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Perilipin 5, a Lipid Droplet Protein Adapted to Mitochondrial Energy Utilization

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Abstract

Purpose of review—We summarize recent mechanistic and physiological studies related to the role of perilipin 5 in regulating lipid droplet accumulation and protection to fatty acids (FAs) in tissues with high lipid oxidative metabolism.

Recent findings—Perilipin 5 (Plin5) is a lipid droplet (LD) targeting protein that promotes association of LDs with mitochondria and is most highly expressed in oxidative tissues, including cardiac and skeletal muscle. Recent in vivo and in vitro data indicate an important role for Plin5 in the regulation of cardiac lipid storage and function. Targeted overexpression of *Plin5* in heart causes cardiac steatosis and mild mitochondria dysfunction and hypertrophy, but without affecting cardiac function. In contrast, whole body ablation of *Plin5* (*Plin5*$^{-/-}$ mice) reduces cardiac lipid droplet formation, increases cardiac fatty acid oxidation, and promotes cardiac dysfunction; cardiac defects can be prevented with anti-oxidative therapy. These data suggest a cytoprotective role for Plin5 to promote lipid storage but to limit FA toxicity, parameters critical for tissues with high lipid oxidative metabolism.

Summary—In vivo and in vitro data suggest that Plin5 is part of a cell adaptive response to high lipid oxidative metabolism to protect LD storage against neutral lipases and, so, limit FA accumulation. While the specific mechanisms that underlie Plin5 LD storage protection in oxidative tissues remain to be fully elucidated, Plin5 provides a basis for the novel cytoprotective nature of LDs.

Keywords

ATGL; steatosis; β-oxidation; lipolysis; FA toxicity

Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

The pandemic rise in lipid-associated metabolic disorders has focused interest on the mechanistic actions of cytosolic lipid droplets (LDs), the organelles essential for regulation of lipid homeostasis in both adipose and non-adipose tissues, [1,2▪,3▪,4▪,5,6]. Although the accumulation of excess LDs in non-adipose tissues (ectopic fat), e.g. liver, heart, and skeletal muscle, is highly correlated with dyslipidemia, insulin resistance, type 2 Diabetes, and cardiovascular disease, studies in mice and humans have demonstrated a more complex relationship, where the presence of ectopic fat is more than a simple predictor of metabolic disorder [7,8,9▪,10▪,11▪,12]. Thus, LD function, which balances neutral lipid storage and utilization and is tightly regulated in a cell type-specific manner, is suggested to also have an essential protective role in the sequestration of cytotoxic fatty acids (FAs) in non-adipose tissues.

Cytosolic LDs are unique storage structures comprised of a core of neutral lipids, triacylglycerols (TAG) and/or cholesteryl ester (CE), surrounded by a phospholipid monolayer. The contrasting chemical natures of hydrophilic lipid metabolic enzymes and their hydrophobic substrates have directed attention to the LD surface as the regulatory interface between the aqueous cytosol and the hydrophobic lipid core. Specifically, perilipin proteins (Plins) are the definitive abundant proteomic markers of LD surfaces in both adipose and non-adipose cells and function as primary mediators for neutral lipid storage/hydrolysis [13–15].

The mammalian genome encodes five *Plin* genes, with unique tissue-dependent patterns of transcription and splice variation, although individual cells often express more than a single Plin type [16]. Perilipin 1 (Plin1) is most abundant in white and brown adipose tissue (WAT, BAT). Perilipin 2 (Plin2) and perilipin 3 (Plin3) are more widely distributed, with Plin2 highly expressed in hepatocytes. Perilipin 4 (Plin4) is observed in adipocytes, cardiomyocytes, and myocytes, and perilipin 5 (Plin5) is generally restricted to tissues/cells that utilize lipids for energy through mitochondrial β-oxidation, e.g. cardiomyocytes, brown and inducible brown adipocytes (also referred to beige or bright adipocytes), liver, and skeletal myocytes [17–19], Here, we review recent progress toward understanding the specialization of Plin5 in the mechanistic interaction of the two critical organelles, LDs and mitochondria, that balance oxidative cellular energy, lipid homeostasis, and cytoprotection.

