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Lipid metabolism dysregulation in Parkinson's disease: Mechanistic insights and therapeutic implications

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective degeneration of nigrostriatal dopaminergic neurons and pathological accumulation of α-synuclein (α-Syn) aggregates. Emerging evidence indicates the important role of lipid metabolism dysregulation in driving these pathological features. As major structural components of brain tissue and critical regulators of neuronal function, lipids are involved in diverse biological processes, including cell membrane formation, intercellular signaling, energy storage, and homeostasis. Their dysregulation directly affects neural functions, such as synaptic transmission, antioxidant defense, and inflammatory modulation. PD is recognized not only as a "proteinopathy" but also as an "organelle communication disorder," involving dysfunction of membrane contact sites across mitochondria, endoplasmic reticulum, lysosomes, and lipid droplets (LDs)—a process that may constitute an early pathogenic event. It is noteworthy that several proteins mediating LDs–organelle contacts are disease-related factors encoded by mutated genes in inherited neurological and metabolic disorders. Despite the extensive communication between intracellular LDs and other organelles through these contact sites, the systematic integration of lipid metabolism dysregulation into core PD pathogenesis remains elusive. This review provides a comprehensive overview of the mechanisms underlying lipid–organelle interactions in PD pathogenesis, with a specific focus on the triangular interplay among the three core pathological hallmarks: α-Syn aggregation, mitochondrial dysfunction, and neuroinflammation, and their convergence with the lipid metabolic network. By analyzing molecular mechanisms and clinical implications, with particular focus on lipid-related biomarkers and therapeutic strategies targeting organelle communication pathways, this review aims to provide new insights into the role of lipid dyshomeostasis in PD pathogenesis and identify feasible therapeutic targets.

Keywords: Parkinson's disease; Lipid metabolism; Organelle communication; α-Synuclein; Mitochondrial dysfunction

1. Introduction

Parkinson's disease (PD), the second most prevalent neurodegenerative disease worldwide, affects more than 10 million individuals with a male-to-female prevalence ratio of approximately 2:1.[1-3] The pathological hallmarks include the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the formation of Lewy bodies—intracellular inclusions primarily composed of misfolded α-synuclein (α-Syn).[4,5] These pathologic changes contribute to both motor symptoms (e.g., resting tremor and bradykinesia) and non-motor manifestations (e.g., hyposmia, sleep disturbances, and cognitive impairment) with symptom severity progressing alongside neuronal loss, severely impacting patients' quality of life.[6,7] While α-Syn aggregation remains a central event in PD pathogenesis, growing evidence implicates mitochondrial dysfunction, oxidative stress, and inflammatory responses as synergistic drivers, with lipid metabolism dysregulation increasingly recognized as a unifying mechanism linking these processes.[8]

Lipids, including cholesterol, fatty acids (FAs), glycerophospholipids, and sphingolipids, serve as critical structural components and key regulators of neuronal function.[9] The human brain, composed of approximately 50% lipids by dry weight, is the most lipid-rich organ after adipose tissue.[10] Notably, lipid homeostasis in the brain is fundamental to key physiological processes essential for maintaining neuronal cell membrane integrity, neural signaling, synaptic function, and inflammatory modulation.[11-17] In PD, disruptions in lipid homeostasis not only lead to decreased cell membrane fluidity, impaired synaptic function, and neuronal death, but also amplify PD pathogenesis by disrupting mitochondrial function and promoting α-Syn aggregation.[10,18-21] Furthermore, dysregulated lipid metabolism activates microglia, driving excessive neuroinflammation and creating a vicious cycle of neuronal damage.[22-25] Therefore, elucidating the mechanisms of lipid dysregulation in PD is important for unravelling the disease's etiology, identifying early diagnostic markers, and developing novel therapeutic strategies.

In PD, lipid metabolism dysregulation manifests through multiple organelle dysfunctions and interplay imbalances.[16,26,27] For example, the dysregulation of mitochondria–lipid droplet (LD) interactions results in both LD accumulation and mitochondrial lipid deficiency.[28] Similarly, impaired phospholipid exchange at mitochondria-associated endoplasmic reticulum (ER) membranes affects cardiolipin (CL) biosynthesis, while lysosomal dysfunction induces abnormal lipid degradation.[26,29] Collectively, organelle-mediated lipid disturbances disrupt energy metabolism, elevate oxidative stress, and promote neuroinflammation, ultimately exacerbating progressive neuronal damage. Dopaminergic neurons, in particular, are extremely sensitive to abnormal lipid metabolism due to their high metabolic demands and strong dependence on FA β-oxidation. Moreover, synaptic function has stringent requirements for the composition and metabolic dynamics of membrane lipids. Consequently, lipid dyshomeostasis directly induces synaptic dysfunction, leading to reduced dopamine release and synapse loss.

