxisome proliferation-activated receptors (PPARs) and retinoid X receptor. The levels of PLIN2 in cells are correlated with the levels of triglyceride storage.[37] When there is a lack of available lipids, macrophage-derived foam cells have fewer lipid droplets. However, the presence of proteasome inhibitor MG132 can protect the levels of PLIN2. Studies have shown that PLIN2 is degraded by the ubiquitin proteasome pathway in the absence of lipids, while it stabilizes lipid droplets in the presence of high intracellular lipid content. This was demonstrated in PLIN2 transfected hamster ovary cells and mouse embryonic fibroblasts.[38,39]

The involvement of the autophagy mechanism in lipid droplet breakdown, through the degradation of PLIN2 and triglycerides in liver cells, is supported by the accelerated lipid accumulation observed when autophagy-related 5 (ATG5) or lysosomal membrane proteins are lost.[40] One study found that PLIN2 is the most upregulated protein in the livers of rodents and humans with fatty liver disease, making it a reliable marker for hepatic lipid droplets.[41] Additionally, PLIN2 promotes triglyceride accumulation, while decreasing fatty acid oxidation and glucose tolerance.[36] This was demonstrated when PLIN2 knockout mice on a high-fat diet were protected from steatosis.[36] Moreover, when PLIN2 was knocked down in mice, hepatic triglyceride levels and genes involved in fatty acid metabolism were reduced.[42] Another study showed that cholesterol and triglyceride levels were significantly reduced in the livers of mice with a whole body knockout of PLIN2. Additionally, this study demonstrated an increase in production of ω-3 and ω-6 long-chain fatty acids in mouse hepatocytes, which in turn reduced cholesterol synthesis and lipogenesis.[43]

However, there is conflicting data regarding the correlation between circulating levels of PLIN2 and factors such as age, body mass index, gender, and proinflammatory markers. One study that analyzed 318 volunteers of Caucasian ancestry reported that women have higher levels of circulating PLIN2 that strongly correlate with body mass index and inflammatory and metabolic markers.[44] In contrast, a study that measured PLIN2 serum levels in 259 critically ill patients found no correlation with obesity, body mass index, total cholesterol, triglycerides, diabetes mellitus, traditional markers of inflammation, such as white blood count and C-reactive protein. However, it did find a strong negative correlation with lipase and adiponectin as well as increased levels in patients with malignant diseases.[45] This suggests that the health status of individuals may significantly impact the quantities of circulating PLIN2, regardless of the typical markers found in obese individuals or patients with diabetes.

A polymorphism of PLIN2, Ser251Pro has recently been reported to disrupt the α-helix of PLIN2, resulting in decreased plasma triglycerides and VLDL. Additionally, the expression of PLIN2 has been associated with oxidative damage, which is a characteristic of ballooned hepatocytes.[31,46] Previous studies have shown that PLIN2 is overexpressed in MASLD and hepatic steatosis. In line with this, recent studies suggest that PLIN2 knockout mice show improvement in MASLD due to impairment of SREBP signaling, which is involved in de novo lipogenesis.[43,47]

It is interesting to note that PLIN2 is associated with the maturation of lipid droplets with the help of the cell death-inducing DFFA-like effector-B protein (CIDEB).

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Overexpression of PLIN2 inhibits the activity of ATGL, which plays an important role in the lipolysis of triglycerides into free fatty acids.[48] PLIN2 also plays a significant role in the formation and maturation of VLDL assembly via CIDEB.

A striking study demonstrated that liver-specific ablation of PLIN2 alleviates diet-induced hepatic steatosis through a mechanisms involving phosphatidylethanolamine N-methyltransferase (PEMT), which is dependent on compensatory changes in proteins involved in phospholipid remodeling, inflammation, and ER stress. This alleviates MASH.[49] Additionally, PLIN2 has actions beyond hepatocytes in cellular lipid metabolism. A study reported that whole-body knockout of PLIN2 protected mice on a Western diet from obesity, insulin resistance, adipose inflammation, and MASH. However, hepatocyte-specific deletion of PLIN2 only protected against hepatic steatosis and not obesity, insulin resistance, or adipose inflammation. Further investigation revealed that in both cases, PLIN2 deletion impaired monocyte recruitment and the polarization of proinflammatory macrophages induced by Western diet. Liver-specific knockout of PLIN2 reduced hepatic lipid levels by decreasing SREBP1c and its regulated lipogenic enzymes, such as acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase and stearoyl-CoA desaturase (SCD1). Whole-body PLIN2 knockout mice prevented fatty liver formation by inhibiting de novo lipogenesis and obesity-dependent activation of PPARα and CD36.[50]