TRANSCRIPTIONAL REGULATION OF PLIN5 CORRELATES WITH A SPECIALIZED FUNCTION IN CELLS THAT UTILIZE LIPID OXIDATION FOR ENERGY

When exposed to an increase in circulating FAs, organs such as heart, skeletal muscle, and liver, respond by inducing genes that regulate FA metabolism. One primary pathway involves the transcription factor family of peroxisome proliferator-activated receptors (PPARs) [20]. Upon activation, through direct interaction with FA-derived ligands, PPARs, in combination with their heterodimerization partners, retinoid X receptors (RXRs), bind at specific genomic sequences (PPAR regulatory elements, PPREs). Cell-specific expression of

PPAR variants, in concert with transcriptional co-factors, such as PGC-1 (PPAR coactivator-1) family members, directs expression of appropriate metabolic enzymes for FA utilization/storage [21]. Accordingly, PPARα and PPARβ/δ are highly expressed in tissues with elevated rates of FA oxidative metabolism (e.g. heart, skeletal muscle, and liver), whereas PPARγ is more preferential in lipogenic tissues (e.g. adipose and liver) [20].

As an LD target protein, *Plin5* expression is enhanced under physiological or pharmacological conditions that promote systemic FA elevation, e.g. fasting (liver, heart), endurance exercise (skeletal muscle), and chronic β3-adrenergic stimulation (liver) [17–19, 22,23▪,24]. Exogenous FAs can also stimulate *Plin5* expression in cell culture [25]. A functionally conserved PPRE site maps to the first intron of *Plin5*, and *Plin5* expression can be induced in liver, skeletal, and cardiac muscle by PPARα agonists, but also in WAT by pioglitazone, a PPARγ agonist [17–19, 26▪▪]. Some agonists, however, are not exclusive, but can cross-activate different PPAR family members.

Although basal *Plin5* mRNA levels (liver, heart) are severely suppressed in *PPARα*$^{-/-}$ mice, *Plin5* induced expression is responsive to fasting, suggesting additional regulatory control. Indeed, PPARβ/δ appears the more potent regulator of *Plin5* than PPARα in skeletal muscle [26▪▪]. *Plins 1*, *2*, and *4* are similarly induced through FA-ligand activation of PPARs, but their expression is more directly influenced by PPARγ action, than by PPARα or PPARβ/δ [27–30].

The preferential activation of *Plin5* expression by PPARα and PPARβ/δ provides a mechanism for selectivity in mammalian tissues that utilize FA for β-oxidation to provide energy or heat. PGC-1α will drive formation of oxidative muscles, fine tune the energy-generating machinery in response to nutrient availability, and promote cellular defenses to metabolic stress [31▪]. Overexpression of PGC-1α in skeletal muscle will also increase *Plin5* transcription [23▪]. The restricted presence of Plin5 to LDs of oxidative tissues may be required for the physical and functional interactions between LDs and mitochondria and the interplay of FA substrate availability to enable exquisite regulation of β-oxidation for both energy (heart, skeletal muscle) and heat (BAT) [32,33▪▪].

UNIQUE PLIN5 REGULATION OF OXIDATIVE LD STORAGE

Cytosolic LDs are often viewed only as storage depots to provide regulated availability of the lipid moieties required for essential and various cellular functions, including β-oxidation, membrane phospholipid synthesis, cell signaling, and steroid production. While true, it is now further recognized that LDs also serve a protective function, by sequestering cytotoxic FA and cholesterol, as TAG and CE, respectively [34–36]. The dynamic nature of LDs balances sequestration and storage, with the regulated cleavage of long-chain TAG to provide sufficient metabolic precursors as polar lipids, while also minimizing cytotoxic effects. The mammalian Plins are not required for LD biogenesis per se, but, as primary regulators of lipolysis, they modulate cellular TAG/CE levels. In general, overexpression of any Plin form can promote LD storage [13–15].