This review provides a systematic examination of the multifaceted roles of dysregulated lipid metabolism in PD. It comprehensively analyzes three key aspects: the effects of lipid homeostasis imbalance on neuronal functions, the mechanisms underlying dysregulated lipid–organelle interactions, and the critical contribution of lipid metabolism abnormalities to PD pathogenesis. Through the integrated analysis, the review elucidates the pivotal role of dysregulated lipid metabolism in PD progression and evaluates its potential as a therapeutic target for disease intervention.

2. Lipid homeostasis

2.1. Lipid homeostasis in the brain

Lipid homeostasis in the brain refers to the dynamic balance of lipid synthesis, metabolism, transport, and distribution.[30] As fundamental structural components of neuronal membranes and key regulators of cellular function, lipids are tightly associated with the etiology, progression, and severity of neurodegenerative diseases.[31]

Phospholipids, a major class of brain lipids, are essential for maintaining neuronal membrane structure and synaptic integrity. Disruptions in phospholipid balance reduce membrane fluidity, impair synaptic function, and accelerate neuronal death.[10] Beyond membrane structure, lipids are vital to mitochondrial function, serving as key constituents of mitochondrial membranes. Dysregulated lipid homeostasis directly impairs mitochondrial energy metabolism (e.g., adenosine triphosphate [ATP] production) and diminishes antioxidant capacity, exacerbating energy deficits in neurons.[32]

Notably, progressive degeneration of nigrostriatal dopaminergic neurons characterizes the central pathological feature of PD. Specific lipids, including sphingolipids, modulate PD pathogenesis by altering α-Syn conformation and aggregation rates. Under conditions of lipid dyshomeostasis, aberrant lipids (e.g., oxidized FAs) promote the formation of toxic α-Syn aggregates, further damaging neurons.[22] Brain lipids, particularly unsaturated

FAs such as monounsaturated FAs (MUFAs) and polyunsaturated FAs (PUFAs), exhibit a high propensity for oxidation under oxidative stress, generating toxic metabolites (e.g., 4-hydroxynonenal [4-HNE]) that amplify neuronal injury.[33] Moreover, lipid imbalance activates microglia and triggers excessive inflammatory responses, creating a vicious cycle that drives neurodegeneration in PD.[22-25]

2.2. Lipid–organelle interactions in PD

Neurons, as highly specialized cells, depend on a dynamic network of lipid–organelle interactions. This network facilitates material and energy exchange among four core organelles—LDs, mitochondria, ER, and lysosomes—with lipids playing dual roles as both structural bridges and signaling molecules.[34-38] Central to this network are membrane contact sites (MCS), specialized regions where organelles serve as hubs for inter-organelle lipid transport. At MCS, dedicated lipid transfer proteins mediate targeted lipid redistribution from synthetic compartments (e.g., ER) to recipient organelles (e.g., mitochondria), ensuring the functional integrity of organelles disconnected from secretory pathways[39,40] Emerging evidence suggests that PD is not only a classical proteinopathy but also a multifaceted "organelle communication disorder." Dysfunction in MCS—particularly those involving mitochondria, ER, lysosomes, and LDs—may represent an early event in disease development.[41] Notably, PD-associated mutations (including but not limited to phosphatase and tensin homolog deleted on chromosome 10-induced kinase 1 [*PINK1*], β-glucosidase 1 [*GBA1*], vacuolar protein sorting 13 homolog C [*VPS13C*], and α-Syn [*SNCA*]) disrupt the function of lipid transport proteins and GTPases, thereby impairing lipid/calcium exchange at critical contact sites, such as mitochondria–lysosomes, ER–mitochondria, and mitochondria–LDs.[40] These defects lead to reactive oxygen species (ROS) bursts and lysosomal inflammation, both of which play key roles in the initiation and progression of PD pathology.

