

## CELL SCIENCE AT A GLANCE

## SPECIAL ISSUE: CELL BIOLOGY OF LIPIDS

## Perilipins at a glance

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## ABSTRACT

Lipid droplets (LDs) are ubiquitous organelles that store and supply lipids for energy metabolism, membrane synthesis and production of lipid-derived signaling molecules. While compositional differences in the phospholipid monolayer or neutral lipid core of LDs impact their metabolism and function, the proteome of LDs has emerged as a major influencer in all aspects of LD biology. The perilipins (PLINs) are the most studied and abundant proteins residing on the LD surface. This Cell Science at a Glance and the accompanying poster summarize our current knowledge of the common and unique features of the mammalian PLIN family of proteins, the mechanisms

through which they affect cell metabolism and signaling, and their links to disease.

**KEY WORDS:** Lipid droplets, Lipid metabolism, Lipid signaling, Perilipins

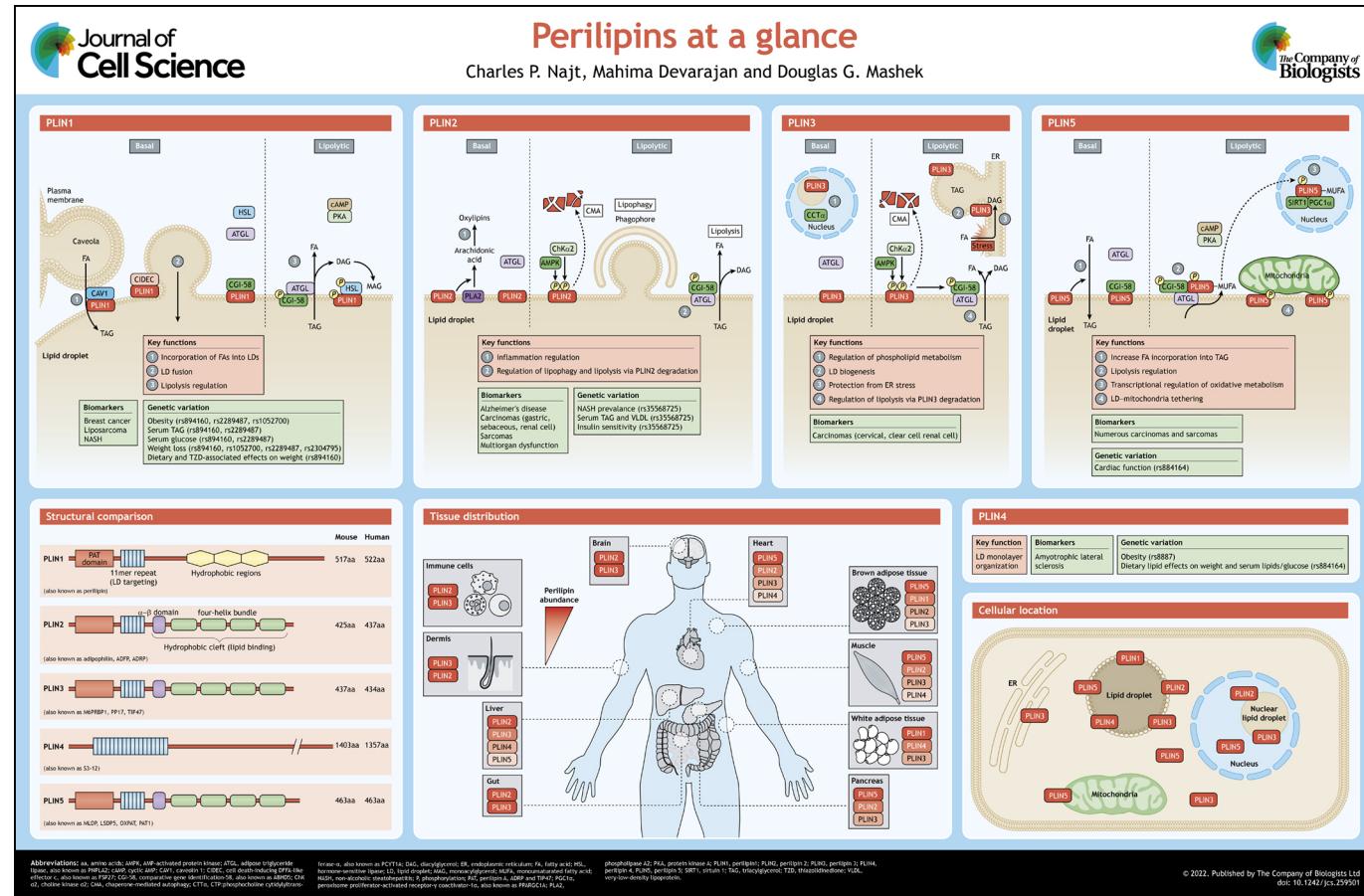
## Introduction

Research on lipid droplet (LD) biology has burgeoned in the past 30 years. From these studies, we know that LDs are formed within the endoplasmic reticulum (ER) phospholipid bilayer and then bud off into the cytosol. The core of LDs is comprised largely of triacylglycerols (TAGs) and cholesterol esters (CEs) in most cell types and is surrounded by a phospholipid monolayer. In addition to the many TAGs, CEs and phospholipid species present, hundreds of other lipids are found in lower abundance (Bartz et al., 2007; Chitruj et al., 2012). LDs may undergo expansion or fusion, which contribute to the heterogeneity of LD sizes observed in most cells. Catabolism of LDs occurs through the action of cytosolic lipases or the autophagic degradation of LDs, a process termed lipophagy (Singh et al., 2009). Many studies have also identified roles for LDs beyond energy storage and shown that LDs are central mediators of

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many aspects of cell signaling and function, which will be discussed in depth in the following sections.

The seminal event that accelerated the field of LD biology forward was the discovery of perilipin 1 (PLIN1) – the first identified LD protein – in adipocytes (Greenberg et al., 1991). There are four splice variants of PLIN1 (PLIN1a–PLIN1d), which feature carboxyl termini of various lengths (Kimmel and Sztalryd, 2016); for the purposes of this review, we will focus on PLIN1a, which