Notably, the alteration of phospholipid monolayer by PLIN2 enables lipid droplet targeting. Under nutrient deprivation, the activation of AMPK catalyzes the phosphorylation of PLIN2. This modification is recognized by HSC70, facilitating the degradation of PLIN2 via chaperone-mediated autophagy.[51] Further studies on PLIN2 revealed that mice lacking PLIN2 and fed a high carbohydrate diet exhibited browning of subcutaneous adipose tissue and an increase in body temperature.[52] The contribution of PLIN2 to systemic energy metabolism in the intestine can be explained by lower lipid absorption, increased fecal content, and reduced enterocyte lipid droplets in mice lacking PLIN2.[53]

3.3 | PLIN3

PLIN3 is ubiquitously expressed, similar to PLIN2, and it localizes to the cytosol and lipid droplets. It is involved in the transport of lysosomal enzymes from the trans-Golgi to the lysosome, which is regulated by its binding to the mannose-6-phosphate receptor (M6PR). PLIN3 binds to the cytosolic domain of M6PR, leading to its inclusion in transport vesicles. However, no study has been reported to date on the role of lipid droplets in lysosome trafficking.[54] The four-helix bundle structure of PLIN3 contains a deep cleft that facilitates fatty acid binding and lipid droplet recruitment.[55]

In the THP-1 macrophage cell line, knockdown of PLIN3 resulted in decreased TG levels, while overexpression of PLIN3 caused an accumulation of triglycerides in these cells.[56] When diglycerides accumulate in the ER, PLIN3 binds to sites of lipid droplet formation. In the retinal pigmental epithelium, the recruitment of PLIN3 to lipid droplets is due to the formation of all-trans-retinoic acid following photobleaching.[57] Similar to PLIN2, PLIN3 is also involved in the formation and stabilization of lipid droplets.[58] Human mast cells and cultured LAD2 mast cells have been shown to have the presence of PLIN2 and PLIN3 coated LD particles.[59] PLIN3 is also detected as the predominant protein in neutrophils, playing a crucial role in lipid droplet formation and PGE2 generation in these cells.[60] It was also shown that PLIN3 knockdown resulted in the inhibition of LD formation and PGE2 secretion. Additionally, PLIN3 was shown to have associations with PGE2 production during inflammation and when HL-60 derived neutrophils were treated with LPS, PLIN3 demonstrated overexpression with increased PGE2 production. These results infer the essential role of PLIN3 in inflammation and fatty liver disease.[60] PLIN3 has a significant role in mouse MASLD as it is upregulated in the livers of mice on a high-fat diet. Furthermore, PLIN3 knockdown reduces hepatic triglycerides and improves insulin sensitivity.[61]

PLIN3 was shown to be expressed in sebocytes, and its knockdown attenuated linoleic acid-induced lipid droplet formation in these cells.[62] Notably, PLIN3 is also a regulator of triglycerides in muscle cells. This was demonstrated by an increase in triglyceride stores in C2C12 myotubes through PLIN3 overexpression.[63] The role of PLIN3 in regulating phospholipid metabolism can be explained by its completion with CCTα, which catalyzes a key step in phosphatdylcholine synthesis. PLIN3 binds to nucleoplasmic lipid droplets to antagonize phosphatidylcholine synthesis.[64]

3.4 | PLIN4

PLIN4 has a molecular weight nearly three times higher than other PLINs and lacks a PAT domain. Like PLIN1, it is predominantly expressed in adipocytes and can be found in both lipid droplets and the cytosol. In the middle to late stages of adipocyte differentiation, PLIN4 is induced along with PLIN1, as confirmed in 3T3-L1 cells and OP9 mouse preadipocytes.[65,66] Additionally, it

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has been shown that olanzapine increases PLIN2 expression during the early phase of human mesenchymal stem cell differentiation and promotes PLIN4 expression in later stages.[65] The upregulation of PLIN4 in hepatocytes is associated with micro-steatosis.[14] Human PLIN4 contains the largest 11-mer sequence, consisting of nearly 1000 amino acids.[67]