2.2.1. LDs as key regulators in PD

LDs are multifunctional organelles that dynamically regulate lipid homeostasis, extending well beyond the conventional perception of them as "inert lipid reservoirs."[42] As primary intracellular storage sites for neutral lipids (e.g., triglycerides and cholesterol esters), LDs are coated with a phospholipid monolayer—primarily phosphatidylcholine (PC) and phosphatidylethanolamine (PE)—along with associated proteins, which collectively confer unique protective functions. One critical function of LDs is acting as a "lipotoxic firewall." By selectively sequestering excess saturated FAs (e.g., palmitic acid [PA]) and neurotoxic sphingolipids (e.g., ceramide [Cer]), LDs prevent ER stress and membrane lipid peroxidation.[43] Another key role of LDs is serving as an energy reservoir: contrary to the traditional view that neurons rely solely on glucose, recent studies reveal that LDs at synaptic terminals act as "backup energy sources"—during glucose deprivation, triglycerides in LDs are catabolized by the lipase DDHD domain containing 2 (DDHD2) to sustain synaptic function.[44] Neuronal LDs are rich in PUFAs (e.g., docosahexaenoic acid [DHA] and eicosapentaenoic acid), which prevent toxic FAs from accumulating in the cytoplasm by esterifying free FAs into less active and less toxic forms, thus avoiding oxidative damage and lipotoxicity. Abnormal accumulation of LDs in neurons and glial cells constitutes a hallmark of neurodegenerative diseases, particularly in PD pathology, where it disrupts lipid homeostasis. LD-specific lipophagy is a key mechanism for the cellular clearance of LDs and the maintenance of lipid homeostasis. Recent discoveries identify autophagy-related gene 14 (ATG14) as a receptor on LDs, recruiting autophagosomes to degrade LDs and thus initiating lipophagy, presenting a promising therapeutic target.[45] Notably, α-Syn inhibits phospholipase D1 (PLD1) activity, blocking phosphatidic acid production, impairing lipophagic flux, and driving abnormal LD accumulation—directly linking lipid metabolism disorders to early PD pathogenesis.[19]

2.2.2. LD–mitochondria interaction

Mitochondria play a key role in lipid metabolism as the primary energy producers of the cell.[13,14] First, they support lipid synthesis by providing substrates (e.g., acetyl-coenzyme A [acetyl-CoA]) and energy (e.g., ATP) through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation.[15,17] Second, mitochondria receive free FAs released from LDs and break them down through β-oxidation to provide energy.[17] However, this balance is disrupted in neurodegenerative diseases, including PD. Saturated FAs accumulated in LDs are converted to fatty acyl coenzyme A derivatives by acyl coenzyme A synthetase 4 (ACSL4) and can generate large amounts of lipid peroxides, such as 4-HNE, when catalyzed by arachidonate 15-lipoxygenase (ALOX15). When lipid peroxides exceed the scavenging capacity of glutathione peroxidase 4 (GPX4), ferroptosis is activated, leading to widespread PUFA peroxidation and plasma membrane collapse.[46]

Mitochondria-LD interactions are mediated by key proteins: the neuron-specific lipase DDHD2 regulates lipolysis to release FAs from LDs, while carnitine palmitoyltransferase 1 (CPT1) transports these FAs into mitochondria for β-oxidation.[44] In PD, defective DDHD2 function or impaired lysosomal degradation (e.g., due

to *GBA1* mutation) results in impaired clearance of LDs and accumulation of intracellular LDs. Proteins such as perilipin-5 (PLIN5) and perilipin-4 (PLIN4) further modulate this interaction: PLIN5 acts as a bridging protein for mitochondria–LD contact; its downregulation weakens this interaction, impairing FA transport to mitochondria, triggering β-oxidation substrate deficiency, energetic crisis, and lipotoxicity.[28,47] In addition, the LD surface protein PLIN4 interacts with α-Syn to promote LD accumulation and inhibit mitophagy; the Src homology 2B adaptor protein 1 (SH2B1)–heat shock cognate 70 (HSC70)–PLIN4 axis or downregulating PLIN4 reduces LD load, restores mitochondrial homeostasis, and alleviates PD-related neurodegeneration.[48-50] Recent studies identify the mitochondrial protein mitoguardin-2 (MIGA2) as a lipid transporter at mitochondria–LD contacts, directly shuttling FAs and phospholipids (e.g., PC and PE) from LDs to mitochondria to maintain mitochondrial morphology and LDs dynamics, highlighting lipids as key mediators of organelle crosstalk in PD.[39]