is the primary form expressed in adipocytes, unless otherwise noted. PLIN1 is a member of a larger family of perilipin proteins (PLINs) that are grouped together based on their sequence homology and their affinity for LDs. The five mammalian PLIN proteins have been numbered in order of their discovery; four of the proteins share a conserved amino-terminal perilipin A, ADRP and TIP47 (PAT) domain (PLIN1, -2, -3 and -5), and all five contain an 11mer repeat sequence of various lengths that is predicted to form amphipathic helices – human PLIN4 contains the largest, at nearly 1000 amino acids in length with 29 tandem repeats of a 33mer sequence (Kimmel et al., 2010) (see poster). The latter region, conserved in all members of the PLIN family of proteins, has been shown to direct targeting of recombinant human PLIN proteins to LDs (Rowe et al., 2016). While the 11mer repeat region anchors the PLIN proteins, it is unclear what permits selective LD localization (Giménez-Andrés et al., 2021; Hansen et al., 2017; McManaman et al., 2003; Nakamura and Fujimoto, 2003). The major isoform of PLIN1 (PLIN1a), PLIN2 and PLIN5 preferentially associate with LDs enriched in TAG, whereas shorter isoforms of PLIN 1 (PLIN1c and PLIN1d) and PLIN 4 preferentially associate with LDs enriched in CE (Hsieh et al., 2012). Retinoid-containing LDs of hepatic stellate cells and retinal pigment epithelial cells have been shown to be coated with PLIN2 and PLIN5 (Blaner et al., 2009; Orban et al., 2011). Strong hydrophobicity clearly promotes LD binding, but specificity to the LD as opposed to membrane bilayers is lost if the protein hydrophobic region is too large; this suggests that there might exist a range of optimal hydrophobicity and hydrophobic moments that enables certain PLINs to target specific LDs of a given lipid composition (Chorlay and Thiam, 2020; Hsieh et al., 2012; Prévost et al., 2018). In addition to hydrophobicity of the LD-targeting sequence, the acyl chain saturation of phospholipids affects the interaction of recombinant forms of human PLIN3 with phospholipid monolayers of varying composition *in vitro* (Mirheydari et al., 2016). Several studies have suggested that phospholipid packing and surface protein crowding differ between LDs and membrane bilayers, conferring unique properties that likely impact protein targeting to LDs (Bacle et al., 2017; Kory et al., 2015; Thiam et al., 2013); a detailed review of LD targeting has recently been published (Dhiman et al., 2020).