3.5 | PLIN5

PLIN5 is highly expressed in heart tissues and is regulated by PPARα as the first intron of PLIN5 contains PPAR regulatory elements. Furthermore, it has been reported to be expressed in pancreatic islet β cells and hepatic stellate cells. A unique characteristic of PLIN5 is that it is present in lipid droplets that are smaller and have an association with mitochondria in cardiomyocytes.[68,69] Cultured cardiac muscle cells obtained from PLIN5 null mice exhibited greater fatty acid oxidation, suggesting that lipid droplets in cardiac muscle play an important role in the reservoir and distribution of fatty acids.[68]

PLIN5 has been shown to regulate lipid metabolism in mouse islet β-cells by enhancing fatty acid incorporation into triglycerides and increasing lipolysis rates in these cells.[70] Furthermore, glucose tolerance was improved with PLIN5 overexpression in mouse β-cells. PLIN5 also restores lipid droplet formation in activated hepatic stellate cells and inhibits fibrotic changes.[69] Therefore, the expression of PLIN5 is involved in mitochondrial damage, ER stress and cytokine regulation making it a crucial target for MASLD studies.

PLIN5 expression and disruption of PLIN5 degradation have been shown to amplify the accumulation of hepatic lipid droplets in MASLD.[71] PLIN5 is composed of 463 residues, and is encoded by 8 exons located on chromosome 19p13.3 in humans.[72] It has been demonstrated that PLIN5 is induced by PPARα agonists in the liver, skeletal muscle, cardiac muscle, and white adipose tissue.[73]

The interaction between PLIN5 and ATGL results in decreased lipolysis.[74] Several transgenic mouse models have been developed to better understand the association of PLIN5 associations between PLIN5 and MASLD. Some notable models are listed in Table 2.

These studies provide valuable information on the signaling and regulation of PLIN5. For example, the improvement of insulin sensitivity in the liver and insulin resistance in the skeletal muscle in PLIN5 null mice can be explained by increased lipolysis derived from fatty acids, which then turn into sphingolipids causing insulin resistance in skeletal muscle but not in the liver.[22] In the same context, liver-specific knockdown of Notch1 in mice caused upregulation of glucose-6-phosphate and PLIN5, leading to the development of insulin resistance. This indicates crosstalk between these genes in glucose response.[77]

Another valuable study provided evidence that statins decrease PLIN5 levels in a steatosis-like model of human hepatocytes, indicating the possibility of PLIN5 as a target for hepatic steatosis.[78] Another recent study showed that a combination of oleic acid and either a PI3K inhibitor or PPARα inhibitor decreased PLIN5 levels in a dose-dependent manner, indicating the role of PLIN5 in lipid droplet formation. In addition, the involvement of the PI3K pathway in ER stress suggests that PLIN5 may act as a mediator in ER stress.[79]

One study demonstrated that overexpression of PLIN5 alleviated the release of proinflammatory markers, such as IL-6, IL-1β and TNF-α, and upregulated Nrf2, HO-1, and NAD(P)H. The same study reported the role of PLIN5 in oxidative stress through AMPK/Nrf2 pathway.[69]

Several studies have reported on the role of PLIN5 in various aspects of MASLD, including dyslipidemia, increased oxidative stress, and ROS production. One study conducted on mice under fasting conditions found that depletion of PLIN5 led to reduced lipid droplet formation and triacylglycerol content in the heart, soleus muscle, white adipose tissue, and brown adipose tissue.[68] Additionally, the same study found that PLIN5 promotes ROS production and inhibits ATGL activity, while the absence of PLIN5 increases fatty acid oxidation in the mitochondria of the heart and decreases triacylglycerol levels.[68]

Another study on PLIN5 in skeletal muscle suggests that overexpression of PLIN5 in the skeletal muscle of mice fed a high-fat diet protected the liver from inflammation. This overexpression was also associated with a decrease in hepatic expression of inflammatory markers such as IL6, TNF-α, and MCP1.[80] In the heart, PLIN5 overexpression increased the expression of *Nrf2* target genes, leading to oxidative stress and upregulation of the NRF2 pathway. This upregulation served as a compensatory mechanism against lipid droplet formation in the heart.[81]

In-vitro studies have suggested that overexpression of PLIN5 reduces ROS levels and stimulates the expression of key genes involved in regulating mitochondrial functions, such as cytochrome C oxidase subunit 2 and 4, and citrate synthase.[82] This indicates that PLIN5 acts as a co-regulator in oxidative response. Furthermore, liver-specific knockout of PLIN5 in mice has been shown to inhibit the induction if inflammation induced by lipopolysaccharides, which triggers the production of inflammatory proteins such as LCN2 and NLRP3. This protective

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TABLE 2 Phenotypic characteristics in mouse whole-body PLIN5 knockout models.