2.2.3. ER and mitochondria crosstalk through mitochondria-associated membranes: Mediated lipid metabolism

Mitochondria-associated membranes (MAMs) are "molecular highways" that coordinate lipid and energy metabolism. The ER, a core site for calcium storage and lipid synthesis, connects tightly to mitochondria through MAMs to facilitate the bidirectional exchange of lipids (e.g., PE and phosphatidylserine [PS]) and calcium ions (Ca^{2+}), and to fine-tune energy metabolism.[51,52] This exchange is critical for neuronal function: MAM-mediated lipid transport supports mitochondrial membrane integrity, while calcium flux synchronously activates mitochondrial TCA enzymes, coupling lipid oxidation to energy production.[53] In PD, this balance is disrupted: pathological α-Syn oligomers bind the major sperm protein domain of vesicle-associated membrane protein-associated protein B (VAPB) through their N-terminus (1–60 aa), disrupting the VAPB–protein tyrosine phosphatase interacting protein (PTPIP51) complex and widening the MAM spacing.[27] This structural disintegration of MAMs has cascading effects: it reduces PE transport efficiency, sharply decreases CL synthesis, disassembles respiratory chain super complexes, and increases electron leakage. These changes ultimately trigger mitochondrial outer membrane permeabilization (MOMP) and apoptotic cascades, contributing to dopaminergic neuron loss.[29] In addition, α-Syn disrupts MAM-mediated lipid metabolism, particularly impairing PE and PS synthesis/conversion, leading to neuronal membrane dysfunction and contributing to synucleinopathies.[54]

2.2.4. Lysosomes: An end processing station for lipid metabolism

As the final processing site for lipid metabolism, lysosomes play a key role in the pathological mechanisms of PD. These bilayer membrane-structured organelles regulate protein degradation and lipid homeostasis through their acidic environment (pH 4.5–5.0) and a suite of hydrolytic enzymes. Under physiological conditions, lysosomes maintain lipid balance through lipophagy: LDs are encapsulated by autophagosomes and fused with lysosomes, where lysosomal acid lipase (LAL) hydrolyzes triglycerides and acid β-glucosidase (GCase) degrades sphingolipids.[55] Degraded cholesterol is translocated to the cytoplasm through NPC1 for membrane synthesis, a process regulated by mechanistic target of rapamycin complex 1 (mTORC1): under nutrient sufficiency, mTORC1 suppresses *ATG*, while energy stress activates AMP-activated protein kinase (AMPK) to phosphorylate Unc-51-like autophagy-activating kinase 1 (ULK1) and initiate autophagosome formation.[56] In PD, this balance is disrupted, particularly in patients with *GBA1* mutations. *GBA1* loss-of-function reduces GCase activity, causing its substrate glucosylceramide (GlcCer) to accumulate in lysosomes. GlcCer directly inhibits the V-ATPase proton pump, raising lysosomal pH from 4.5 to approximately 6.0, which inactivates LAL and impairs lipophagy.[20,21,57,58] In addition, the normal tetramer–monomer balance of α-Syn is disrupted, making it more prone to form easily aggregated monomers. These α-Syn aggregates co-localize with the lysosomal membrane marker lysosomal-associated membrane protein 1 (LAMP1) and form lipid-rich aggregates within lysosomes.[26] Notably, elevated GCase activity increases lysosome ($LAMP1^+$)–GCase colocalization and reduces LDs ($Plin2^+$) accumulation, indicating the coordinated regulation of α-Syn and lipid homeostasis by lysosomes and LDs—an interaction disrupted in PD.

3. Lipid metabolism mechanisms in PD

3.1. FA metabolism: Imbalance between neuroprotection and toxicity

FA metabolism is a finely regulated process, including the key steps of FA synthesis, catabolism (β-oxidation), and transport, and it involves the catalysis and regulation of multiple enzymes.[59] Dysregulation in these processes drives metabolic imbalance, a key feature of PD pathogenesis that links energy deficits, oxidative stress, and α-Syn aggregation. The brain exhibits unique FA metabolism due to its lipid richness and blood–brain barrier (BBB) restriction: the BBB limits peripheral lipid entry, rendering the central nervous system (CNS) dependent on local lipid

synthesis and vulnerable to pathological disruption. In addition, regional metabolic heterogeneity exists—e.g., the midbrain, cerebellum, and olfactory bulb show higher FA synthesis rates than the hippocampus and cortex, with a bias toward ω-3/ω-6 PUFAs (e.g., DHA and arachidonic acid [AA]) compared to the synthesis of MUFAs in peripheral tissues.[60] This compartmentalized synthesis profile is essential for neuronal function and synaptic plasticity; its disruption directly contributes to PD-related neuronal dysfunction.