PLIN1 has an additional three sequences of hydrophobic amino acids with central proline residues in its carboxyl terminus that mediate its targeting to LDs in cultured cells independent of the 11mer repeat sequences (Garcia et al., 2003; Subramanian et al., 2004). The hydrophobic amino acids coupled to the central proline are thought to form a hydrophobic hairpin structure that embeds into the core of the LD, similar to predicted hairpin structures of other LD-targeted proteins, such as diacylglycerol O-acyltransferase 2 and long chain acyl-CoA synthetase 3 (also known as ACSL3) (Kory et al., 2016). In contrast to PLIN1, the perilipins PLIN2, PLIN3 and PLIN5 contain a carboxyl-terminal hydrophobic cleft consisting of a four-helix bundle and a unique  $\alpha$ - $\beta$  domain, which has been highlighted in the crystal structure of PLIN3 (Hickenbottom et al., 2004; PDB:1SZI) and modeled in PLIN2 (Najt et al., 2014) and PLIN5 (Najt et al., 2020). It is this proposed

### Box 1. Expression of PLINs as disease biomarkers

LD accumulation is typically associated with detrimental cellular effects, such as insulin resistance, mitochondrial dysfunction and inflammation, among others. Consequently, the expression of PLINs is commonly linked with a plethora of diseases, especially cancer (Cruz et al., 2020; Zhang et al., 2017). Because of their tight associations with disease prevalence, some PLINs have been proposed as biomarkers for various diseases (see poster). PLIN1 expression is diagnostic for breast cancer (Zhou et al., 2016), liposarcoma (Westhoff et al., 2017) and NASH (Carr et al., 2017). PLIN2 has been proposed as a biomarker for Alzheimer's disease (Conte et al., 2021), as well as numerous types of carcinomas (Ostler et al., 2010; Sun et al., 2020; Tolkach et al., 2017) and sarcomas (Straub et al., 2019). Serum PLIN2 is also predictive of multi-organ dysfunction in critically ill patients (Kurt et al., 2021), which is consistent with its general inflammatory effects. PLIN3 has been linked to several forms of carcinoma (Szigeti et al., 2009; Wang et al., 2018), and PLIN4 is proposed as a biomarker for amyotrophic lateral sclerosis (Zhu et al., 2021). Finally, PLIN5 has been proposed as a diagnostic marker for numerous types of carcinomas and sarcomas (Asimakopoulou et al., 2019; Hashani et al., 2018). Given the intimate relationship between the expression levels of various PLINs and the abovementioned diseases, defining the mechanisms through which these proteins contribute to disease etiology warrants research attention.

carboxyl-terminal structure that is responsible for binding non-membrane-associated lipids, such as cholesterol and various fatty acids (FAs) (Hickenbottom et al., 2004; Najt et al., 2014, 2020). In addition, the carboxyl-terminal region in PLIN1 and PLIN5 bind the lipase co-activator comparative gene identification-58 (CGI-58, also known as ABHD5), whereas no study has shown CGI-58 binding to PLIN2 or PLIN3 (Patel et al., 2014). While much remains to be elucidated regarding the unique structural features of the PLINs, the regions outlined above contribute to the shared and unique biological functions of each of the PLINs, which we discuss below, together with their roles in disease (see also Boxes 1 and 2).