Four major proteins, in addition to Plin1, have been identified in the neutral lipid catabolic pathway of adipocytes, hormone sensitive lipase (HSL), adipose triglyceride lipase (ATGL),

comparative gene identification 58 (CGI-58), a positive regulator of ATGL, and G0/G1 Switch (G0S2), a negative regulator of ATGL [37,38]. In adipocytes, access to LD surfaces can be regulated by Plin1. Unphosphorylated Plin1 restricts ATGL and HSL from LDs and suppresses lipolysis [39], whereas PKA-phosphorylated Plin1 permits ATGL/CGI-58 and HSL association with LD surfaces to activate lipolysis. Thus, under stimulatory conditions that activate adenylyl cyclase (AC) and elevate intracellullar cAMP levels, lipolytic rates rise ~50-fold [40]. G0S2 inhibits lipolysis through direct interaction with and inhibition of ATGL [38].

ATGL, HSL, CGI-58 are also essential regulators of lipid hydrolysis in non-adipose tissue and Plin5 can interact with all 3 proteins [41–44]. FRET experiments indicate that ATGL and CGI-58 bind toward the C-terminal half of Plin5, whereas the HSL binding sites are thought to reside in the N-terminal PAT-1 domain that is common to all perilipins [42]. The precise interactive sites on Plin5 are not known, but binding of ATGL and CGI-58 to Plin5 appears to be mutually exclusive [41,43]. However, in vivo associations have not been comparatively explored in oxidative cells that are lipolytically dormant or activated. Although G0S2 is expressed in oxidative tissues, a functional role in control of lipolysis is not yet defined.

Plin5 acts to protect LD stores, likely by suppressing lipolysis. Thus, cardiomyoctes that overexpress Plin5 have a lipid phenotype similar to those deficient in ATGL, increased LD accumulation [45▪▪,46▪▪,47,48], and cardiac lipid droplet depletion in *Plin5*$^{-/-}$ mice can be reversed by a lipase inhibitor [49▪▪]. Although Plin5 only minimally affects ATGL activity in reconstituted lipolytic in vitro assays using free triolein as a substrate [45▪▪,46▪▪], ATGL-mediated lipolysis is significantly inhibited using Plin5-coated LD substrates in contrast to LD controls, isolated from cells that do not express Plin5 [46▪▪]. Thus, Plin5 is modeled as a regulated lipolytic barrier that sequesters LD substrates from ATGL [46▪▪]. Cellular lipolytic activation could elicit a structural re-organization of Plin5 at the LD surface to facilitate ATGL/CGI-58 (and perhaps HSL) access to lipid substrates (Figure 1A). In this context, ATGL/CGI-58 interactions are elevated in contracted muscle cells relative to resting cells, without an accompanying alteration in relative Plin5 association with either ATGL or CGI-58 [50]. A potential role for HSL is not defined, but HSL phosphorylation at serine 600 is increased during endurance exercise [51▪].

Several observations suggest possible mechanistic targets that could modulate ATGL/LD access. Since the binding of ATGL and CGI-58 to Plin5 is mutually exclusive, ATGL may associate with LDs in basal oxidative cells, while being sequestered from its co-activator CGI-58 (Figure 1B). A regulatory path that multimerizes Plin5 could facilitate interactions of proximal ATGL and CGI-58 to elicit efficient lipolysis [43]. Plin5 may also reside in non-LD cellular compartments [52,53]. Although it is suggested that Plin5 may undergo re-partitioning to or from LDs to facilitate lipolytic activation, a differential recruitment of Plin5 to lipid droplets has not been observed in contracted muscle [54].

