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REVIEW

Seipin: A central lipid rheostat

Abdou Rachid Thiam[1] and Maxime Carpentier[1]

Seipin is a conformationally flexible, oligomeric scaffold that regulates cellular lipid homeostasis beyond lipid droplet (LD) biogenesis. Seipin senses local lipid composition and membrane features to direct metabolic flux toward specific pathways and organelles. Its ring adopts multiple conformations, influenced by cofactors such as the LD assembly factor 1 and adipogenin, as well as lipid ligands including phosphatidic acid, diacylglycerol, and triacylglycerol, conferring broad functional versatility. Although seipin is an ER-resident protein primarily enriched at ER-LD junctions, a fraction relocates to mitochondria-associated membranes under specific metabolic conditions, where it regulates lipid synthesis, turnover, and local Ca^{2+} levels, thereby facilitating interorganelle communication and maintaining metabolic stability. Seipin dysfunction disrupts this multinodal regulation, causing lipid imbalance, organelle abnormalities, and a range of metabolic and neuronal disorders. We propose a unified model in which seipin functions as a multistate proteolipid regulatory hub: a rheostat whose structure and interactome dynamically adjust to control lipid pathway decisions in response to metabolic signals across organelle contact networks.

Introduction

Seipin is a remarkable protein first identified in clinical genetics and recognized as a key player in lipid biology. In 2001, its gene (BSCL2) was linked to congenital generalized lipodystrophy (CGL) type 2 (Magré et al., 2001), a disorder marked by an almost complete absence of adipose tissue. This discovery immediately underscored a vital role for seipin in adipose development and lipid metabolism. Subcellular studies showed that seipin localizes to the ER and ER–lipid droplet (LD) junctions, where it is crucial for LD formation, regulating LD size and number, and ensuring efficient delivery of lipids and proteins into developing LDs (Fei et al., 2008; Szymanski et al., 2007; Binns et al., 2010; Wang et al., 2016; Salo et al., 2016).

A distinct disease class called seipinopathies expanded the clinical picture in the mid-2000s. Gain-of-function BSCL2 mutations cause distal hereditary motor neuropathy type V and hereditary spastic paraplegia type 17 through seipin misfolding, toxic aggregate formation, and chronic ER stress, leading to progressive motor neuron degeneration (Hölttä-Vuori et al., 2013; Fei et al., 2011a; Windpassinger et al., 2004). Crucially, seipin is highly expressed in neurons (Garfield et al., 2012; Liu et al., 2016), which have far fewer LDs than most cell types, pointing to roles beyond neutral lipid storage.

In this review, we present seipin as a lipid rheostat: a molecular machine that adjusts the routing of lipid substrates, most critically palmitoyl-CoA, between competing biosynthetic pathways, with LDs as a primary endpoint. We focus on four interconnected themes: (1) the structural plasticity of the seipin complex, including how cofactors and lipid ligands form proteolipid complexes that modulate its conformation and activity; (2) the regulation of phosphatidic acid (PA) and sphingolipid fluxes by seipin; (3) its function at mitochondria-associated ER membranes (MAMs) in overseeing lipid synthesis, Ca^{2+} signaling, and organelle homeostasis; and (4) how these molecular roles integrate into a complex regulatory network, where failure leads to the full range of seipin-related pathologies.

Seipin dynamic structure and lipid affinities

Conformational plasticity: The open–closed spectrum

Seipin is an ER membrane protein that assembles into an oligomeric ring, an 11-mer in yeast and humans, a 12-mer in *Drosophila*, with each protomer contributing two transmembrane (TM) helices spanning the ER bilayer (Li et al., 2025; Yan et al., 2018; Sui et al., 2018; Klug et al., 2021). The seipin luminal domain presents a C2-like β-sandwich scaffold with a central hydrophobic pocket, reminiscent of the cholesterol transporter NPC2 (Yan et al., 2018) (Fig. 1 A). Short hydrophobic segments at the cytosolic–luminal interfaces stabilize the ER-LD neck (Cartwright et al., 2015). Across species, the conserved pairing of hydrophobic TM anchors and lipid-binding domain provides the molecular framework for concentrating neutral lipids and nucleating LDs (Renne et al., 2022; Molenaar et al., 2021; Zoni et al., 2021; Kim et al., 2022; Salo, 2023; Klug et al., 2024; Walther et al., 2023; Prasanna et al., 2021) (Fig. 1 A).

[1]Laboratoire de Physique de l'École Normale Supérieure, ENS, Université PSL, CNRS Sorbonne Université, Université Paris-Diderot, Sorbonne Paris Cité, Paris, France.

Correspondence to Abdou Rachid Thiam: thiam@ens.fr.

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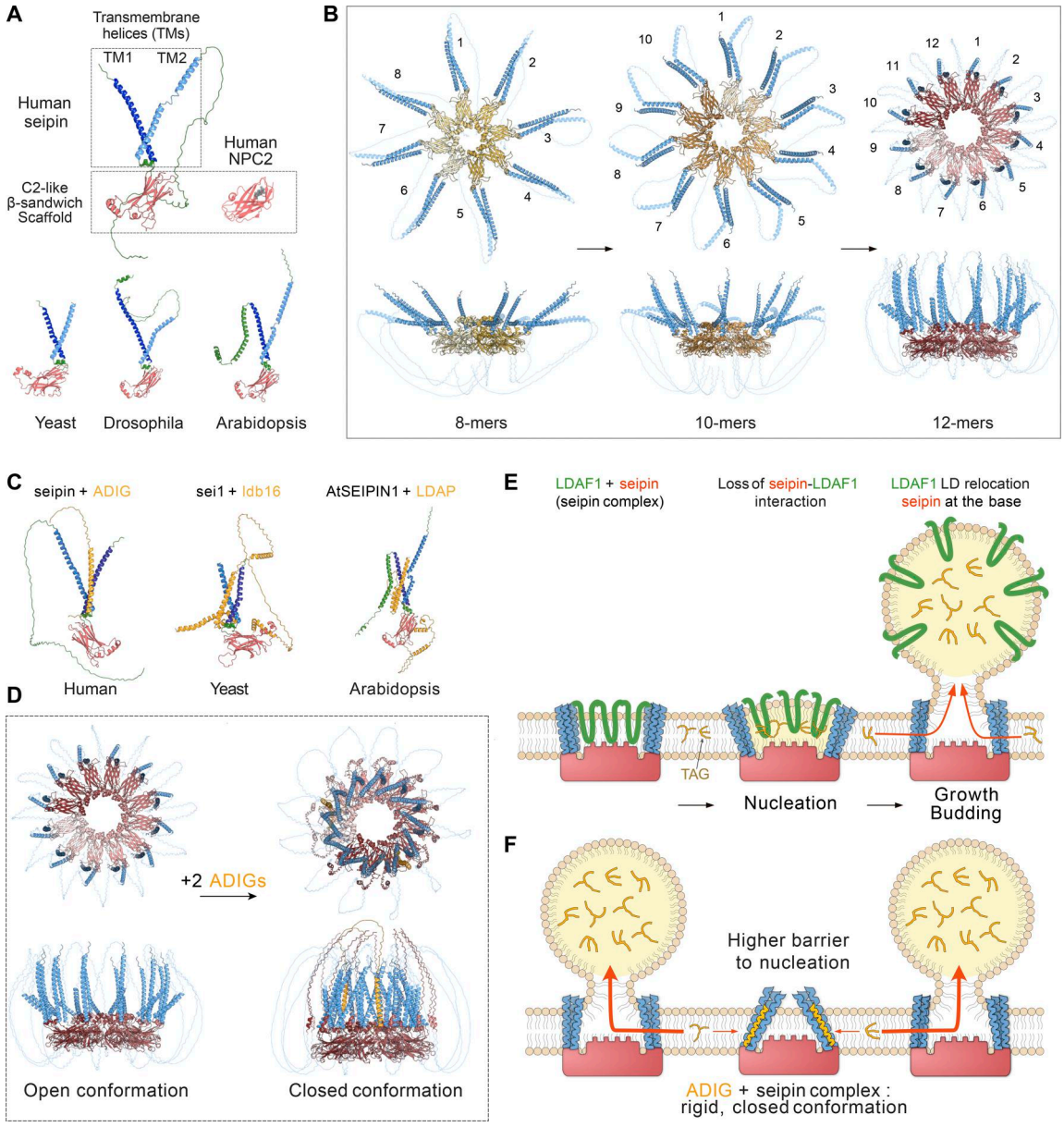

Figure 1. **Seipin structural conformations guide LD formation. (A)** AlphaFold structure of human seipin and its conserved orthologs in yeast, *Drosophila*, and *Arabidopsis thaliana*. TM2 contains a flexible upper helix. **(B)** AlphaFold structures of human seipin oligomers ranging from 8 to 12 monomers; increasing oligomer size results in progressively more closed TM helix conformations. **(C)** Association of monomeric human seipin with ADIG and its orthologs in yeast and *Arabidopsis thaliana*. **(D)** AlphaFold structures of the human seipin 12-mer in the presence or absence of two ADIG monomers; ADIG association promotes a closed multimeric conformation. **(E)** Schematic model of LD formation: seipin TM domains interact with LDAF1, and conformational changes upon TAG lens formation lead to loss of LDAF1 association. **(F)** Schematic model of seipin associated with ADIG: ADIG binding induces a more rigid conformation, preventing interaction with LDAF1 and limiting TAG flux into preexisting LDs.