Organ/type of knockout	Phenotypic characteristics	Reference
Heart/whole-body	There are no lipid droplets in the heart and decreased triacylglycerol and fatty acid content; increased cardiac oxidative stress; reduced expression of *Plin2*; increased fatty oxidation and oxidative stress in cardiomyocytes	Kuramoto et al.[68]
	Reduction of cardiac triacylglycerol content and lipid content; reduced lipid droplet size due to increased ATGL-mediated lipolysis	Mason et al.[22]
Liver/whole-body	Lowered hepatic glucose production and expression of insulin-sensitive gluconeogeneic genes; improvement of insulin sensitivity	Mason et al.[22]
	Increased triacylglycerides and fatty acids during fasting periods; lowered triacylglycerides and fatty acid in fed states	Kuramoto et al.[68]
	Decreased hepatic lipid content and lipid droplet sizes due to elevated lipolysis rates; livers show enhanced mitochondrial oxidative capacity; hepatocytes show signs of lipotoxic injury, increased rates of lipid oxidation, elevated mitochondria proliferation, possibly by increased expression of PPARα	(Wang et al.[75])
	In a MASLD and MASLD-HCC model, the loss of Plin5 was associated with reduced steatosis, mitochondrial oxidation, altered expression of genes involved in lipid metabolism and immune responses; the mice were protected mice from activation of inflammatory signaling and hepatocellular carcinoma; during MASLD progression to HCC, the loss of *Plin5* favors a milder outcome	Mass Sanchez et al.[23]
Liver/Hepatocyte specific	Hepatocytes showed decreased fatty acid uptake and storage, fatty acid oxidation, and reduced triglyceride secretion combined with reduced contacts between lipid droplets and mitochondria; livers exhibited activation of c-Jun N-terminal kinase, insulin resistance	Keenan et al.[76]
Muscle/whole-body	Formation of skeletal muscle insulin resistance associated with ceramide accumulation	Mason et al.[22]

effect is crucial for preventing liver injury.[83] Additionally, in a MASH model with a methionine-choline deficient diet, LCN2, an acute inflammatory protein and regulator of lipid uptake, has been found to regulate PLIN5. Interestingly, this regulation occurs independently of PPAR activation. Even when stimulated with a PPARα agonist, LCN2 expression was not suppressed.[84]

Recently, it was demonstrated that *Plin5*$^{-/-}$ whole-body null mice were protected against MASLD and the subsequent development of HCC.[23] In this model, the mice were exposed to a single dose of the carcinogen 7,12-dimethylbenz(a)anthracene and then subjected to a 30-week high-fat diet supplemented with glucose/fructose. Importantly, compared to wild-type mice the loss of *Plin5* reduced steatosis, mitochondrial oxidation, altered the expression of genes involved in lipid metabolism and immune response, protected mice from activation of inflammatory signaling, while not improving glucose tolerance.[23] All these changes were associated with a lower tendency to develop HCC, suggesting that the loss of Plin5 protects against worsening MASLD by reducing inflammatory signaling. During the progression of MASLD to HCC, the loss of *Plin5* favors a milder outcome.

In summary, these studies demonstrate the broader impacts of PLIN5 in regulating lipotoxicity, inflammatory response, and mitochondrial dynamics, all of which are involved in the pathogenesis of MASH (Figure 3). In addition, the effects of PLIN5 are tissue specific, and its depletion can have contradictory outcomes, depending on the tissue and the factors that regulate PLIN5 expression in cells.

It is evident that all perilipins have different function during progression of MASLD.[85] During the initiation and progression of MASLD, each member exhibits a characteristic pattern of expression, which may be crucial in controlling the formation and/or stability of lipid droplets at different stages. In particular, PLIN5 regulates numerous biological activities that impact the pathogenesis of MASLD and MASH (Figure 4).