Recent proteomic [55] and phospho-labeling [44] studies indicate phosphorylation target sites on Plin5. Differential phosphorylation of Plin5 could alter interactions with ATGL and/or CGI-58, thus limiting or activating TAG hydrolysis [44,56] (Figure 1C). Although

this has analogy to Plin1 function, functional differences to Plin1 are evident. Unlike Plin1, which does not interact with ATGL regardless of phospho-state, Plin5 readily binds ATGL. In addition, although the Plin5 kinase(s) have yet to be identified, PKA may be less significantly involved. Although mouse (and human) Plin5 does have a potential PKA phosphorylation site, phospho-incorporation into Plin 5 and lipolysis are elevated <2-fold upon AC activation of a cultured Plin5-cell system [44].

The precise molecular mechanism(s) by which Plin5 controls oxidative LD storage remains to be further clarified and the postulated models are not mutually exclusive. Important clues will require definitive identification of Plin5 phosphorylation sites and regulatory kinases. FRET approaches may be considered to probe Plin5 and LD surfaces. DAG enrichment at the surface of LDs will recruit Plin5 [53], and Plin5 is preferentially localized to TAG-enriched LDs, in contrast to CE organelles [57▪]. Studies focused to characterize Plin5/LD surfaces will help evaluate the ability of Plin5 to regulate substrate/lipase sequestration. However, difficulties in purifying the Plins have limited their use in classical biophysical techniques to investigate Plin/LD surfaces and regulation of lipase activity [58]. An inhibitory role for G0S2 in oxidative tissue is suggested, but must be investigated mechanistically.

SPECIFIC ROLE OF PLIN5 IN OXIDATIVE CELLS, INVOLVING PHYSICAL LD-MITOCHONDRIAL ASSOCIATIONS

Plin1, Plin2, and Plin5 regulate LD storage by separate mechanisms, reflecting their unique adaptations to cell/lipid utilization (Figure 2). Plin1 facilitates TAG storage in adipocytes for systemic energy homeostasis, whereas Plin2 is expressed more globally to allow TAG storage (ectopic fat) under conditions of starvation or obesity. Plin5 in myocytes and other oxidative cells balances FA availability for mitochondrial oxidation with sequestration to protect against cytotoxicity. Loss-of-function mutants for *Plin1, 2,* or *5* all have decreased LD stores and increased β-oxidation in their respective tissues, compared to WT [49▪▪,59–60,62▪▪], despite compensating expression by other Plin forms; $Plin1^{-/-}$ adipocytes have increased Plin2 at their LD surface, but elevated rates of lipolysis. Since Plin2 is unable to compensate for Plin1 for lipolytic regulation, $Plin1^{-/-}$ mice are protected to diet-induced obesity [59,60]. $Plin2^{-/-}$ hepatocytes have increased Plin5, but also a marked reduction in LD content in response to starvation or high-fat diet [61,62▪▪]. Although Plin5 may be less protective to LD accumulation in hepatocytes than is Plin2, overexpression of Plin5 in $Plin2^{+/+}$ hepatocytes can increase TAG storage [63]. Certainly, Plin5 (and the other Plin forms) may respond and function with extreme cell-type specificity, but, importantly, Plin1, Plin2, and Plin5 are not simply operationally redundant for LD storage and regulation.

Plin5 is localized at the surface of LDs in oxidative cells, but also in connection with mitochondria [32,33▪▪]. Overexpression of Plin5 in fibroblasts directs a close association of LDs and mitochondria [32]. Although Plin2 alone is unable to promote a similar re-organization, a Plin2 chimera with the C-terminal 67 amino acids of Plin5 (including 20 essential amino acids) has the ability to tether mitochondria to LDs [32] in fibroblasts.

The physiological significance to promote the association of LDs and mitochondria in oxidative tissue is yet to be determined. However, mitochondria/LD associations, observed in heart and skeletal muscle cells where lipids are utilized for energy, are further enhanced by exercise [64]. In accord, exercise in mice and humans increases PGC-1α expression in skeletal muscle, which promotes expression of *Plin5* and other genes involved in LD assembly and mobilization and remodeling of mitochondria [23▪].