De novo FA synthesis in mammals involves acetyl-CoA carboxylase and FA synthase (FASN), converting acetyl-CoA to PA; this product is subsequently modified by stearoyl-CoA desaturase 1 (SCD1) and elongases to form MUFAs and PUFAs.[59,60] Studies indicate that the abnormal accumulation of PUFAs and cholesterol lipids promotes α-Syn misfolding and aggregation, while aberrant binding of α-Syn to oxidized lipid metabolites damages key organelles such as mitochondria.[61,62] Notably, PUFAs are significantly reduced in the SNc of PD patients—particularly the members of the ω-3 PUFA families (such as DHA) and the ω-6 PUFA families (such as AA). As PUFAs, especially AA, are major substrates for lipid peroxidation, their depletion reduces membrane fluidity and the production of neuroprotective mediators.[63-65] Notably, decreased PUFAs may reflect or exacerbate the severe oxidative stress state in PD.[59,66] Furthermore, FA metabolic dysregulation impairs the activity and efficiency of FA oxidation enzymes.[67] Oxidative stress products (e.g., 4-HNE) directly damage neurons and accelerate α-Syn oligomerization and fibrillization.[68] Concurrently, reduced early CPT1 activity observed in PD patients causes the accumulation of long-chain acyl cofactors (e.g., acylcarnitine [16:0] and acylcarnitine [16:1]), which inhibits mitochondrial respiratory chain complexes, reduces ATP production, and disrupts neuronal energy metabolism.[69]

Short-chain FAs (SCFAs) are saturated aliphatic organic acids with 1–6 carbon atoms, primarily comprising 60% acetate (two carbon atoms, C2), 20% propionate (three carbon atoms, C3), and 20% butyrate (four carbon atoms, C4).[70-72] As key gut–brain axis regulators, SCFAs modulate CNS function through multiple pathways: their deficiency disrupts intestinal metabolic homeostasis, facilitating α-Syn misfolding and prion-like propagation.[73-78] PD patients exhibit gut dysbiosis—reduced abundance of SCFA-producing genera (e.g., *Roseburia* and *Prevotella*)—causes an approximately 30% decrease in total fecal SCFAs, predominantly affecting acetate, propionate, and butyric acids.[74,76] Conversely, intestinal mucosal barrier disruption leads to abnormal SCFA leakage into the bloodstream, significantly elevating plasma propionate, butyrate, and valerate levels.[76,77] This distributional imbalance enables gut-derived SCFAs to indirectly exacerbate CNS pathology by abnormally activating microglia, promoting α-Syn misfolding, and impairing protein degradation systems. Specifically, butyrate acts as a histone deacetylase (HDAC) inhibitor. Insufficient butyrate levels inhibit HDAC-dependent autophagy gene expression and impair ubiquitin-proteasome system function, ultimately leading to misfolded protein accumulation, mitochondrial dysfunction, and neuroinflammatory responses.[71,78-83] These findings highlight SCFAs' dual roles in CNS pathophysiology, which are concentration- and distribution-dependent—i.e., exerting neuroprotective or neurotoxic effects based on their compartmental distribution and metabolic context, thereby linking gut dysbiosis to PD pathogenesis and offering potential targets for dietary or probiotic intervention.