AlphaFold3 confirms structural data by revealing the topology and flexibility of seipin TM helices. The two helices cross, with TM2 folding back to position a hydrophobic helix between TMs, likely aided by a flexible linker (Fig. 1 A). Beyond this, the protein extends into a disordered region that contacts the luminal surface (an orientation that would require traversal of the ER bilayer and is therefore likely artifactual). The models also show an extended C-terminal "arm" on the cytosolic side that may interact with cytosolic lipids, proteins, or organelles, as evidenced in yeast (Cartwright et al., 2015). The modeling also suggests that rings as small as 8-mers could form, adopting a more open architecture with tilted TM helices, thereby revealing mechanical constraints within the ring. As the complex approaches the 12-mer state, the ring compacts, TMs become vertically aligned, and a narrow bottleneck forms (Fig. 1 B).

The structural dynamics of seipin are further illustrated by its association with LD assembly factor 1 (LDAF1) during LD biogenesis (Castro et al., 2019; Chung et al., 2019; Arlt et al., 2022). The seipin luminal β-sandwich ring forms a cage base, while the TM helices form flexible spokes whose

alternating conformations confer structural plasticity (Arlt et al., 2022). LDAF1 integrates into this scaffold via its TM helix and cytosolic N terminus, stabilizing the seipin ring and tuning cage symmetry and flexibility (Fig. 1 E). In an initially closed state, the seipin–LDAF1 complex can sequester TAG within its core (Chung et al., 2019). Upon LD initiation, conformational shifts in the TMs, regulated by hinge-like switch regions and modulated by LDAF1, allow the cage to open laterally or expand, enabling nascent LD emergence while maintaining ER-LD continuity for LD expansion (Arlt et al., 2022) (Fig. 1 E). LDAF1 depletion impairs LD formation, though less severely than seipin loss (Chung et al., 2019; Prasanna et al., 2021). Mutations in seipin that alter switch regions or LDAF1-binding interfaces disrupt oligomer stability, hinder TAG sequestration, and generate abnormal LD morphologies, such as clusters or supersized droplets, underscoring the central role of seipin–LDAF1 dynamics in lipid homeostasis (Chung et al., 2019; Prasanna et al., 2021; Arlt et al., 2022).

The adipocyte-specific protein adipogenin (ADIG) has recently been identified as a direct interactor of seipin (Li et al., 2025). ADIG inserts between TM1 and TM2 via a hydrophobic α-helical segment (Li et al., 2025), stabilizing the complex in a more rigid dodecameric state (Fig. 1 C). This increased rigidity raises the energy barrier for ring opening, thereby limiting LD nucleation and favoring the growth of LDs where seipin has already adopted an open conformation. At the monomer level, ADIG binding restricts the flexibility of the extended TM2 helix (Fig. 1 A). Although structural predictions are partly confounded by the behavior of disordered regions, models lacking the luminal arm indicate that this helix is intrinsically flexible but becomes more constrained and tightly packed, forming a longer TM2 upon ADIG binding. Thus, ADIG reduces seipin flexibility and modulates its functional output, especially in LD nucleation (Fig. 1, D and F).

Importantly, ADIG binding is reversible (Li et al., 2025), allowing seipin to dynamically switch between open and closed states. Reduced LD nucleation with ADIG therefore reflects a functional shift, not inactivity, toward other ER roles. The ADIG: seipin ratio thus determines whether seipin primarily drives LD biogenesis or other ER functions, with even small stoichiometric changes having outsized effects on structure and activity (Li et al., 2025; Wu and Yang, 2025). For instance, AlphaFold models indicate that as few as two ADIG molecules per dodecamer can shift the complex toward a more closed conformation (Fig. 1 D).

Evolutionarily conserved ADIG-like interactions are found across eukaryotes. In plants, the LDAF1 homolog LDIP binds seipin isoforms to stabilize the complex and promote LD nucleation and expansion, working with LDAP (Fig. 1 C) (Pyc et al., 2017; Pyc et al., 2021). In yeast, Ldo45, along with its overlapping ORF Ldo16, functions similarly. Ldb16 binds the Sei1 TM helices (yeast seipin), stabilizing them in a rigid structure (Klug et al., 2021; Klug et al., 2024; Wang et al., 2024; Diep et al., 2024) (Fig. 1 C). This limits nucleation sites, promotes Ldo45 recruitment, and subsequently recruits lipid storage factors for LD growth. Conversely, Ldo16 promotes TAG catabolism and lipophagy. A balance between Ldo45 and Ldo16, regulated by Ldb16 and sensitive to seipin folding, guides LD growth versus breakdown (Eisenberg-Bord et al., 2018). These conserved cofactor strategies support viewing seipin as a flexible scaffold, whose functional state is actively adjusted by protein and lipid inputs.

Lipid affinities and membrane sensing

The structural flexibility of seipin likely enhances its interactions with lipids. The seipin β-sandwich and TM domains bind TAG and negatively charged lipids, including PA, a key intermediate in TAG and phospholipid synthesis and a signaling lipid (Yan et al., 2018; Prasanna et al., 2021; Zoni et al., 2021; Renne et al., 2022; Chung et al., 2019; Kim et al., 2022). These regions, along with the extended helix and disordered C-terminal segment, may also interact with DAG, cholesteryl esters, phospholipids, and sphingolipids, as well as proteins (Zoni et al., 2021; Renne et al., 2022). This adaptability likely enables seipin to regulate multiple lipid metabolic pathways by sensing and adjusting local lipid composition.

Beyond lipid binding, seipin flexibility may also act as a membrane sensor or organizer (Santinho et al., 2020; Santinho et al., 2024). Its luminal helix and disordered C terminus contain charged residues that could specifically interact with anionic phospholipids or sphingolipids, enabling the complex to respond to biophysical cues such as membrane thickness, order, and curvature stress (Santinho et al., 2020). Seipin may also scaffold metabolic enzymes and ER-shaping proteins at ER-LD junctions (Joshi et al., 2018; Joshi et al., 2021), placing it at the intersection of lipid synthesis, membrane remodeling, and LD formation (Thiam and Ikonen, 2020). Through coordinated lipid and protein interactions, seipin may concentrate PA, DAG, and TAG synthesis in curvature-prone ER microdomains, promote oil lens formation, and stabilize ER-LD contacts to support efficient LD maturation (Choudhary et al., 2018; Choudhary et al., 2020; Santinho et al., 2020; Adeyo et al., 2011; Zoni et al., 2021; Schneiter and Choudhary, 2022).

Although the physiological significance of seipin interactions with diverse lipids remains incompletely understood, the best-characterized roles involve neutral lipid esters and DAG during lipogenesis (Renne et al., 2022; Prasanna et al., 2021; Zoni et al., 2021). During TAG synthesis, seipin diffuses along the ER but becomes less mobile at microdomains enriched in these lipids, which serve as nucleation sites for LD formation (Chung et al., 2019; Wang et al., 2016; Salo et al., 2016; Choudhary et al., 2020; Khatri et al., 2026) (Fig. 1 E). At ER-LD contact sites, seipin orchestrates LD nucleation, growth, and maturation, ensuring efficient channeling of lipids and proteins from the ER into developing LDs.

Collectively, seipin conformational states, from the open LDAF1-bound form to the rigid ADIG-stabilized closed form, represent at least two distinct functional modes that gate different lipid-routing decisions: LD nucleation frequency, PA flux toward TAG versus phospholipids, and palmitoyl-CoA partitioning between glycerolipid and ceramide synthesis. Below, we develop each of these links in mechanistic detail.