### PLIN1

PLIN1 is expressed primarily in adipocytes found in adipose and breast tissue, but lower levels of expression are also detected in steroidogenic cells and in hepatocytes from subjects with non-alcoholic steatohepatitis (NASH), a liver pathology consisting of fat buildup, inflammation and fibrosis (Servetnick et al., 1995; Straub et al., 2008). Perhaps the most studied function of PLIN1 is its role in lipolysis, a highly orchestrated process entailing the catabolism of esterified lipids to their FA constituents (Coleman and Mashek, 2011). In adipocytes, adipose triglyceride lipase (ATGL, also known as PNPLA2) catalyzes the initial step in the lipolytic cascade – the hydrolysis of TAG – and is followed by hormone-sensitive lipase (HSL), which facilitates diacylglycerol (DAG) hydrolysis into monoacylglycerol (MAG). ATGL is regulated by interactions with numerous proteins, including its primary co-activator CGI-58. Under basal (unstimulated) conditions, PLIN1 interacts with CGI-58 at the LD surface and renders it inaccessible to ATGL (Granneman et al., 2007) (see poster). Upon lipolytic stimulation following activation of the cyclic AMP–protein kinase A (PKA) pathway, PKA phosphorylates PLIN1 (Zhang et al., 2003) as well as CGI-58 (Sahu-Osen et al., 2015) and HSL (Anthonsen et al., 1998). Following the phosphorylation of PLIN1, its interactions with CGI-58 are disrupted, allowing CGI-58 to bind and recruit ATGL to the LD surface (Granneman et al., 2007, 2009) (see poster). Phosphorylation of PLIN1 also drives its interactions with HSL (Granneman et al., 2007; Miyoshi et al., 2007), whereby cytosolic

**Box 2. Genetic variation of PLINs and disease**

Numerous polymorphisms of various PLINs have been identified that associate with the prevalence of several diseases or disease biomarkers (see poster). Frameshift mutations in the PLIN1 gene result in partial lipodystrophy in humans, which is characterized by an abnormal distribution of adipose tissue, highlighting the importance of this protein in systemic lipid homeostasis (Gandotra et al., 2011). Numerous variants of PLIN1 are associated with obesity (Qi et al., 2004, 2005), resistance to weight loss (Aller et al., 2017; Corella et al., 2005; Ruiz et al., 2011; Smith et al., 2008), as well as serum levels of TAG and glucose (Qi et al., 2004). In addition, the rs894160 gene variant of PLIN1 mediates the effects of diet composition on weight gain (Smith et al., 2008). Specifically, subjects with the minor allele of this variant have lower incidence of obesity when consuming diets with higher complex carbohydrate intakes, whereas in subjects with lower carbohydrate intake, the minor allele is associated with increased obesity. Similarly, the PLIN4 rs8887 gene variant is associated with obesity, and both rs8887 and rs884164 gene variants of PLIN4 differentially impact obesity and serum lipid profiles based upon dietary lipid composition (Richardson et al., 2011). The S251P variant of PLIN2 is linked to NASH development (Faulkner et al., 2020) and increased serum lipids (Magné et al., 2013), but surprisingly associates with insulin sensitivity (Sentinelli et al., 2016). An extension of the genomic repeat sequence of the PLIN4 amphipathic helices, resulting in an additional 33 amino acids, is associated with increased aggregation of PLIN4 and aggrephagy in a rare form of myopathy (autosomal-dominant progressive myopathy with rimmed ubiquitin-positive autophagic vacuolation; Ruggieri et al., 2020). While alterations in PLIN5 have not been extensively studied, the PLIN5 rs884164 gene variant is linked to alterations in cardiac function (Drevinge et al., 2016). Collectively, these studies further highlight the importance of PLINs as drivers of disease development rather than simply markers of disease presence.

HSL is recruited to the LD surface to increase lipolysis (Shen et al., 2009). Through its direct interaction with HSL and CGI-58, and its indirect effects on promoting ATGL activity, PLIN1 is recognized as a major regulator of lipolysis. Consistent with this role, ablation of PLIN1 leads to higher rates of basal lipolysis but blunts the effects of  $\beta$ -adrenergic stimulation of lipolysis (Martinez-Botas et al., 2000; Tansey et al., 2001). The higher rates of basal lipolysis are thought to drive the increase in thermogenesis and browning observed in adipose tissue in PLIN1-knockout mice (Martinez-Botas et al., 2000; Saha et al., 2004; Tansey et al., 2001). PLIN1 is also required for autophagic proteins to recognize and catabolize LDs during lipophagy, which provides an additional mechanism through which PLIN1 coordinates LD turnover (Lizaso et al., 2013). Converse to its anti-lipolytic effects, PLIN1 may aid the synthesis and growth of LDs by enhancing FA uptake. PLIN1 interacts with caveolin 1 (CAV1) in caveolae – plasma membrane invaginations that act as hubs for signaling and metabolism – to coordinate the transfer and incorporation of exogenous FAs into TAG stored within LDs (Ost et al., 2005; Simard et al., 2010) (see poster). PLIN1 also interacts with cell death-inducing DFFA-like effector c (CIDEC, also known as FSP27), a key LD protein that drives fusion of LDs, to facilitate the formation of unilocular LDs that are characteristic of white adipocytes (Sun et al., 2013).