4 | PERLIPINS IN SARCOPENIA AND MASLD

Skeletal muscle and liver are both target organs of insulin, playing important roles in glucose metabolism. In sarcopenia, insulin resistance is a key factor in both

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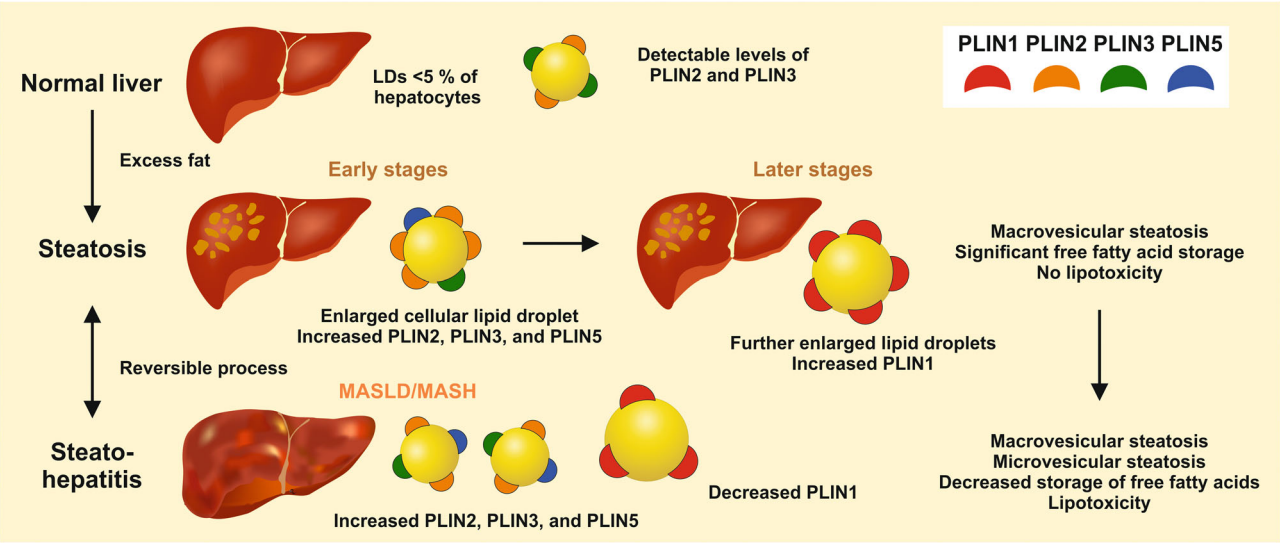


FIGURE 3 Cellular function of PLIN5 in the pathogenesis of MASLD/MASH development. In the liver, PLIN5 serves various functions. It regulates proinflammatory cytokine and cell response, increases the synthesis of arachidonic acid, impacts mitochondrial structure and function, is involved in the control of endoplasmic reticulum stress, and plays a key role in controlling fatty acid metabolism and lipid droplet formation. In hepatocytes, PLIN5 stimulates the expression of lipocalin 2 through the NF-κB/IL-1β axis.