An intimate physical association between LDs and mitochondria in oxidative tissue may be essential to coordinate cellular energy homeostasis, but also to protect mitochondria against locally elevated toxic levels of FA and lipid intermediates. Ultimately, LDs can utilize the same substrates as mitochondria (Figure 2), so increased LD storage can be protective to FA cytotoxicity [65▪]. In addition, elevated rates of FA β-oxidation contribute to increased mitochondrial reactive oxygen species (ROS) [65▪]. Plin5 may reduce ROS production by transiently channeling excess FA into LDs. Although LD storage is a hallmark of cellular stress, it may serve more to ameliorate cytotoxicity, rather than to be a causal agent.

The regulated hydrolysis of TAG in Plin5-LDs may not only direct FAs to the mitochondria, but may also provide functional signals for PPARα and PPARβ/δ activation. More specifically, a PPAR ligand has been proposed that is derived from ATGL-mediated LD hydrolyses [48] and that may regulate expression of genes involved in FA metabolism, mitochondrial biogenesis, and protective anti-oxidative pathways [48,66▪▪,67–69].

PLIN5 IN CARDIAC/SKELETAL MYOCYTE FUNCTION AND SYSTEMIC HOMEOSTASIS

Although there is direct relationship between Plin5 expression levels and LD accumulation, connections among β-oxidation, ROS, and cardiac function are less well-defined. Whole body loss-of-function *Plin5*$^{-/-}$ mice have depleted cardiac LDs, increased β-oxidation, but also increased ROS production and cardiac dysfunction, which may be minimized with anti-oxidative therapy [49▪▪]. Cardiac-specific overexpression of Plin5 in mice results in massive steatosis, a mild defect in mitochondria β-oxidation, but also increased ROS, without cardiac dysfunction [45▪▪]. Although here, the Nrf2-antioxidant response pathway is activated, which increases expression of the protective gluthatione enzymes [45▪▪], a mechanistic link of Plin5, increased LDs, and Nrf2 activation is yet to be established; the ROS sources in these respective models also remained to be clarified.

While cardiac steatosis may be associated with cellular dysfunction, enhanced LD accumulation is not always detrimental. Thus, genetic deficiencies in *ATGL* or *CGI-58* compromise lipase function and cause cardiac steatosis and cardiomyopathy [47,70▪,71▪] whereas cardiac overexpression of diacylglyceride acyltransferase 1 (DGAT-1), the rate-limiting TAG-synthesizing enzyme, promotes steatosis, but without corresponding cardiac defects during a similar time-frame [72]. The *Plin5* mouse models [45▪▪,46▪▪,49▪▪] further exemplify the dissociation of cardiac steatosis and cardiac tissue dysfunction.

Overall results suggest a cytoprotective role of Plin5 to cardiac steatosis and FA toxicity, involving the structural re-organization of oxidative LDs and mitochondria [11▪,15,32,33▪▪,

73]. Still, the relationship of Plin5 levels to FA β-oxidation and connection to cardiac ROS remains to be resolved. Potentially, the protective nature of Plin5 overexpression may partially derive from compensatory adaptive mechanisms that activate anti-oxidative Nrf2 functions [45▪▪,49▪▪].

The whole body *Plin5*$^{-/-}$ mouse does not exhibit changes in systemic lipid and glucose homeostasis on a standard chow diet [49▪▪]. Systemic and tissue-specific functions remain to be investigated under conditions of obesity, exercise, and cold challenge [49▪▪]. Relation to insulin sensitivity can only be partially inferred. Selective skeletal muscle Plin5 overexpression results in increased muscle LD content, a gene expression profile favoring β-oxidation, but without compromising or improving muscle sensitivity for insulin-mediated glucose uptake during diet induced obesity [74▪▪]. By contrast, overexpression of Plin2 in skeletal muscle also leads to increased LD stores, but suppressed β-oxidation and partially improved muscle insulin-mediated glucose uptake in response to diet-induced obesity [75▪]. Plin specificity at LD surfaces may differentially impact lipid stores in oxidative tissue (Figure 2). Plin5 may participate more in an adaptive cell mechanism in response to higher rates of FA β-oxidation by mitochondria.