Consistent with higher rates of basal lipolysis, PLIN1-knockout mice are resistant to diet-induced obesity (Tansey et al., 2001). Ablation of PLIN1 also reduces the expression of lipid synthetic genes and increases expression of oxidative genes, suggesting that PLIN1 can bidirectionally regulate lipid metabolism through transcriptional signaling (Castro-Chavez et al., 2003). Despite the resistance to obesity, PLIN1-knockout mice display adipose tissue inflammation and insulin resistance, which may be mediated by the

recruitment of pro-inflammatory macrophages (Sohn et al., 2018). Surprisingly, overexpression of PLIN1 in adipose tissue results in reduced adipose tissue and also conveys resistance to diet-induced obesity (Miyoshi et al., 2010; Sawada et al., 2010). Although knockout and overexpression models have similar anti-obesity effects, adipose overexpression of PLIN1 improves glucose tolerance and insulin sensitivity, unlike the effects seen in mice lacking PLIN1 (Miyoshi et al., 2010). These studies suggest that PLIN1 plays a key role in balancing adipose tissue lipid homeostasis with insulin sensitivity, although the detailed mechanisms defining how PLIN1 links lipid metabolism to insulin signaling remains to be elucidated.

**PLIN2**

PLIN2 is ubiquitously expressed and plays a more significant role in non-adipose tissues. Although PLIN2 is not known to interact with or sequester proteins involved in lipolysis, it reduces ATGL localization to LDs and slows rates of lipolysis (Listenberger et al., 2007; Sapiro et al., 2009). While the exact mechanism explaining this reduced lipolysis is not known, PLIN2 may impact other LD-targeted proteins through its alteration of the phospholipid monolayer; indeed, PLIN2 interacts with the components of the monolayer but not the neutral core of LDs (McIntosh et al., 2012; Storey et al., 2011). PLIN2 interactions with the phospholipid monolayer may determine which proteins are able to target the LD; therefore, PLIN2 turnover is a key determinant of protein targeting and LD metabolism. Under nutrient deprivation, AMP-activated protein kinase (AMPK) becomes activated and catalyzes the phosphorylation of PLIN2 (Kaushik and Cuervo, 2016) (see poster). This modification leads to the recognition of PLIN2 by the heat shock cognate protein of 70 kDa (HSC70, also known as HSPA8), which facilitates the degradation of PLIN2 via chaperone-mediated autophagy (CMA). PLIN2 is also phosphorylated by choline kinase  $\alpha$ 2 (encoded by *CHKA*) in response to glucose deprivation, leading to CMA-mediated degradation (Liu et al., 2021). The loss of PLIN2 allows ATGL and proteins involved in lipophagy to access LDs and initiate the hydrolysis of lipid stores (Kaushik and Cuervo, 2015; Liu et al., 2021). In addition, amino-terminal acetylation of non-LD-bound PLIN2 promotes its ubiquitylation and subsequent degradation when insufficient LDs are available for stabilization of the protein (Nguyen et al., 2019). Thus, degradation of PLIN2 appears to be a key node in regulating LD catabolism.