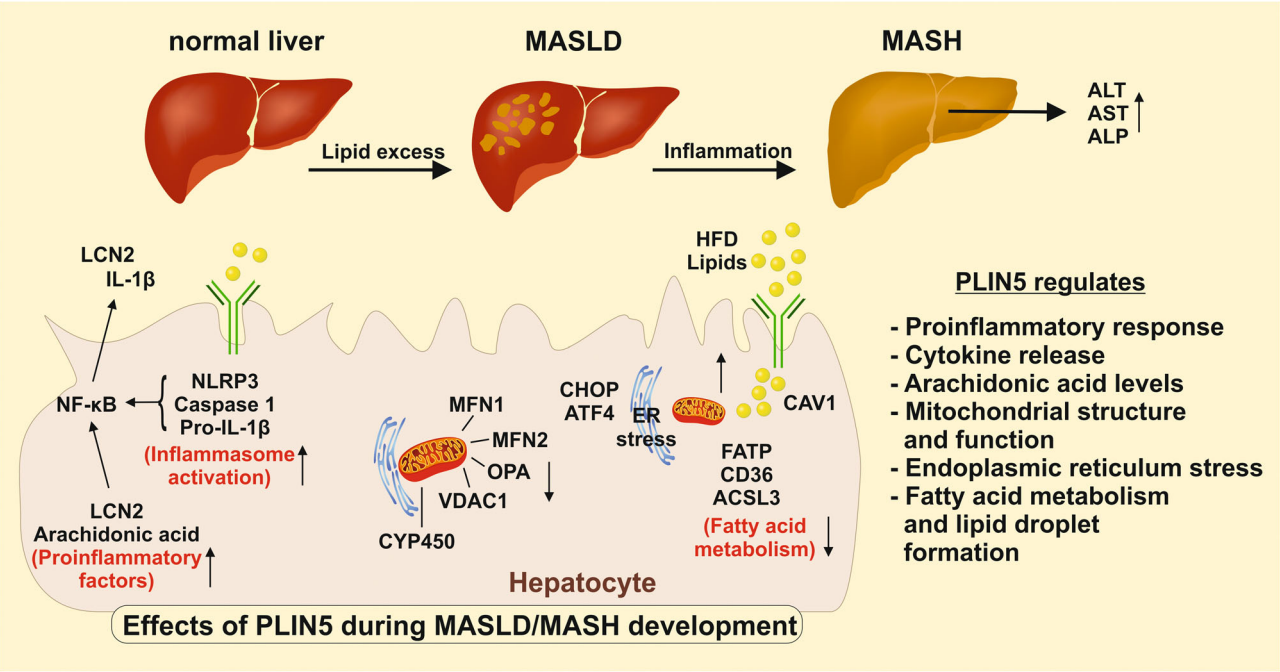


FIGURE 4 Perilipin 5 in the pathogenesis of MASLD/MASH. In a normal liver, where less than 5% of all hepatocytes contain lipid droplets, there are low quantities of PLIN2 and PLIN3 detectable. However, during steatosis and steatohepatitis, the number of hepatocytes carrying lipid droplets increases. Depending on the progression of the disease, the quantities of perilipins change. In the early stages, the lipid droplets enlarge and the expression of PLIN2, PLIN3, and PLIN5 increases. In later stages PLIN1 expression is significantly increased. Importantly, in steatosis, the expression of PLIN2, PLIN3, and PLIN5 is further elevated, while the expression of PLIN1 is decreased. Abbreviations used are: ACSL3, Acyl-CoA synthetase long chain family, member 3; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; ATF4, activating transcription factor 4; CAV1, caveolin 1; CD36, cluster of differentiation 36; CHOP, C/EBP-homologous protein; CYP450, cytochrome P450; ER, endoplasmic reticulum; FATP, long chain fatty acid transport protein; IL-1β, interleukin-1β; HFD, high-fat diet; LCN2, lipocalin 2; MFN1, mitofusin 1; MFN2, mitofusin 2; NF-κB, nuclear factor kappa-ligh-chain-enhancer of activated B-cells; NLRP3, NLR family pyrin domain containing 3; OPA, OPA1 protein; VDAC1, voltage-dependent anion channel 1.

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the development of sarcopenia and MASLD.[86,87] Inflammatory cytokines lead to skeletal muscle protein breakdown, low adiponectin levels, decreased insulin sensitivity, and hyperleptinemia, factors that are similar in MASLD.[88] Aging causes significant changes in body mass composition, with an increase in fat mass and shift in distribution from subcutaneous adipose tissue to visceral depots and ectopic sites. Free fatty acids accumulate as triglycerides, DAG, and ceramides, leading to lipotoxicity and associated conditions such as insulin resistance, hepatic steatosis, sarcopenia, and cardiovascular disorders.[89] The accumulation of intramuscular triglycerides (IMTGs) due to lipotoxicity compromises muscle function, strength, and thickness, a process that is exacerbated by aging and age-related conditions. Sarcopenia is the gradual progressive wasting and loss of skeletal muscle mass and functions, typically occurring after the age of 40.[89]

The accumulation of ectopic fat in the form of IMTGs has been proposed as a mechanism for understanding the role of PLIN2 and PLIN5 in sarcopenia. It is well known that PLIN2 and PLIN5 are the most prominent lipid droplet-associated proteins in skeletal muscle. Interestingly, in elderly subjects, the proportion of IMTGs and PLIN2 in the *vastus lateralis* muscle is increased and is inversely associated with quadriceps strength.[90] Furthermore, PLIN2 expression is linked to MURF-1, p53, and atrogin, which are genes related to muscle atrophy, suggesting the involvement of PLIN2 in muscle wasting.[91] Additionally, studies have shown that knockout of PLIN2 prevents high-fat diet-induced obesity, hepatic steatosis, and insulin resistance, while elevated levels of PLIN2 improve insulin sensitivity in skeletal muscle.[36,92]