CONCLUSIONS

The Plin5 studies underscore the concept for specialized pools of “oxidative” LDs in highly energetic mammalian cells. In contrast to other Plin forms, Plin5 has the unique ability for LD storage during energetic demands of FA oxidation and to promote the close proximity of LDs with mitochondria, the oxidative site. It may be speculated that LD-mitochondrial associations assure advantageous fuel delivery for energetic efficiency but also to provide a localized cytoprotective sink for excess toxic FA and lipid intermediates. The mechanistic functions of Plin5 are still to be fully elaborated, but Plin5 remains a focus to understand the adaptive cellular mechanisms to high lipid oxidative metabolic states and their failure in earlier stages of metabolic disease.

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sensitivity in skeletal muscle despite elevated intramuscular lipid levels. Diabetes. 2012; 61:2679–2690. [PubMed: 22807032] ▪ These studies show that in vivo specific overexpression of Plin2 in skeletal muscle results in increased LD stores, decreased β-oxidation profiles, but improved muscle insulin sensitivity during diet induced obesity.

KEY POINTS

- Plin5 is metabolically and physically linked to LDs and mitochondria in tissues with high β-oxidative activity.
- Overexpression of Plin5 in heart promotes steatosis, by inhibiting lipolysis, but in the absence of corresponding cardiac dysfunction.
- Cardiac muscle in *Plin5*$^{-/-}$ mice have reduced LD stores, but lipotoxicity that induces cardiac dysfunction.
- Plin5 may exert a cytoprotective role against FA-induced lipotoxicity by channeling FA into LD stores.