Seipin coordinates PA and sphingolipid flux

One of the earliest lipid abnormalities reported in BSCL2 patients and later in knockout models is a remodeling of the

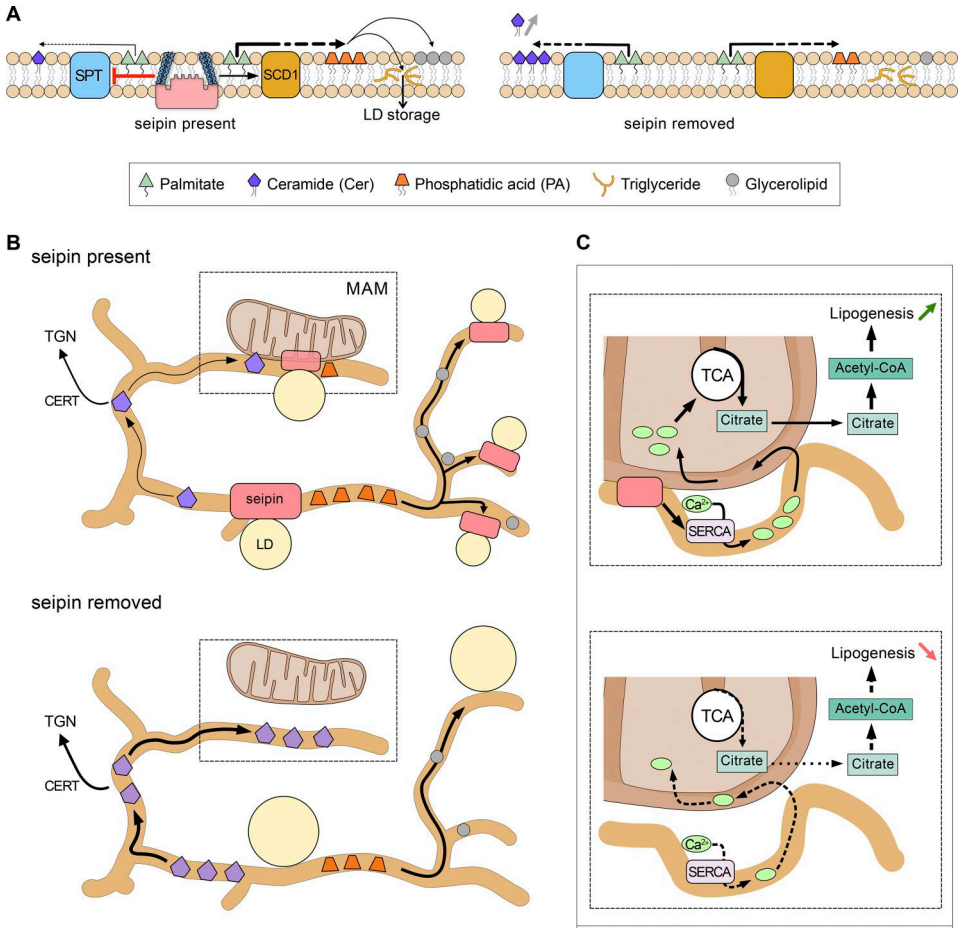

Figure 2. **Seipin regulates ER lipid homeostasis and MAM stability and functions. (A)** Schematic of ER lipid metabolism regulated by seipin through activation of SCD1 and inhibition of SPT, and the effects of seipin loss on ceramide and PA levels. **(B)** Diagram showing ceramide and PA fluxes at the ER with seipin (top), which promotes proper mitochondria–ER contact site (MAM) formation, and the accumulation of ceramides when seipin is absent (bottom), leading to MAM disruption. **(C)** Role of seipin in stabilizing SERCA at MAMs, enabling Ca^{2+} transfer from the cytosol to the ER lumen and then to the mitochondrial matrix. Increased mitochondrial Ca^{2+} enhances TCA cycle activity, increasing citrate export to the cytosol and its conversion to acetyl-CoA, which promotes lipogenesis. When seipin is lost, SERCA destabilization and MAM disruption impair mitochondrial Ca^{2+} flux, reducing acetyl-CoA levels and lipogenesis.

lipidome characterized by increased lipid saturation (Boutet et al., 2009), linked to altered stearoyl-CoA desaturase-1 (SCD1) in seipin-null cells and in mice with adipocyte-specific seipin deletion (Carpentier et al., 2025). This signature, that is, the accumulation of saturated lipids and ceramides, was found in yeast and other mammalian cell lines (Carpentier et al., 2025; Su et al., 2019; Liu et al., 2014a; Lounis et al., 2017) (Fig. 2 A) and reflects increased flux toward sphingolipid biosynthesis, driven by ceramide production via serine palmitoyltransferase (SPT) in the ER (Carpentier et al., 2025; Hanada, 2003; Schilling et al., 2013; Su et al., 2019). Several parallel studies spotlighted impairment in PA metabolism (Han et al., 2015; Romanauska et al., 2024; Fei et al., 2008; Cartwright et al., 2015; Fujimoto, 2022).

Ceramide overproduction and downstream consequences

Elevated ceramide levels in seipin-deficient cells disrupt membrane properties, induce ER stress, and activate the unfolded protein response (Liu et al., 2014b). In mitochondria, excess ceramide compromises membrane integrity, promotes fission, and triggers apoptosis (Siskind et al., 2002). Ceramide overload also hampers the CERT-OSBP relay at the ER-TGN contact (Mesmin et al., 2013; Carpentier et al., 2025), which supports TGN cholesterol/sphingomyelin microdomains vital for protein secretion or glycosylation (Carpentier et al., 2024, *Preprint*; Carpentier et al., 2025; Mesmin et al., 2017; Stalder and Gershlick, 2020; Ramazanov et al., 2021; Kovács et al., 2023). These alterations in ceramide/cholesterol transport also impair OSBP cycling and disrupt cellular cholesterol homeostasis (Carpentier et al., 2025).

Seipin deficiency leads to ceramide imbalances that disrupt multiple interorganelle contact sites, resulting in widespread defects in lipid and organelle homeostasis (Carpentier et al., 2024, *Preprint*; Carpentier et al., 2025; Palard et al., 2025, *Preprint*). These alterations propagate to broader metabolic dysfunction across diverse physiological and pathological contexts. Among the most prominent consequences are neurological defects. Seipin deficiency has been associated with impaired spinal

cord myelination (Chen et al., 2025), as well as cognitive deficits and hypomyelination. These phenotypes correlate with reduced expression of genes involved in sphingolipid metabolism in oligodendrocyte precursor cells (Cui et al., 2024). Given that myelin requires controlled sphingomyelin and glycosphingolipid levels, efficient sphingolipid biosynthesis is essential for its formation and maintenance. In this context, disruption of seipin function perturbs ER lipid homeostasis and sphingolipid production, exacerbates ER stress, and ultimately impairs myelin biosynthesis. These findings support the notion that sphingolipid dysregulation is a central driver of the neurological manifestations of seipin deficiency.

PA dysregulation

Seipin deficiency also causes abnormal PA accumulation in the ER and the inner nuclear membrane (INM), likely due to passive diffusion of PA from the ER to the nucleus or to loss of the direct function of seipin at the INM (Han et al., 2015; Romanauska and Köhler, 2018; Sołtysiko et al., 2021; Fujimoto, 2022; Romanauska et al., 2024). In both yeast and mammalian seipin-knockout cells, PA buildup is linked to abnormal TAG synthesis and storage, indicating a disruption or redirection at the PA branch point (Gao et al., 2019; Pagac et al., 2016). In yeast sei1Δ mutants, overall, PA levels are higher, particularly at ER-LD junctions and the INM (Fei et al., 2011b; Han et al., 2015; Cartwright et al., 2015; Romanauska et al., 2024). Notably, in yeast, LD formation itself is essential for PA accumulation at ER-LD junctions: sei1Δ cells that lack LDs do not show PA buildup, but inducing sterol ester–only or TAG-only LDs in sei1Δ backgrounds restores abnormal PA buildup at these sites (Han et al., 2015; House et al., 2025). This suggests that the LD environment, rather than the ER membrane alone, may be the primary site where seipin normally prevents PA mislocalization, at least in yeast.