Interestingly, intramuscular lipids impair mitochondrial function and enhance the secretion of proinflammatory myokines responsible for muscle dysfunction and skeletal muscle inflammation.[93] Furthermore, intramyocellular lipid accumulation develops when the inflow of fatty acids exceeds the oxidative capacity of skeletal muscle. These excess lipids activate PKC and phosphorylate serine of IRS1, thereby interfering with PI3K activation and blocking GLUT4 translocation. GLUT4 dysfunction results in decreased glucose utilization and free fatty acid oxidation in the mitochondria. Additionally, increased free fatty acid inflow leads to an increase in the ATP/ADP ratio in the mitochondria resulting in decreased mitochondrial respiration, an increase in ROS formation, myocyte toxicity, and the development of sarcopenia.[94] Thus, PLINs embedded in lipid droplets act as regulators of lipid metabolism and mitochondrial oxidation.

It has been reported that overexpression of PLIN5 in skeletal muscle increases the expression of genes involved in fatty acid oxidation by targeting a cluster of genes that are under control of PPARα and PPARγ coactivator 1α (PGC1α).[95] In cultured myocytes, PLIN2 was shown to increase the expression of NLRP3 inflammasome, resulting in impaired insulin stimulated glucose uptake.[96] In humans, elevated levels of PLIN2 are present in patients with sarcopenia and hepatic steatosis.[97] Thus, PLIN2 expression affects the severity of sarcopenia and MASLD while its downregulation mitigates some of these effects. In summary, therapeutic interventions targeting PLIN2 and PLIN5 might open new avenues for treating MASLD and sarcopenia due to their close association.

5 | POTENTIAL THERAPEUTIC IMPLICATIONS

As discussed the different perlipins play roles in the enlargement of lipid droplets. In the liver, elevated lipids induced steatosis, steatoheptitis, microvesicular and macrovesicular steatosis, processed that are characterized by lipotoxicity.[86] The formation of large lipid droplets is triggered by the activity of the fatty specific protein 27 (FSP27) that mediates lipid droplet growth by promoting directional lipid transfer from smaller to larger lipid droplets (Figure 5).

Therefore, in addition to perilipins, targeting FSP27, a member of the cell death inducing DFF45-like effector (CIDE) protein family that is highly expressed in MASLD, may offer an effective way to reduce the number and size of lipid droplets formed during the course of MASLD. This protein is abundantly expressed in white adipose tissue and brown adipose tissue and highly expressed in the steatotic liver.[98,99] Importantly, transcriptional activation of Fsp27 in mouse hepatocytes and the human HepG2 cell line promoted lipid droplet enlargement and triacylglycerol accumulation in the liver.[99] *Vice versa*, preliminary data showed that therapeutic silencing of Fsp27 by antisense oligonucleotides significantly reduced body weight gain and visceral adiposity, prevented diet-induced hypertriglyceridemia, and reduced atherosclerotic lesion size in LDL receptor knock-out mice.[100] Similarly, a transgenic mouse model, in which human FSP27 was overexpressed in the adipose tissue, protected against high-fat diet-induced glucose intolerance and lowered levels of triglycerides, cholesterol, and low-density lipoproteins compared to their littermate controls when fed a high-fat diet. This suggests that Fsp27 is a potential druggable target to reverse obesity-induced lipotoxicity and glucose intolerance.[101] Interfering with the expression or function of lipid droplet-associated perilipins that affect the biogenesis of lipid droplets and various aspects of lipid homeostasis