Loss-of-function studies have highlighted various physiological roles of PLIN2. The first mouse knockout model of PLIN2 showed reduced hepatic TAG levels and protection against hepatic steatosis, but not protection from obesity (Chang et al., 2006). However, interpretation of the findings from this model was complicated by the discovery of an incomplete deletion of PLIN2 resulting in expression of a truncated form of the protein. A subsequent global knockout of PLIN2 with no truncated form validated the original finding that PLIN2 ablation leads to reduced hepatic TAG levels, but also revealed a resistance to diet-induced obesity (Orlicky et al., 2018). Upon high-carbohydrate feeding, PLIN2-knockout mice exhibit increased body temperature and browning of subcutaneous adipose tissue, which could also contribute to the obesity resistance (Libby et al., 2018). Further studies have shown that PLIN2-knockout mice display reduced enterocyte LDs in response to dietary lipids, lower lipid absorption, increased fecal lipid content, as well as alterations in the gut microbiome (Frank et al., 2015; Xiong et al., 2017). Taken together, these results suggest that PLIN2 in the intestine may contribute to systemic energy metabolism.

Perhaps the most studied effects of PLIN2 loss have been in the liver, where tissue-specific deletion of PLIN2 robustly reduces diet- or genetically-driven steatosis, inflammation and fibrosis (Griffin et al., 2021; Imai et al., 2007, 2012; Najt et al., 2016). Moreover, PLIN2 ablation alters phospholipid metabolism and signaling to promote very-low-density lipoprotein (VLDL) secretion from mouse liver (Magnusson et al., 2006; Martínez-Uñá et al., 2015; Najt et al., 2016; Tsai et al., 2017), enhance FA oxidation (Griffin et al., 2021; Najt et al., 2016; Tsai et al., 2017) and suppress *de novo* lipogenesis (Libby et al., 2016; Varela et al., 2008), all of which may contribute to the effects of reduced PLIN2 expression in lowering levels of TAG. As expected, overexpression of PLIN2 leads to LD accumulation in numerous tissues including heart (Ueno et al., 2017), liver (Tsai et al., 2017) and muscle (Bosma et al., 2012).

While many mechanisms likely underlie the different effects of PLIN2, its role in inflammation is undoubtedly a major contributor (see poster). PLIN2 expression and the coinciding accumulation of LDs are increased in response to lipopolysaccharide (LPS) or other inflammatory stimuli (Khatchadourian et al., 2012; Llorente-Cortés et al., 2007; Wang et al., 2012). PLIN2 expression is also increased in tissues or cells characterized by chronic inflammation, including microglia from aged mice (Marschallinger et al., 2020), foam cell and atherosclerotic plaques (Paul et al., 2008), non-alcoholic steatohepatitic livers (Carr et al., 2017) and numerous cancers (Cruz et al., 2020; Straub et al., 2010). PLIN2 ablation attenuates, and overexpression exacerbates, LPS-mediated inflammation (Cho and Kang, 2015; Wang et al., 2012). Tissue-specific or global deletion of PLIN2 broadly reduces inflammation associated with obesogenic diets (McManaman et al., 2013; Najt et al., 2016) and protects against atherosclerosis (Paul et al., 2008). Further linking PLIN2 and inflammation, recombinant murine PLIN2 binds various lipids but shows the highest affinity for cholesterol and arachidonic acid (Najt et al., 2014). Cholesterol and its metabolites are known to have pro-inflammatory effects (Tall and Yvan-Charvet, 2015), and arachidonic acid is the initial substrate for the generation of eicosanoids, a diverse family of oxidized lipids (oxylipins) that drive inflammation. As LDs have emerged as major sites of eicosanoid generation (Accioly et al., 2008; Dichlberger et al., 2016; Moreira et al., 2009), these data implicate a potential role of PLIN2 as a key player in this important lipid-mediated signaling pathway. PLIN2 ablation, likely through enhanced lipolysis and FA mobilization, also commonly increases signaling through the PPAR family of transcription factors (Bosma et al., 2012; Feng et al., 2017; Sapiro et al., 2009). While the PPARs have profound effects on metabolism, they also increase the expression of numerous anti-inflammatory genes (Straus and Glass, 2007), which may also contribute to the beneficial effects of PLIN2 ablation.