Several mechanisms may contribute to PA accumulation. First, seipin can bind and sequester specific PA pools, preferentially monounsaturated ones (e.g., POPA) over saturated ones (e.g., DPPA), thereby buffering acyl-chain pools (Yan et al., 2018). Second, impaired LD biogenesis diverts PA flux that would normally be converted to DAG and TAG, resulting in ER accumulation of PA (Gao et al., 2019; Pagac et al., 2016). For example, in yeast, Sei1 and the Nem1-Spo7 complex organize ER subdomains dedicated to neutral lipid production and storage (Choudhary et al., 2020); their absence may allow PA to escape conversion into TAG. Third, seipin can repress GPAT4 in the ER; without seipin, GPAT4 activity increases, boosting lysophosphatidic acid (LPA) and subsequent PA production (Gao et al., 2019; Pagac et al., 2016). LPA buildup has been linked to metabolic and neurological disorders (Geraldo et al., 2021; David and López-Vales, 2021; Sakuma et al., 2023; Navab et al., 2015), mirroring phenotypes of seipin deficiency. Because PA recruits proteins involved in membrane curvature, fission/fusion, and signaling, elevated levels can produce diverse, sometimes opposing cellular effects, making it difficult to interpret PA-specific seipin phenotypes.

Together, these PA and sphingolipid imbalances, arising from direct seipin loss and adaptive responses, support a model in which seipin regulates the PA branch point that connects glycerophospholipid and TAG biosynthesis, with interactions involving specific lipids, proteins, and membrane physical properties.

Seipin and MAMs: Structural and functional insights

Seipin, sphingolipids, and MAMs

Mitochondria are the primary source of acetyl-CoA, which is exported to the cytosol for fatty acid elongation. This process generates saturated species that are transported to the ER as precursors for glycerolipids and sphingolipids. Many of these steps occur at MAMs, which are enriched for key glycerolipid and sphingolipid enzymes (Aaltonen et al., 2022; Man et al., 2006). Ceramides produced at MAMs are essential for membrane organization and signaling. Their levels must be carefully regulated: moderate amounts support organelle communication, whereas high levels stiffen membranes, disrupt contacts, and trigger apoptosis (Kinoshita and Matsumori, 2022; Dadsena et al., 2019). Disruption of MAMs blocks lipid trafficking, including phosphatidylserine (PS) transfer, leading to an accumulation of saturated lipids and ceramides in ER and mitochondrial membranes. This creates a self-perpetuating cycle: increased ceramide worsens ER stress, reduces membrane fluidity, and destabilizes MAM tethering complexes, further impairing phospholipid trafficking and increasing ceramide buildup (Huo et al., 2025; Hammerschmidt et al., 2019; Hammerschmidt et al., 2023; Hernández-Alvarez et al., 2019; Mignard et al., 2020).

Seipin deficiency–induced ceramide accumulation is accompanied by disrupted lipid flux and MAM architecture (Fig. 2 B) (Palard et al., 2025, *Preprint*; Carpentier et al., 2025). In both HeLa and 3T3 adipocytes, these defects can be rescued by overexpressing SCD1 (Carpentier et al., 2025), thereby reducing the likelihood that palmitic acid is converted to ceramides. Inhibiting fatty acid synthase (FASN) also rescued the seipin deletion phenotype by reducing saturated lipid production (Carpentier et al., 2025). Artificially reinforcing MAM contacts with synthetic linkers partially corrected seipin deficiency (Palard et al., 2025, *Preprint*), highlighting the necessity of the physical proximity of organelles in lipid metabolism (Herker et al., 2021; Voeltz et al., 2024).

Conversely, treating WT cells with excess palmitate or ceramides recapitulates the MAM defects observed in seipin-knockout models (Carpentier et al., 2025; Rieusset, 2017; Shinjo et al., 2017). Notably, ceramide-driven MAM disruption and saturated lipid accumulation also occur in obesity and type 2 diabetes (Tubbs et al., 2018; Rieusset, 2017; Fucho et al., 2017), mirroring the seipin deficiency phenotype (Fig. 2 B). These parallels reinforce the role of seipin in preventing ceramide overload and maintaining MAM integrity.

Seipin, PA, and MAMs

During stimulated lipogenesis or nutrient deprivation, seipin relocates from the bulk ER to MAMs, where transient PA accumulation promotes its recruitment (Guyard et al., 2022; Combot et al., 2022). This process depends on the ER-anchored lipid

transfer protein ORP5 (Galmes et al., 2016). ORP5 facilitates the transfer of PS to the plasma membrane (PM) in exchange for PI(4)P (Chung et al., 2015) and to mitochondria to support phosphatidylethanolamine synthesis and mitochondrial integrity (Chung et al., 2015; Monteiro-Cardoso et al., 2022). Notably, ORP5 may also transfer PA from mitochondria to the ER in reconstituted MAMs. ORP5 loss decreases PA levels at MAMs, prevents seipin recruitment, and hampers LD biogenesis and growth (Guyard et al., 2022; Monteiro-Cardoso et al., 2025, *Preprint*). ORP5-driven PA enrichment thus serves as a crucial signal for seipin subcellular localization, though whether this occurs through direct PA binding, changes in membrane properties, or interactions with protein partners at the MAM remains unclear (Monteiro-Cardoso and Giordano, 2024).

PA is crucial for mitochondrial phospholipid synthesis: it serves as a precursor converted to CDP-DAG, which drives the synthesis of cardiolipin and phosphatidylglycerol in the inner mitochondrial membrane. PA and cardiolipin regulate mitochondrial dynamics: PA at fission sites recruits DRP1, and their balance influences OPA1-mediated fusion (Kameoka et al., 2018; Blunsom and Cockcroft, 2020; Bustillo-Zabalbeitia et al., 2014).

Genetic ablation of seipin reduces MAM content in mouse tissues and in cultured 3T3 adipocytes (Palard et al., 2025, *Preprint*), underscoring its critical role in maintaining MAM integrity and coordinating PA-mediated crosstalk among the ER, mitochondria, and LDs.

Seipin, calcium, and MAMs

Seipin interacts with the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), potentially increasing pump activity in both *Drosophila* and human cells (Ding et al., 2018; Bi et al., 2014). By enhancing ER Ca^{2+} uptake, seipin helps maintain the ER–cytosol gradient required for proper protein folding, lipid synthesis, and adipose tissue development (Fig. 2 C). In seipin-deficient models, reduced SERCA activity depletes ER Ca^{2+} stores and impairs mitochondrial Ca^{2+} transfer at MAMs, disrupting TCA cycle function, energy production, and lipid storage, thereby promoting lipodystrophy-like metabolic problems (Combot et al., 2022; Ding et al., 2018; Bi et al., 2014) (Fig. 2 C).

Mitochondrial Ca^{2+} levels regulate the balance between lipogenesis and β-oxidation. Transient increases in mitochondrial Ca^{2+} activate key TCA dehydrogenases, thereby boosting citrate production. Cytosolic citrate is converted to acetyl-CoA, the building block for fatty acid synthesis (Fig. 2 C). In contrast, low mitochondrial Ca^{2+} promotes acetyl-CoA oxidation in the TCA cycle (Ding et al., 2018; Bi et al., 2014; Gherardi et al., 2020). By supporting SERCA activity and maintaining ER Ca^{2+} stores, seipin ensures effective Ca^{2+} delivery to mitochondria via MAM-localized channels (e.g., IP_3 receptors and MCU), thereby guiding metabolic flow toward lipid synthesis or energy generation.

Lipid and Ca^{2+} homeostases at MAMs are closely linked. Accumulation of saturated lipids or ceramides can alter Ca^{2+} channel activity and tethering proteins, thereby disrupting signaling. Changes in Ca^{2+} fluxes influence lipid-metabolizing enzymes and phospholipid trafficking, further compromising MAM structure (Combot et al., 2022; Palard et al., 2025, *Preprint*). Seipin may help maintain this delicate balance by coordinating lipid flow and Ca^{2+} regulation to prevent organelle dysfunction.

In summary, at MAMs, seipin may play a unique role in simultaneously regulating PA fluxes, limiting ceramide accumulation, and maintaining SERCA-dependent Ca^{2+} flux, which in turn controls mitochondrial acetyl-CoA production and lipogenesis. These three functions are interconnected: ceramide buildup impairs SERCA activity; reduced Ca^{2+} flux decreases lipogenesis; and disrupted PA-to-TAG routing affects ER membrane composition. This makes MAM the key site where the function of seipin as a lipid rheostat is most apparent. We expect that other lipids, such as sterols and ether lipids, will also be regulated there.

Seipin as a palmitoyl-CoA metabolic rheostat

The central lipid-routing decision seipin may control is the partitioning of palmitoyl-CoA between the glycerolipid and sphingolipid biosynthetic pathways. This decision is made at MAMs, where competing enzyme cascades converge on a shared pool of activated fatty acids.