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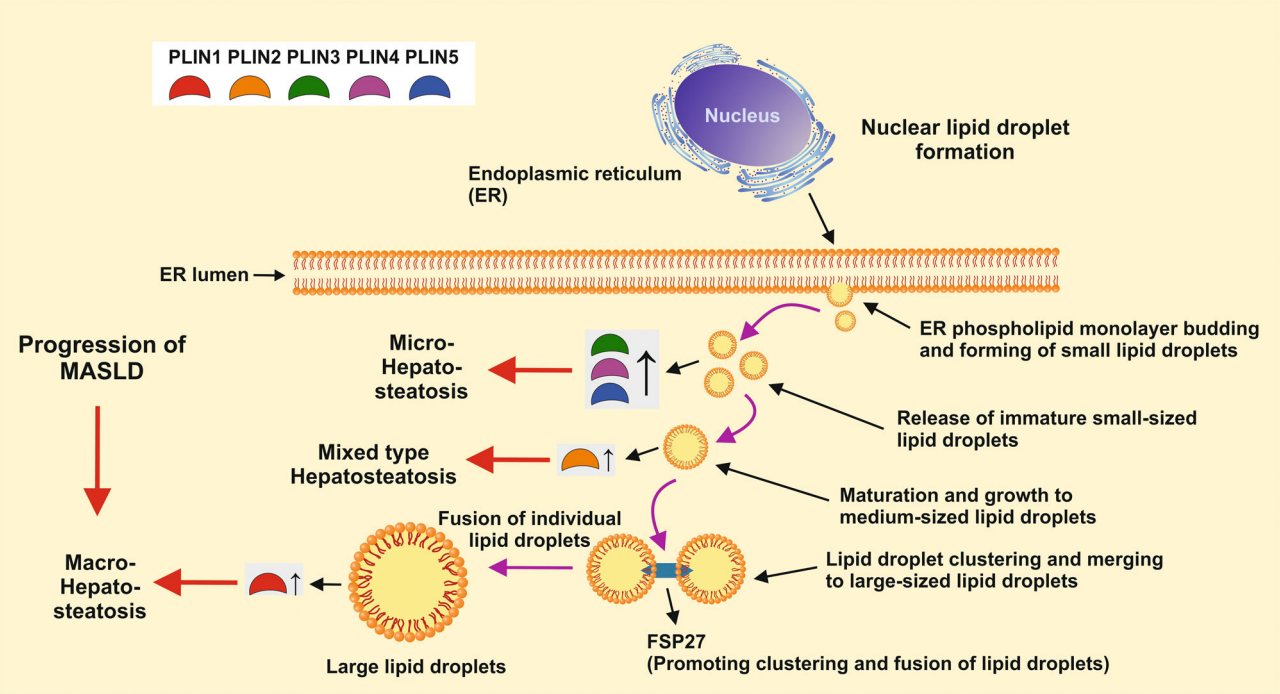


FIGURE 5 Function of the fatty acid protein 27 (FSP27) in the formation of large lipid droplets. Increased lipid droplet formation through budding and maturation is crucial in the pathogenesis of microhepatosteatosis and macrohepatosteatosis. FSP27 plays a key role in driving lipid clustering and merging into large-sized lipid droplets by facilitating lipid exchange and transfer at contact sites between lipid droplets. Similar to perilipins, which are important for lipid droplet maturation, FSP27 represents a potential therapeutic target for the treatment of fatty-associated diseases.

may offer additional viable targets for intervention in the pathogenesis of MASLD.

6 | CONCLUSION

The perilipins play essential roles in lipid droplet formation, a process that is highly dynamic, and can vary in different organ according to metabolic cues. The remarkable characteristics of the PLIN family of proteins suggest that they could be potential targets for fatty liver disease and sarcopenia, as these lipid droplet proteins provide a vital clue to maintaining normal lipid homeostasis. The five members of the PLIN family of proteins have different functions and have emerged as key components in regulating cell signaling and metabolism in addition to their indispensable role in lipid droplet metabolism and structure. Recent studies have shown that dysregulation of perilipins plays a significant role in the formation of hepatic steatosis and MASLD. Further mechanistic insights and characterization of PLINs can help identify novel therapeutic targets for MASLD and metabolic disorders. Therefore, understanding and expanding our knowledge of PLIN family protein targets in distinct stages of MASLD will help expand therapeutic targeting for MASLD.

ACKNOWLEDGMENTS

Ralf Weiskirchen is supported by grants from the German Research Foundation (grants WE2554/13-1, WE2554/15-1, and WE2554/17-1), the Deutsche Krebshilfe (grant 70115581), and the Interdisciplinary Center for Clinical Research within the faculty of Medicine at the RWTH Aachen University (grant PTD 1-5). None of the funders had a role in the design of this article or in the decision to publish it. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

Ralf Weiskirchen is Editorial Board member of the Journal of Cellular Biochemistry. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Chandrasekaran P, Weiskirchen S, Weiskirchen R. Perilipins: a family of five fat-droplet storing proteins that play a significant role in fat homeostasis. *J Cell Biochem*. 2024;125:e30579. doi:10.1002/jcb.30579

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