### PLIN3

PLIN3 is ubiquitously expressed and plays significant roles in the formation of TAG and LD biogenesis (Bulankina et al., 2009; Nose et al., 2013; Wolins et al., 2001). PLIN3 is rapidly recruited to LDs upon FA exposure, and knockdown of PLIN3 attenuates LD formation (Bulankina et al., 2009; Wolins et al., 2001). PLIN3 binding to DAG, which is enriched at sites of LD biogenesis on the ER, is instrumental to this recruitment (Skinner et al., 2009) (see poster). Consistent with its role in LD formation, PLIN3 knockdown prevents diet-induced hepatic steatosis and reduces VLDL secretion (Carr et al., 2012; Ferguson et al., 2017). Interestingly, PLIN3 is also required for replication of hepatitis C virus and the steatosis associated with viral infection (Ferguson et al., 2017; Ploen et al., 2013; Vogt et al., 2013). Another role of

PLIN3 is to help protect cells from ER stress and apoptosis in response to exogenous FAs or alcohol, both of which promote TAG synthesis (Gu et al., 2019; Urahama et al., 2008). This is in line with earlier findings showing that FA incorporation into LDs is important to prevent ER stress and lipotoxicity (see poster; Listenberger et al., 2003). A further role of PLIN3 is to regulate phospholipid metabolism. Specifically, PLIN3 competes with CTP:phosphocholine cytidylyltransferase- $\alpha$  (CCT $\alpha$ , also known as PCYT1A), which catalyzes a key step in phosphatidylcholine synthesis, for binding to nucleoplasmic LDs as a means to antagonize phosphatidylcholine synthesis (Soltysiak et al., 2019) (see poster). Interestingly, this competition occurs on nuclear LDs, which have only been recently identified and are the subject of intense research (Uzbekov and Roingeard, 2013). Thus, PLIN3 impacts TAG synthesis and LD biogenesis through numerous mechanisms.

Unlike PLIN1 and PLIN5, the effects of PLIN3 on lipolysis are less clear. Several studies suggest that PLIN3 ablation enhances lipolysis and can activate PPAR- $\alpha$  (also known as PPARA) and oxidative metabolism similar to PLIN2 ablation (Bell et al., 2008; Lee et al., 2018). In support of these studies, and like PLIN2, PLIN3 is phosphorylated by AMPK and choline kinase  $\alpha$ 2 and is subsequently degraded via CMA in fasting conditions to allow LD degradation (Kaushik and Cuervo, 2015; Liu et al., 2021) (see poster). PLIN3 abundance in muscle correlates with FA oxidation and exercise training (Chow et al., 2017; Covington et al., 2014, 2015; MacPherson et al., 2013; Shepherd et al., 2017). Collectively, these data suggest that PLIN3 promotes LD biogenesis and protects LDs from degradation until lipolytic stimuli are present, at which time it is degraded to allow for LD catabolism.

### PLIN4

PLIN4 is the least studied member of the PLIN family. In adipocytes, PLIN4 is rapidly recruited to LDs upon FA exposure (Wolins et al., 2003), and its expression is increased during adipocyte differentiation (Nimura et al., 2015; Wolins et al., 2005). Global deletion of PLIN4 does not affect adipose tissue but does lower cardiac TAG levels; however, cardiac PLIN5 expression is also reduced in this model, making it difficult to ascertain whether these effects are direct or indirect (Chen et al., 2013). PLIN4 also appears to be critical for phospholipid monolayer organization (Copić et al., 2018). The oversized 11mer repeat region of the protein aids in stabilizing PLIN4 at the LD surface (Giménez-Andrés et al., 2021). PLIN4 function has also been associated with neurodegenerative disease (see Box 1); its levels are increased in neurons in an animal model of Parkinson's disease and its downregulation in cultured neurons reduces LDs and restores mitophagy to overcome mitochondrial damage and dysfunction (Han et al., 2018).