Newly synthesized palmitate (C16:0) from FASN is delivered to MAMs, where the long-chain acyl-CoA synthetases ACSL1 and ACSL4 convert it to palmitoyl-CoA. There, it enters two competing routes into the glycerolipid and sphingolipid pathways (Deng et al., 2025; Küch et al., 2014; Young et al., 2018). In contrast, ACSL3, localized primarily on the ER and LDs, directs activated fatty acids toward TAG storage (Kassan et al., 2013; Poppelreuther et al., 2012).

Palmitoyl-CoA can be elongated by the very-long-chain fatty acid elongase 6 to stearoyl-CoA (C18:0), which SCD1 then desaturates to oleoyl-CoA (C18:1), forming the monounsaturated acyl-CoA pool preferred for glycerolipid synthesis (Guo et al., 2025; Matsui et al., 2012). These activated chains are incorporated via the Kennedy pathway enzymes GPAT, AGPAT, lipin/PAP, and DGAT into Lyso-PA, PA, DAG, and ultimately TAG. This metabolic "assembly line" may operate near seipin-enriched ER subdomains, where newly formed LDs bud and expand, at least in yeast (Choudhary et al., 2020; Greenwood et al., 2023).

Palmitoyl-CoA also serves as a substrate for ceramide synthesis at MAMs. SPT, the rate-limiting enzyme in ceramide biosynthesis, condenses palmitoyl-CoA with serine to form 3-ketosphinganine, which is rapidly converted to dihydroceramide and then to C16-ceramide by MAM-localized ceramide synthases CerS5 and CerS6 (Hammerschmidt et al., 2019; Bionda et al., 2004; Dadsena et al., 2019). These ceramides can remain local to modulate membrane properties and signaling or be transported to mitochondria or the Golgi for further remodeling into complex sphingolipids.

Seipin shifts the balance away from ceramide production and toward glycerolipid synthesis through two coordinated actions (Carpentier et al., 2025). First, it enhances SCD1 activity, likely by recruiting SCD1 to MAMs or increasing its local concentration there, thereby raising monounsaturated acyl-CoA pools that favor glycerolipid synthesis over sphingolipid synthesis (Lounis et al., 2017; Carpentier et al., 2025). Although total SCD1 protein levels appear unchanged in seipin-deficient HeLa

cells (Carpentier et al., 2025), SCD1 overexpression rescues the phenotype, indicating that local concentration at MAMs, rather than total amount, is important. Second, seipin restrains SPT activity, limiting the flow of palmitoyl-CoA into ceramide synthesis (Carpentier et al., 2025; Su et al., 2019). Together, these two actions redirect palmitate toward TAG storage rather than toward ceramide synthesis.

Excess C16-ceramide at MAMs and mitochondrial membranes promotes mitochondrial fission, impairs bioenergetics, and triggers ER stress (Dadsena et al., 2019; Wei et al., 2006), which partly causes the seipin-knockout phenotypes (Palard et al., 2025, *Preprint*; Carpentier et al., 2025; Ding et al., 2018). Maintaining low, tightly regulated levels of ceramide and saturated lipids is therefore crucial for MAM integrity, lipid transfer, calcium homeostasis, and overall cellular health. Seipin may help organize enzyme clusters and regulate lipid fluxes into a functional metabolon, preventing toxic ceramide accumulation and balancing storage with signaling or membrane lipids.

The proteolipid regulatory complex: A modular LEGO rheostat

The synthesis of lipids, such as glycerolipids, sphingolipids, and sterols, at the ER membrane requires precise spatiotemporal coordination of multiple enzymatic cascades. Seipin is ideally positioned to contribute to this coordination: its ring oligomer may enable it to form multiple interactions simultaneously. By directly or indirectly interacting with lipid-modifying enzymes and their substrates, it likely forms dynamic proteolipid complexes whose composition and shape respond to metabolic cues, enabling the cell to fine-tune lipid fluxes.

The metabolic fate of palmitoyl-CoA depends on the conformational state of seipin and its associated protein–lipid environment. We suggest that seipin, along with ADIG, LDAF1, and likely other cell type–specific adaptors, forms a dynamic proteolipid complex whose structure, and thus its enzyme interactions, is continuously adjusted by cofactor occupancy and lipid ligands. In this way, ADIG and LDAF1 act as modular LEGO adaptors: like interchangeable connectors, they reconfigure the seipin scaffold to engage different enzyme partners and influence lipid-routing choices. We propose that the seipin–ADIG–LDAF1–lipid ligand proteolipid complex functionally extends traditional systems (e.g., the INSIG–SCAP–SREBP–sterol complex), in which dissociation and association events finely tune distinct biological and transcriptional responses.

Cofactors reconfigure the seipin interactome

The structural flexibility of seipin allows it to adopt multiple conformations that support diverse functions. ADIG is crucial in this process, regulating the oligomeric state of seipin and its capacity to form new LDs (Fig. 1 F) (Li et al., 2025). Increasing the ADIG/seipin ratio makes the complex more rigid and reduces LD nucleation (Fig. 1, D and F). The reversible binding of ADIG allows the seipin complex to switch between open and closed states in response to metabolic signals, thereby tuning its activity. Structural and biochemical evidence show that seipin interacts directly with GPAT4 and that ADIG competes with this interaction. This shift enables enzymes such as GPAT4 to move from the ER to existing LDs (Wu and Yang, 2025; Pagac et al., 2016). Together, these observations show how cofactor dynamics between seipin and its cofactors influence the localization and activity of lipid-metabolizing enzymes. This also shows that reduced LD nucleation in the presence of ADIG does not mean seipin becomes inactive. Instead, it indicates a functional shift toward regulating lipid metabolism, especially in LD storage. This switch likely reconfigures seipin's interactome to redirect lipid-metabolizing enzyme activity, particularly at MAMs, toward glycerolipid or sphingolipid synthesis rather than LD nucleation.

LDAF1 dissociation from seipin, triggered by rising TAG levels, primes the seipin ring for LD budding (Fig. 1 E). After dissociation, LDAF1 relocates to the LD surface, where it serves as a reporter of TAG accumulation and LD emergence in the cytosol. This may activate transcriptional programs via LD surface proteins that cycle between the cytoplasm and nucleus, such as MLX or HSL (Dufau et al., 2025; Mejhert et al., 2020; Li et al., 2012). In this view, the LD number and surface area become key variables that influence gene expression. At this stage, ADIG can no longer interact with seipin because the complex has transitioned to an LDAF1-removal state that locks seipin in an open conformation.

Lipid ligands, such as PA, sphingolipids, and specific glycero lipids, add an extra layer of regulation. Recruitment of certain lipids can trigger a conformational change that alters the complex's interaction with enzymes that modify the same lipid. Therefore, each seipin–ADIG–LDAF1–lipid proteolipid complex adopts a conformation determined by its bound lipid ligand, which, in turn, influences how it interacts with metabolic enzymes. To illustrate this concept, we refer to our recent findings in mammalian cells showing that seipin regulates the partitioning of palmitic acid between glycerolipid and sphingolipid synthesis pathways involving SCD1 and SPT. Using AlphaFold, we examined potential direct interactions between seipin, SCD1, and ADIG and explored how ADIG and lipid ligands, such as palmitic and oleic acids, might modulate these interactions. Since it remains unclear whether seipin functions mainly as a monomer or an oligomer, we focused on predicted interactions involving the monomeric subunit (Fig. 3 A).

AlphaFold3 predicts a strong direct interaction between seipin and SCD1 but not between seipin and SPTLC1, an SPT subunit (Fig. 3 A). ADIG slightly weakens seipin–SCD1 binding by competing for seipin association (Fig. 3 A). Interestingly, within the seipin–ADIG–SPTLC1 complex, ADIG enhances SPTLC1 binding by directly contacting SPTLC1. These predictions support the idea that ADIG can act as an adaptor that modulates the topology of seipin and selectively blocks or recruits metabolic enzymes.