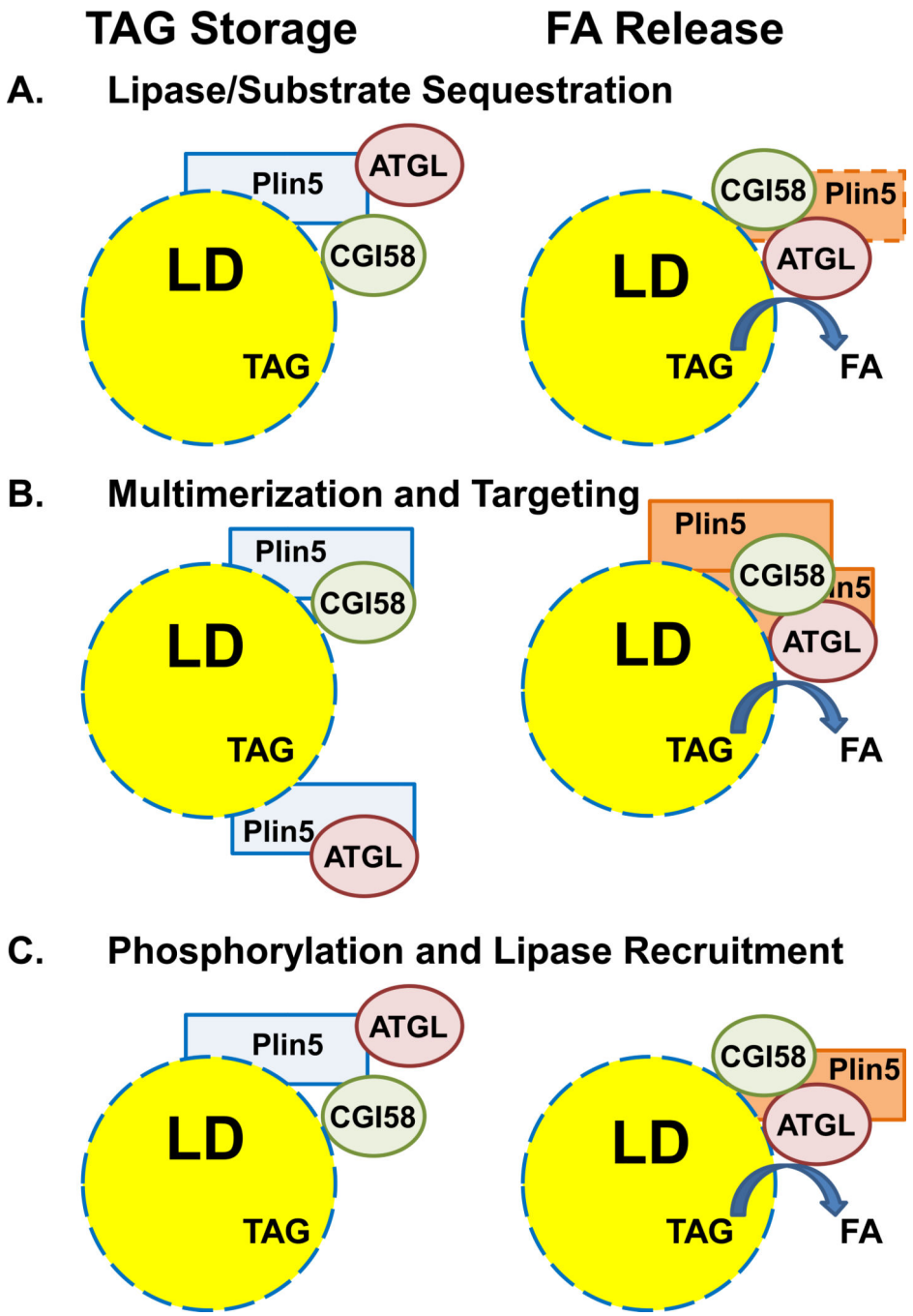

Figure 1. Models for Plin5 regulation of lipolysis

In basal cells, Plin5 coats LDs, which limits TAG access of ATGL; TAG is stored. Plin5 is able to bind both ATGL and CGI-58, but the precise relationships and relative cellular localizations of all the components are not known; representations are diagrammatic, but CGI-58 is presumed to be at the LD surface in basal cells. Several models postulate how Plin5/ATGL/CGI-58 associations with LDs become altered in activated cells, where FAs are released. The models do not incorporate additional positive or negative regulators (e.g. G0S2), which may be contributory.

A. Structural re-organization of Plin5 promotes ATGL/substrate access and ATGL/CGI-58 interactions.

B. ATGL and CGI-58 bindings to Plin5 are mutually exclusive. Plin5-multimerization allows proximate interaction of ATGL and CGI-58.

C. Plin5 is a phospho-protein. By analogy to Plin1 regulation of lipolysis in adipocytes, differential phosphorylation of Plin5 facilitates ATGL/substrate access and ATGL/CGI-58 interactions.