### PLIN5

PLIN5 is arguably the most dynamic of the PLIN proteins as it appears to have a multitude of cellular functions. PLIN5 shows the highest expression in highly oxidative tissues, such as brown adipose tissue, heart, muscle and liver tissue, and is induced in response to exercise training (Louche et al., 2013; Shepherd et al., 2017) or fasting (Gemmink et al., 2016; Zhang et al., 2020). PLIN5 also regulates lipolysis through its direct interactions with ATGL and CGI-58 (see poster). Under basal conditions, PLIN5 sequesters CGI-58 to prevent its interaction with ATGL, similar to PLIN1 in adipose tissue (Granneman et al., 2009, 2011; Wang et al., 2011). In support of these mechanistic findings, global deletion of PLIN5

reduces LD accumulation in numerous oxidative tissues (Kuramoto et al., 2014; Mason et al., 2014; Wang et al., 2015), whereas overexpression of PLIN5 commonly promotes LD accumulation (Harris et al., 2015; Pollak et al., 2013). Despite its anti-lipolytic effects under basal conditions, PLIN5 enhances lipolysis under PKA-stimulated conditions (Pollak et al., 2014; Wang et al., 2011). Indeed, PKA-mediated phosphorylation of murine PLIN5 at Ser155 is a critical modification that alters its binding to ATGL, resulting in a switch from anti-lipolytic to pro-lipolytic activity (Keenan et al., 2021).

PLIN5 expression is tightly linked to mitochondrial biogenesis and oxidative metabolism across tissues (Mason and Watt, 2015). There appear to be at least two mechanisms underlying this association. First, PLIN5 directly interacts with mitochondria through its carboxyl-terminal 20 amino acids, and acts as a tether between LDs and mitochondria (Wang et al., 2011) (see poster). This association increases in response to PKA signaling, similar to fasting, and is dependent on phosphorylation at Ser155 (Keenan et al., 2021). It has been proposed that these bridges would exist to allow for the direct transfer of FAs from LDs to mitochondria for oxidation during nutrient-deprived conditions (Rambold et al., 2015). However, other studies refute these findings and instead suggest that PLIN5 and LD–mitochondria interactions exist to facilitate lipid anabolic pathways, including TAG synthesis (Benador et al., 2018). In support, PLIN5 increases FA incorporation into TAG (Montgomery et al., 2019; Trevino et al., 2015; Zhang et al., 2020). Second, PLIN5 can facilitate mitochondrial biogenesis and oxidative metabolism by playing a key role as a transcriptional co-regulator. In response to PKA signaling and phosphorylation on Ser155, PLIN5 binds lipolytically derived FAs, especially monounsaturated FAs (MUFAs), and traffics them to the nucleus (Najt et al., 2020). Once inside the nucleus, PLIN5 forms a complex with peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC1 $\alpha$ , also known as PPARGC1A) and sirtuin 1 (SIRT1) (Gallardo-Montejano et al., 2016; Najt et al., 2020), the latter of which is allosterically activated by the PLIN5-delivered MUFAs. SIRT1 is known to deacetylate PGC1 $\alpha$ , which promotes mitochondrial biogenesis and oxidative metabolism in part through its co-activation of the transcription factor PPAR- $\alpha$  (Rodgers et al., 2005). SIRT1–PGC1 $\alpha$ –PPAR $\alpha$ -dependent signaling also regulates other key cellular pathways, including the induction of autophagy and suppression of inflammation (Zhang et al., 2020). Detailed studies have yet to parse apart the distinct contributions of the LD–mitochondria-tethering role and the transcriptional regulatory role of PLIN5 to its many downstream effects.

## Conclusions and future perspectives

The PLINs have emerged as a key family of proteins orchestrating cell signaling and metabolism, well beyond their classically viewed roles as LD structural proteins that simply govern lipolysis. A large body of literature highlights links between PLINs, as well as other LD-associated proteins and lipids, and an expanding list of diseases. Despite these advances in our understanding of the PLINs, there are many aspects of PLIN biology that remain scantly explored. These include but are not limited to their unique structural aspects, including their role in lipid binding, and how alterations (expression level, post-translational modifications, variants) of PLINs alter LD metabolism and/or signaling and cell function. The links between LD accumulation and alterations in lipid metabolism in many metabolic and aging-related diseases justify future studies to further characterize the PLINs, identify novel mechanisms through which

they impact cell and tissue homeostasis, and develop genetic or pharmaceutical approaches to manipulate their function to alleviate disease.

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## Competing interests

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