AlphaFold3 also predicts that palmitate significantly weakens the seipin–SCD1 interaction, whereas oleate has only a mild effect. Notably, in the presence of ADIG, palmitate, but not oleate, is predicted to promote the formation of a stable seipin–SCD1–ADIG complex, even within a seipin dodecamer containing only two ADIG molecules (Fig. 3 B). The SCD1–seipin interactions occur near ADIG. For SPTLC1, predictions suggest that these lipid substrates may influence the stability of the SPTLC1–seipin–

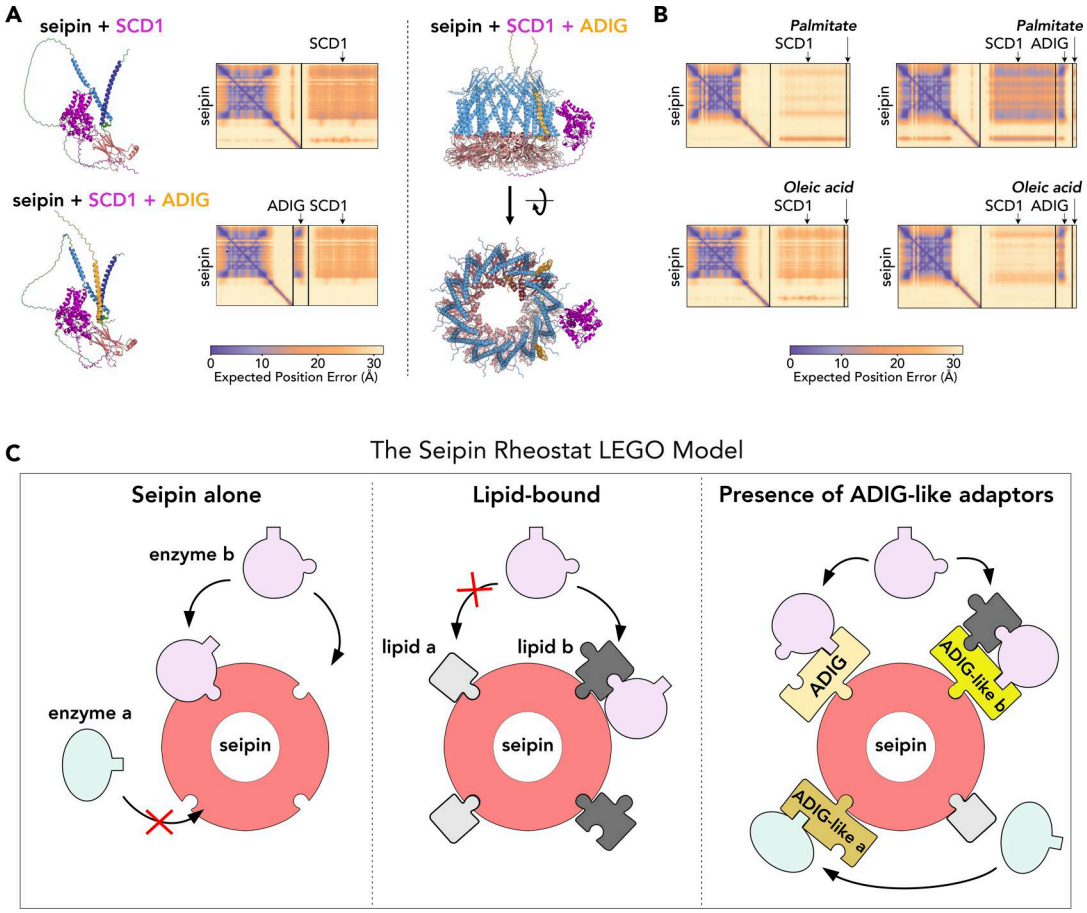

Figure 3. **ADIG-like adaptors and lipids modulate seipin–enzyme interactions and metabolic decision nodes. (A)** AlphaFold models of monomeric and multimeric seipin interacting with SCD1, with or without ADIG. PAE maps display the interaction between monomeric seipin and SCD1, with or without ADIG. **(B)** PAE from AlphaFold interaction models between monomeric seipin and SCD1 in the presence of fatty acids alone or combined with ADIG. **(C)** Schematic depiction of potential seipin–enzyme interactions through which seipin may regulate enzymatic activity. Lipids can either inhibit or promote these interactions, as shown in the central panel. ADIG and potential ADIG-like mini-proteins serve as adaptors, facilitating the recruitment of additional enzymes and modulating the strength of enzyme–seipin interactions, either independently or along with lipids. PAE, Predicted Aligned Error.

ADIG assembly. These predictions highlight how dynamic proteolipid complexes centered on seipin could regulate the routing of palmitate toward glycerolipid versus sphingolipid synthesis. They align with reported changes in saturated lipids and SCD1 associated with seipin dysfunction (Lounis et al., 2017; Carpentier et al., 2025). Additionally, they suggest that experimental methods such as cryo-EM or co-immunoprecipitation may require carefully controlled conditions and timing to capture potential ligand-dependent states.

In the highly regulated MAM environment, several lipid-metabolizing enzymes compete for palmitate and other substrates, underscoring the need for precise local control. In addition to SCD1 and SPT, many other MAM-resident enzymes involved in lipid biosynthesis, modification, or transport could interact with, regulate, or be regulated by seipin (Table 1).

Conservation of the modular principle across eukaryotes

The modular cofactor logic of the seipin–proteolipid complex appears conserved. In yeast, the Ldb16-Ldo16-Ldo45 complex functions as a counterpart to the mammalian ADIG-LDAF1 system (Leite and Bohnert, 2025): these cofactors reorganize the seipin ring, guide LD initiation and growth, redistribute lipid-modifying enzymes, and remodel ER subdomains, including the ER–vacuole interface (Diep et al., 2024; Álvarez-Guerra et al., 2024). In plants, LDAPs and LDIPs act as seipin-linked adaptors that shape the ER microenvironment and coordinate LD formation with stress responses and energy mobilization (Pyc et al., 2017; Pyc et al., 2021); the presence of three seipin paralogs in plants (Cai et al., 2015) may enable load sharing through paralog-specific interactions. The conserved architecture, characterized by a conformationally flexible seipin ring regulated by modular adaptors and lipid ligands, suggests a deep evolutionary basis for lipid routing. Overall, these yeast and plant examples demonstrate how conserved adaptor proteins may regulate seipin's shape changes and link metabolic signals to the spatial and temporal control of lipid-processing activities.

In summary, metabolic enzymes interact with seipin via shared lipid substrates, either independently or together with ADIG and potential ADIG-like proteins. ADIG modulates seipin's interactions with ER enzymes and lipid ligands; LDAF1 plays analogous roles at the LD

Table 1. **Lipid metabolism at MAM and potential seipin interactors: example enzymes, lipid transfer proteins, and lipoprotein assembly that may localize at MAM and MAM organelles (Vance, 2014; Guyard et al., 2022; Yeo et al., 2021; Monteiro-Cardoso and Giordano, 2024; Bui et al., 2026; Fugio et al., 2020; Harned et al., 2023; Rone et al., 2009; Freyre et al., 2019)**

Category	Lipid/ function	Example proteins	MAM role
Phospholipids	PS, PE, PC, PA	PSS1/2, PEMT, PSD, ORP5/8, VPS13A, PTPIP51	PS synthesis, PS-PE conversion, PE-PC methylation, interorganelle lipid transfer
TAG/neutral lipids	TAG, DAG, FAs	DGAT2, lipin-1, SCD1, FATP4, ACSL4	TAG biosynthesis, FA desaturation and activation; localized at MAM
Sphingolipids	Ceramide	CerS2/6, CERT, SPT	Ceramide synthesis and ER–Golgi transport
Ether lipids	Plasmalogens	GNPAT, AGPS, FAR1, MFF, PEX16	Ether lipid synthesis and peroxisome–MAM lipid exchange
Cholesterol and derivatives	Cholesterol, esters, oxysterols	ACAT1/2, STARD1/3/5, GRAMD1s, ORP5/8, CH25H, CYP11A1	Sterol metabolism and steroid biosynthesis
Lipid transfer and tethering	Multiple lipid types	VPS13A/C, PDZD8, Mfn2, MIGA2, VAPs	ER–mitochondria–LD lipid flow and organelle tethering; MIGA2 tethers mitochondria, ER, and LDs to promote lipid trafficking
Lipoprotein assembly	ApoB-containing lipoproteins	ApoB, MTP, SURF4, TMEM24	ApoB scaffold and VLDL assembly; MTP transfers TAG and cholesteryl esters to ApoB; SURF4 facilitates ApoB exit; TMEM24 is a potential phospholipid transporter

PE, phosphatidylethanolamine.

interface (Fig. 3 C). In this dynamic network, seipin functions as a regulatory hub that integrates metabolic signals to control lipid processing, thereby surpassing the capabilities of traditional regulatory systems. ADIG, LDAF1, and possibly other cell-specific (mini-) proteins act as modular adaptors that modulate seipin's structure and its interactions with partner enzymes. Lipid ligands further fine-tune this system: for instance, rising DAG or TAG levels weaken LDAF1 binding and trigger conformational changes that prime the complex for LD formation (Chung et al., 2019; Castro et al., 2019; Arlt et al., 2022; Zoni et al., 2021; Prasanna et al., 2021) (Fig. 1 E).