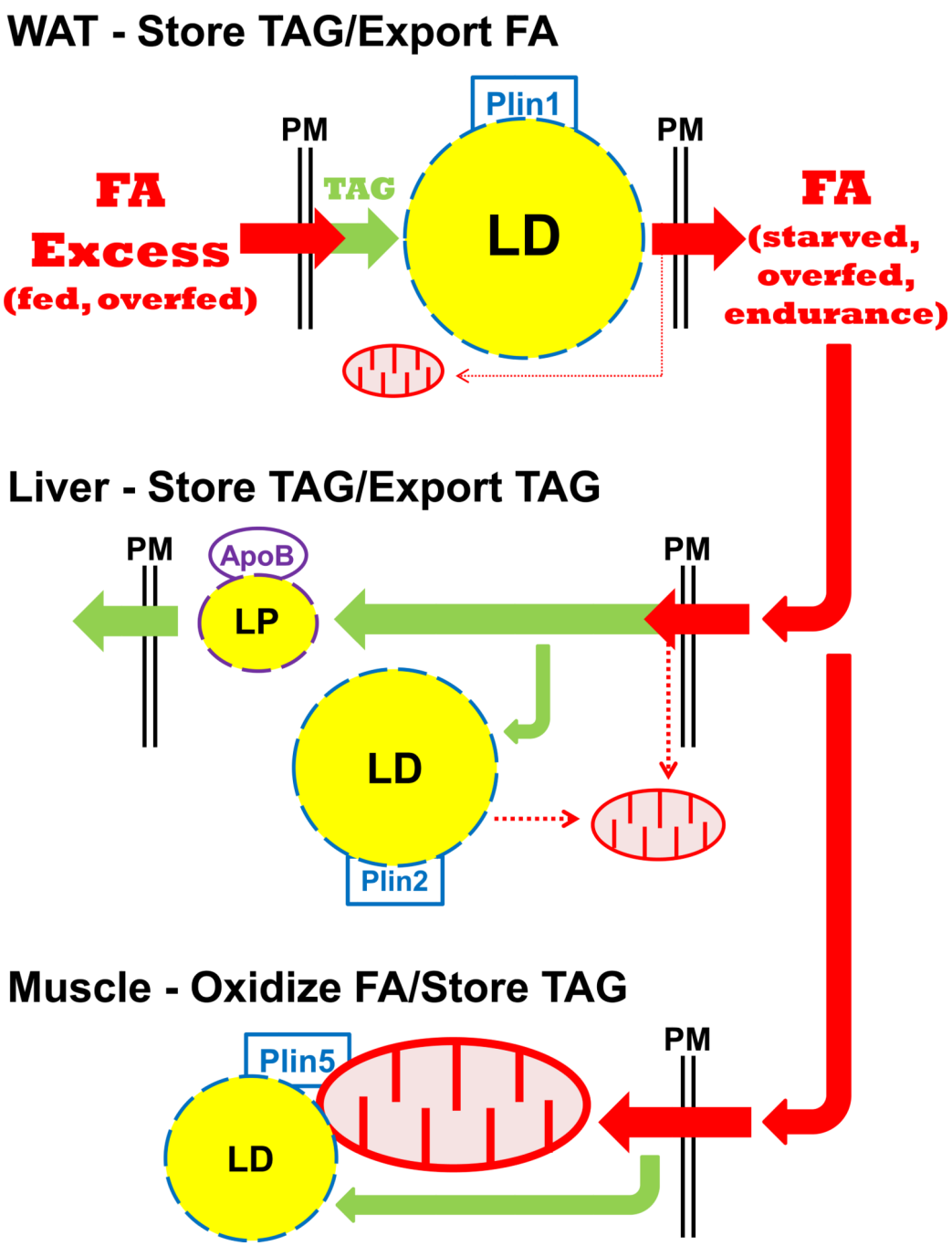

Figure 2. Plin/tissue-specific utilization of FA; a cytoprotective role for Plin5 in oxidative tissue

Plin1 and WAT: During fed conditions, excess energy as FA (fatty acid) is stored in Plin1-coated LDs. Upon fasting, endurance exercise, or overfeeding, adipose tissue secretes FAs for use by other organs. Limited intracellular FA is utilized for mitochondrial oxidation.

Plin2 and liver: Excess FA supply leads to an increase in TAG biogenesis, stored as Plin2-coated LDs (ectopic fat) or secreted as ApoB-coated LP (lipoprotein) particles. Some intracellular FA is available for mitochondrial oxidation.

Plin5 and cardiac/skeletal muscle: A significant degree of excess FA supply is utilized for mitochondrial oxidation. Additional FAs are directed to TAG biogenesis, which is stored as Plin5-coated LDs, tethered to mitochondria. TAG storage in Plin5-LDs may protect mitochondria from FA toxicity and promote mitochondrial function.