3.2. Phospholipid remodeling: From mitochondrial failure to α-Syn aggregation

3.2.1. CL

CL, a unique diphosphatidylglycerol enriched in the inner mitochondrial membrane, maintains membrane ultrastructure, respiratory chain assembly, mitochondrial dynamics, and mitophagy.[84] Its biosynthesis involves phosphatidylglycerol conversion to immature CL through CL synthase (CRLS1), followed by remodeling (e.g., tafazzin-mediated replacement of FA chains with unsaturated species such as linoleic acid) to form mature CL.[85] Dysregulation of CL metabolism, characterized by alterations in its content, structure, and distribution, impairs mitochondrial function. These abnormalities lead to pathological processes such as oxidative stress and apoptosis, which are implicated in various disease states, particularly PD. Abnormal CL metabolism fragments mitochondrial cristae, disrupts respiratory chain complex I/III assembly, reduces electron transfer efficiency, and triggers ROS bursts—a key source of oxidative stress in PD.[85,86] CL translocates ectopically to the outer mitochondrial membrane, serving as a molecular platform for BCL2-associated X (BAX) protein oligomerization and MOMP, driving apoptosis in dopaminergic neurons.[87,88]

Physiologically, CL binds the N-terminal domain of α-Syn through electrostatic interactions, maintaining its α-helical conformation and preventing misfolding. In PD, decreased CL content or oxidative damage (e.g., complex II-derived ROS attacking CL dienophile bonds) causes α-Syn dissociation, promoting β-sheet-rich toxic oligomers and Lewy body formation.[18,86] Recent studies show that the SNc from PD patients exhibits reduced total CL content and decreased levels of unsaturated FAs; these

changes directly impair membrane fluidity and respiratory chain function. The A53T-α-Syn mutant significantly disrupts the CL maturation pathway by downregulating CRLS1 expression and inhibiting tafazzin activity, leading to immature CL accumulation and a functionally defective phenotype.[89] In addition, the binding of α-Syn oligomers to MAMs inhibits calcium exchange and lipid transfer, leading to disruption of MAM integrity, which in turn exacerbates CL dyshomeostasis and mitophagy disorders.[27,29] These findings highlight CL metabolism as a potential therapeutic target, with strategies to restore CRLS1/tafazzin activity or reduce CL oxidation under preclinical investigation.

3.2.2. PC and PE

PC and PE are the two most abundant core structural lipids in eukaryotic cell membranes.[90-93] PC accounts for more than 50% of most eukaryotic cell membrane phospholipids. It is predominantly distributed in the outer leaflet of the plasma membrane and is synthesized through the cytidine diphosphate (CDP)–choline pathway; its polar head group imparts rigidity to the membrane structure, and PC serves as a precursor for acetylcholine (ACh) production through hydrolysis.[94,95] In contrast, PE is enriched in the inner leaflet, generated through the CDP-ethanolamine pathway and by the PS decarboxylase. Its smaller head group and tapered molecular structure can facilitate the formation of membrane curvature, which is essential for vesicle trafficking and autophagosome membrane assembly.[93,94]

Synergistically, PC and PE maintain membrane asymmetry, fluidity, and transmembrane signaling efficiency. PC is an ACh precursor, while PE serves as an essential substrate for mitochondrial CL synthesis. Together, they regulate neurotransmitter metabolism and energy homeostasis. Dysregulation of PC/PE metabolism alters their content, composition, and distribution, potentially affecting membrane stability, permeability, and signaling, thereby contributing to disease pathogenesis.

In PD, reduced PC levels impair membrane integrity and neuronal function. Lipidomic analyses have revealed a significant PC/PE imbalance in the brains and peripheral tissues of PD patients. This was evidenced by reduced levels of PC (34:5), PC (36:5), and PC (38:5) in the brain, and increased levels of PC (44:5) and PC (44:6) alongside reduced levels of PC (35:6) and PE (34:1) in plasma.[96,97] In 6-hydroxydopamine (6-OHDA)-treated rats, most PC levels in the substantia nigra were decreased.[93,98] Meanwhile, lysophosphatidylcholine (LPC) levels exhibited biphasic changes—elevated neurotoxic species such as LPC (16:0) and LPC (18:1), and decreased neuroprotective species.[93,98] Furthermore, PC/PE metabolic disorders drive pathological α-Syn aggregation through multiple mechanisms. Studies have shown that PC (32:0) and PC (34:1) are associated with Lewy vesicles.[99] The sn-1 position vinyl ether bond of plasmalogen–PE stabilizes the α-Syn N-terminal α-helical structure. A reduction in plasmalogen-PE levels in PD causes α-Syn to unfold into a β-sheet conformation and increases the rate of α-Syn aggregation.[100,101]