Control of metabolic decision nodes

Seipin's structural plasticity, lipid-binding selectivity, and dynamic cofactor recruitment enable it to function at multiple metabolic decision points, where local lipid composition, conformational state, and nutritional context converge to direct substrates into distinct pathways. These decision points are interconnected (Fig. 4), and their disruption due to seipin loss or mutation leads to the full spectrum of CGL2 pathology. Importantly, the pathological effects are not solely due to impaired LD formation; they also involve altered fluxes and levels of essential lipids across various organelles.

Spatial itinerancy: Cofactor-encoded subcellular targeting

Seipin's cofactor state encodes its subcellular localization. The LDAF1-bound open ring resides preferentially at ER-LD junctions; the ADIG-negative or PA-recruited ring may relocate to MAMs (Guyard et al., 2022). This spatial itinerancy implies that seipin could sample different membrane contact sites (MCS) depending on the metabolic state, with each MCS presenting a distinct lipid environment that both recruits seipin and determines which lipid and enzymatic partnerships it forms (Figs. 3 D and 4).

Beyond MAMs and ER-LD junctions, seipin-enriched ER subdomains overlap with peroxisome biogenesis sites: LDs and peroxisomes share nascent ER platforms for assembly (Joshi et al., 2018; Wang et al., 2018b) (Fig. 4). This suggests that seipin scaffolding may influence peroxisomal and LD formation. This is physiologically important because peroxisomes are the sole site of plasmalogen synthesis and make critical contributions to cholesterol esterification, both of which are rate-limiting for myelin sheath assembly (Lodhi and Semenkovich, 2014; Poitelon et al., 2020; Barnes-Vélez et al., 2023). A seipin-dependent defect in this shared ER platform could therefore impair peroxisomal lipid output and contribute to hypomyelination in seipin-deficient neurons and oligodendrocytes (Cui et al., 2024; Chen et al., 2025).

At ER–lysosome contacts, lipophagy delivers LD cargo to the lysosomal lumen; cholesterol and ceramide liberated by lysosomal hydrolases must be recycled to the ER to sustain lipid homeostasis (Ballabio and Bonifacino, 2020). A potential presence of seipin at these contacts, though not yet demonstrated, would extend its rheostat function to the catabolic–recycling axis (Fig. 4). Taken together, seipin does not merely act as a rheostat at a single node; it functions as a whole-cell lipid-routing system embedded within the MCS network, with its cofactors and local lipids serving as molecular switches that determine which node is active at any given moment.

PA partitioning: TAG storage versus phospholipid synthesis

PA, a key intermediate in glycerolipid metabolism, can be dephosphorylated by lipin/PAP to DAG for TAG storage or converted by CDP-DAG synthase to CDP-DAG, a precursor of mitochondrial phospholipids such as cardiolipin. Seipin may regulate this bifurcation by binding specific PA species, limiting free PA for the CDP-DAG synthase while enriching local PA for lipin access, and repressing GPAT3/4 activity (Yan et al., 2018). Hyperactivation of these GPATs increases PA levels, at least

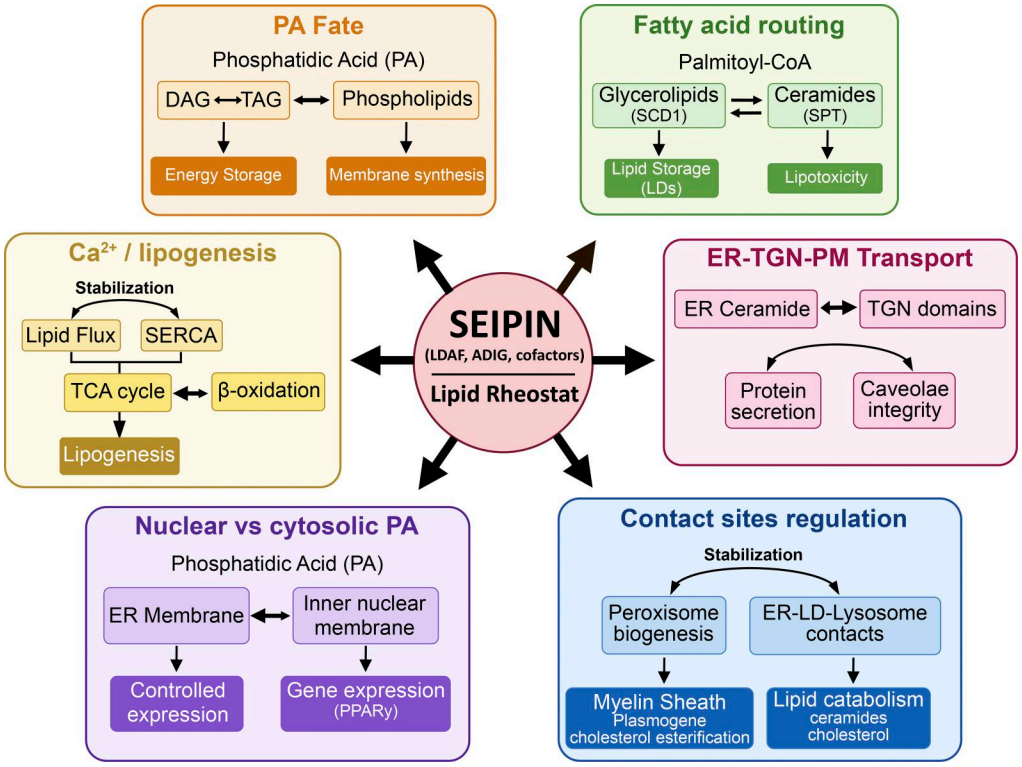

Figure 4. **Seipin as a multinode lipid rheostat.** Seipin and its cofactors (LDAF1, ADIG, etc.) act as a central lipid regulator that influences multiple metabolic decisions. At ER and ER-LD contact sites, seipin manages PA partitioning between pathways for energy storage and membrane synthesis. On MAM, it coordinates the routing of palmitoyl-CoA between lipid and ceramide synthesis, thereby preventing lipotoxicity. By supporting SERCA, seipin helps maintain ER Ca^{2+} levels, activate the TCA cycle, and balance lipogenesis with β-oxidation. At the ER-TGN-PM interface, it limits ceramide buildup, preserving membrane integrity for protein secretion and caveola stability. Seipin also controls PA distribution, preventing excess from affecting gene regulation while "directing" PA toward storage. Lastly, it stabilizes MCS, supporting lipid processing and organelle communication, which are essential for cellular lipid homeostasis.

transiently, and redirects PA toward phospholipids or nuclear signaling (Pagac et al., 2016). At MAMs, ORP5-delivered PA recruits seipin, forming microdomains that promote DAG/TAG synthesis for storage rather than mitochondrial phospholipids when necessary (Guyard et al., 2022; Monteiro-Cardoso et al., 2025, *Preprint*).

In nutrient-rich adipocytes, this routing maximizes TAG storage in LDs, ensuring safe lipid buffering and preventing ectopic accumulation. This storage occurs through the formation of large LDs, which requires PA (Barneda et al., 2015). Indeed, PA interacts with LD-associated proteins in a cell type–specific manner, binding CIDEA in brown adipocytes (Barneda et al., 2015) and CIDEC in white adipocytes (Wang et al., 2018a) to promote LD-LD fusion or ripening (Thiam et al., 2013; Thiam and Forêt, 2016) and the formation of large unilocular LDs typical of mature adipocytes (Gong et al., 2011; Fei et al., 2011b).

During membrane biogenesis or proliferation, the balance shifts toward phospholipid synthesis to expand membranes (Fig. 4). Seipin may act as a tunable valve, matching PA fate to cellular needs for storage or growth. In tissues, the role of seipin differs: in adipocytes, it is crucial for forming large TAG-rich LDs that buffer lipids, whereas in hepatocytes, overexpression impairs VLDL assembly by trapping lipids in LDs, worsening steatohepatitis, and reducing ApoB lipidation and lipoprotein export (Dong et al., 2026).

Fatty acid routing toward glycerolipid versus ceramide synthesis

This decision node is the mechanistic core described in Section 4. Briefly, seipin promotes glycerolipid synthesis over ceramide production by increasing the local concentration of SCD1 at MAMs, elevating monounsaturated acyl-CoA pools, and restraining SPT activity (Su et al., 2019; Carpentier et al., 2025). Loss of seipin shifts palmitate flux toward SPT, leading to ceramide production and ER stress (Fig. 4).