3.3. Sphingolipid: Drivers of neuroinflammation and proteinopathy

Sphingolipids, core components of eukaryotic cell membranes, constitute a complex metabolic network centered on sphingosine as the backbone, encompassing Cer, sphingomyelin (SM), glycosphingolipids (GSLs), and the signaling molecule sphingosine-1-phosphate (S1P).[102] They regulate membrane structural stability (e.g., myelin formation), cell signaling (e.g., apoptosis/survival balance), lysosomal homeostasis, and synaptic plasticity; their dysregulation is a well-established risk factor for PD. The central hub of sphingolipid metabolism is Cer.[102-104] Its *de novo* synthesis begins with the condensation of serine with palmitoyl-CoA in the ER to form 3-ketosphingosine, which is reduced to sphinganine.[102] Sphinganine is then acylated to dihydroceramide, which is desaturated to form Cer, and then converted to SMs or GSLs in the Golgi apparatus. Downstream degradation depends on lysosomal enzymes: acid sphingomyelinase hydrolyzes SM to Cer, and GCase catalyzes GlcCer degradation to glucose and Cer.[105]

3.3.1. Ceramide

Sphingolipid metabolic disorders are closely associated with PD.[105] Total Cer and SM levels are significantly reduced in the anterior cingulate cortex of PD patients, with Cer acyl chain lengths shifting toward shorter species (increased C18:0, decreased C24:1), indicating disturbed Cer metabolism.[106] Cer acts as a pro-apoptotic messenger, and its accumulation impairs mitochondrial function. Notably, decreasing Cer levels or stimulating its β-oxidation improves the PINK1-deficient phenotype, suggesting novel therapeutic targets for PD.[107] Emerging evidence reveals that ethanol-induced Cer production causes neuronal apoptosis by increasing myeloid cell leukemia 1S-mediated MAMs dysfunction.[108] Excessive sphingosine kinase 1 (SPHK1) expression is associated with PD;[109] drugs such as pramipexole and fingolimod (FTY720) ameliorate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neuron loss in PD mice through Akt/SPHK1 activation, wherein SPHK1 catalyzes sphingosine conversion to S1P.[109] In PD, disorders of sphingolipid metabolism drive progressive loss of dopaminergic neurons through a triple

cascade of "α-Syn pathology–mitochondrial dysfunction–neuroinflammation." GCase mutations increase PD risk, and its substrate GlcCer acts as a scaffold to promote α-Syn oligomerization.[110] As discussed in Section 2.2.4, GlcCer accumulation also leads to lysosomal damage, further exacerbating microglia-mediated inflammation and neuronal loss.[111] In addition, thyroid hormone receptor interactor 12 (TRIP12) acts as the E3 ubiquitin ligase for GCase, promoting its degradation by ubiquitinating the K293 residue; inhibiting TRIP12 restores GCase activity, reduces α-Syn pathology, and protects neurons.[112]

3.3.2. Gangliosides GM1 and GM3: Angels and demons in PD

Gangliosides are a class of GSLs primarily found on neuronal cell membranes, characterized by one or more sialic acid residues within their molecular structure. They play a pivotal role in maintaining the structural integrity of nerve cells, signal transduction, and cell recognition. The equilibrium of ganglioside metabolism is vital for neuronal survival and functional maintenance. Disruption of this equilibrium is closely associated with the onset and progression of various neurodegenerative diseases, particularly playing a significant role in the pathogenesis of PD.[113-115]

Within the context of lipid metabolism, gangliosides are considered pivotal molecules driving neurodegeneration in PD. As two representative classes of gangliosides, GM1 and GM3 exhibit markedly opposing functional roles in PD pathogenesis: GM1 is considered neuroprotective, earning it the epithet "angel," while GM3 predominantly promotes pathological progression, assuming the role of "demon."[116-118] Disruptions in their expression levels or metabolic equilibrium directly contribute to dopaminergic neuron loss and abnormal α-Syn aggregation, thereby accelerating disease progression.