Importantly, ceramide production is not inherently harmful. During adipocyte differentiation, transient increases in de novo sphingolipid synthesis support membrane remodeling. This process is tightly controlled by ORM proteins, which are negative regulators of SPT and help maintain ceramide levels within a physiological range (Breslow et al., 2010). Seipin likely contributes to this regulatory balance, ensuring that sphingolipid production remains adaptive rather than toxic.

To prevent lipotoxicity in adipocytes and hepatocytes during fed states, excess fatty acids are directed into inert TAG stores. In seipin deficiency, ceramide accumulation in preadipocytes from unchecked SPT activity, combined with nuclear PA buildup, may impair lipid storage and adipocyte differentiation, leading to lipodystrophy, insulin resistance, diabetes, and hepatic steatosis (Magré et al., 2001; Capeau et al., 2010). Notably, CGL type 1 (AGPAT2 mutations) potentially decreases specific

PA production but increases LPA and hinders TAG synthesis, while LPIN1 knockout similarly causes PA accumulation, highlighting the crucial role of PA homeostasis across CGL subtypes.

In cells with high seipin and low LD levels, such as neurons and oligodendrocytes, SPT-restraining mechanisms maintain low ceramide levels, which are essential for myelin integrity and axonal health. Disrupted sphingolipid metabolism genes in oligodendrocyte precursor cells (Cui et al., 2024), defective spinal cord myelination (Chen et al., 2025), and cognitive impairments in seipin-deficient models likely reflect failure of this node. Peroxisomal lipid output for plasmalogen synthesis, possibly also regulated through the shared ER platform discussed above, may also contribute to the hypomyelination phenotype.

Ca^{2+}–lipid coupling at MAMs

ER Ca^{2+} levels directly regulate lipid enzyme activity, mitochondrial energy production, and acetyl-CoA supply for new fat synthesis. Seipin physically interacts with SERCA, boosting its Ca^{2+}-pump activity and maintaining high luminal ER Ca^{2+} (Combot et al., 2022; Bi et al., 2014; Ding et al., 2018). This supports IP_3R/MCU-mediated Ca^{2+} transfer to mitochondria, which activates TCA cycle enzymes, increases citrate export, and supplies cytosolic acetyl-CoA for fatty acid synthesis (Fig. 4). At the same time, seipin-organized MAM microdomains coordinate PA and ceramide flow with Ca^{2+} signaling. Elevated ceramides can destabilize tethering proteins and Ca^{2+} channels, while excess saturated PA alters membrane shape and SERCA efficiency. Therefore, seipin links Ca^{2+} balance to lipid transport in a two-way feedback loop. In fat cells, this connection may ensure that mitochondrial Ca^{2+} oscillations during feeding promote fat synthesis rather than breakdown, supporting efficient fat storage. In neurons and muscle, it prevents Ca^{2+}-driven ceramide buildup that could otherwise cause cell death or insulin resistance. The same process might explain why seipin deficiency disrupts mitochondrial function and mimics features of type 2 diabetes and neurodegeneration.

Nuclear PA versus cytosolic TAG storage

PA produced at the ER can either be converted into DAG and TAG for storage in LDs or diffuse into the INM, where it functions as a signaling lipid. Seipin may regulate this balance by sequestering specific PA species within its luminal β-sandwich structure and at specialized ER microdomains, thereby limiting the pool of free PA available for nuclear diffusion. The sequestered PA could then be funneled into the DAG/TAG synthesis pathway through the coordinated action of lipin/PAP and DGAT2, potentially at MAMs, and at ER-LD contact sites (Man et al., 2006). In this way, seipin may transiently restrict excess PA from reaching the nuclear envelope and consequently suppress aberrant nuclear LD formation (Fujimoto, 2022; Sołtysiko et al., 2021; Romanauska et al., 2024).

Importantly, the nuclear PA pool, particularly its lyso-PA derivatives, can modulate the activity of transcription factors such as PPARγ, as well as chromatin remodeling complexes, thereby establishing a direct mechanistic connection between lipid trafficking and gene expression programs (Fig. 4). During adipocyte differentiation, tightly controlled nuclear PA levels appear to fine-tune PPARγ-dependent lipogenic gene expression, while the majority of PA is preferentially directed toward cytosolic TAG storage to support membrane remodeling and safe lipid buffering. Under nutrient-rich conditions, this seipin-mediated partitioning toward cytosolic storage may prevent inappropriate nuclear PA signaling that could otherwise induce ectopic lipogenesis or stress response pathways in nonadipose tissues. In neurons and other cell types with limited LD capacity, such regulation may additionally preserve nuclear envelope integrity and protect against PA-driven transcriptional dysregulation that could impair differentiation or contribute to neurodegeneration.

ER-TGN-PM axis and caveola integrity

Caveolae are small (60–80 nm), flask-shaped invaginations of the PM, enriched in cholesterol and sphingomyelin, and organized by caveolin-1 (CAV1) and cavin-1 proteins. These specialized membrane domains function as platforms for fatty acid uptake, insulin and adrenergic signaling, and mechanosensing. Their formation relies on a tightly regulated cholesterol–sphingomyelin balance, supplied from the ER via the Golgi apparatus (Lamaze et al., 2017; Parton et al., 2020). Caveola regulation clearly demonstrates seipin's role as a lipid coordinator: ER defects propagate through Golgi sorting and PM organization. Ceramide synthesized in the ER or at MAMs must be balanced with glycerolipid flux to maintain the cholesterol–sphingomyelin ratio required for TGN membrane order, cargo sorting (Kovács et al., 2023), and delivery of CAV1 to the PM. Seipin manages this long-range process by limiting ER ceramide synthesis, by promoting SCD1 and repressing SPT, and by indirectly organizing ER-TGN contact sites that coordinate CERT- and OSBP-mediated lipid exchange (Carpentier et al., 2025). By preventing ceramide overload, seipin preserves the ordered lipid environment of the TGN, which is critical for CAV1 oligomerization, trafficking, and insertion into cholesterol-rich PM domains (Lolo et al., 2023) (Fig. 4). This aligns with the significant metabolic effects of caveola disruption: CAV1-null mice develop lipodystrophy-like features, including reduced adipose tissue, increased circulating free fatty acids, impaired insulin and adrenergic signaling in fat cells, and systemic metabolic inflexibility (Asterholm et al., 2012). Intact caveolae support efficient fatty acid uptake and insulin-stimulated glucose uptake while aiding LD biogenesis (Carpentier et al., 2025; Ocket et al., 2025, *Preprint*). During adipogenesis, the ER-TGN-PM axis ensures proper membrane expansion and caveola formation, both of which are crucial for the large, unilocular LDs characteristic of white adipocytes. In neurons and muscle cells, where LDs are rare, this process maintains PM lipid organization, vital for synaptic signaling and mechanoprotection. Seipin deficiency thus uncouples ER lipid metabolism from PM organization, contributing to caveola defects seen in various forms of CGL (CGL2-4) and linking seipin dysfunction to insulin resistance and metabolic syndrome.

Together, these decision nodes (Fig. 4) illustrate how seipin may function as a multinode lipid rheostat: each node is linked by the flexible scaffold of seipin, lipid-binding selectivity, and dynamic cofactor recruitment. Similar mechanisms likely

operate in cardiomyocytes and neurons (Liu et al., 2025; Wu et al., 2021; Cui et al., 2024; Chen et al., 2025). The system continuously monitors lipid composition and nutritional status across multiple MCS and adjusts metabolic fluxes in real time to maintain organelle stability and prevent lipotoxicity.

Conclusion and future directions

Major questions remain about how seipin senses changes in lipid composition and membrane stress, allocates flux between TAG production and ceramide synthesis, and organizes distinct metabolic states at ER-LD contact sites and MAMs. Its contributions to interorganelle communication, tissue-specific functions, and potential compensatory pathways in cells with low seipin expression also require clarification. What additional adaptor proteins beyond ADIG and LDAF1 modulate the function of seipin in neurons, hepatocytes, cardiomyocytes, and immune cells?

Future studies integrating structural biology, spatial proteolipidomics, and functional approaches will be essential to unravel these mechanisms and to understand how they influence caveola dynamics, sphingolipid profiles, and broader lipid homeostasis. In particular, defining how seipin assembles proteolipid complexes with ADIG and LDAF1 and identifying the lipids that modulate its interactions with associated enzymes will be crucial to decoding its central role in lipid metabolism. Illuminating these complex relationships holds promise for identifying new therapeutic targets for lipodystrophies, metabolic diseases, and neurodegenerative disorders.

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