In PD, genes associated with GM1 synthesis (e.g., *B3GALT4* and *ST3GAL2*) exhibit reduced expression, leading to diminished GM1 production and subsequently impairing neuronal health.[119] Chiricozzi *et al.*[120] investigated the therapeutic potential of GM1 oligosaccharides in a *B4galnt1*$^{+/-}$ mouse model of PD. They found that administration of GM1 oligosaccharide effectively penetrated the BBB to reach the brain and significantly ameliorated PD-related pathological features, including restored motor function, reduced abnormal α-Syn levels, and recovery of tyrosine hydroxylase expression and neurotransmitter concentrations. Furthermore, Kumar *et al.*[121] demonstrated the colocalization of GM1 and α-Syn within neuronal cytoplasm, revealing that GM1 effectively inhibits α-Syn aggregation and thereby clarifies its protective mechanism in PD pathology. On the other hand, GM1 exhibits significant anti-inflammatory properties, suppressing pro-inflammatory responses in microglia in response to inflammatory stimuli.[118] This function depends on its sialic acid residues and lipid tail structure. Conversely, GM3 demonstrates pro-inflammatory activity, amplifying neuroinflammation and further exacerbating PD progression.[113,118]

Age factor is also associated with changes in gangliosides. Research indicates that GM1 and GD1a levels decline with age in non-CNS tissues of normal mice, coinciding with deteriorating motor and cognitive functions. This suggests that age-related reduction in gangliosides may constitute a significant factor in the development of peripheral symptoms in PD.[122]

Regarding therapeutic strategies, research has also explored non-invasive routes for ganglioside administration. Intranasal infusion of GD3 and GM1 in the PD mouse model significantly reduced α-Syn levels and restored tyrosine hydroxylase expression.[123] This finding implies a potential mechanism by which modulating chromatin states could alleviate the accumulation of neurotoxic proteins and restore neuronal functions, offering novel therapeutic insights into PD treatment. Furthermore, mice with GM1 synthase deficiency (accompanied by GM3 synthase dysfunction) exhibited pronounced motor and short-term spatial memory impairments. Exogenous GM1 replacement therapy markedly improved these deficits, further supporting GM1's therapeutic potential in GM3-related metabolic disorders such as PD.[124] In summary, GM1 and GM3 play opposed roles in the pathogenesis and progression of PD. Balancing their regulation may represent a novel therapeutic target for future disease-modifying interventions.

3.4. Lysophospholipids

Lysophospholipids (LPLs) are a class of monoacylglycerophospholipids, mainly including LPC, lysophosphatidylethanolamine, and lysophosphatidic acid. These bioactive lipids are generated through phospholipase A2 (PLA2)-mediated hydrolysis of PC, a process that simultaneously releases free FAs.[125] The liberated free FAs can be further metabolized to pro-inflammatory mediators (e.g., prostaglandins and leukotrienes) or oxidized lipids (e.g., hydroxyeicosatetraenoic acids [HETEs]), thereby initiating a "lipid-inflammatory" cascade network. LPLs affect neuronal excitability and synaptic transmission by regulating cell membrane fluidity, ion channel activity, and G protein-coupled receptor signaling.[126,127] Dysregulation of LPL metabolism significantly alters their levels *in vivo*, potentially triggering pathological processes,

such as inflammatory responses, oxidative stress, and the disruption of cell membrane structure.[128,129] Such disturbances in LPL homeostasis have been implicated in the pathogenesis of various diseases, particularly neurodegenerative disorders.

In PD, LPC levels exhibit complex regional variations: reduced in some brain tissues but elevated in others.[130] These changes suggest a bidirectional LPC imbalance in PD. Normally, the balance between LPC and α-Syn is essential for the physiological function of α-Syn. Disturbance of this balance contributes to PD pathology. Activation of the G protein-coupled receptor 35 (GPR35)–extracellular signal-regulated protein kinases (ERK) signaling pathway by LPC disrupts Golgi structure and impedes the transport of GCase to lysosomes, leading to GlcCer accumulation, which facilitates α-Syn aggregation and exacerbates cognitive impairment.[131] LPC binding prevents α-Syn conversion to β-sheet oligomers, whereas mutations in the PLA2 Group VI (*PLA2G6*) gene interfere with LPL production and impair the interaction between LPC and α-Syn, thereby promoting α-Syn aggregation and neurodegeneration.[132,133]

Furthermore, LPC exerts pathological effects through inflammatory pathways. The inflammatory properties of LPC are exemplified by LPC (16:0)-induced leukocyte extravasation and elevation of pro-inflammatory mediators, in contrast to the anti-inflammatory effects of LPC (20:4) and LPC (22:6).[134] In addition, PLA2 activity is modulated by inflammation and can impair mitochondrial function, particularly in male patients.[130] In summary, abnormal LPL metabolism is a significant contributor to PD pathogenesis, involving key pathological components, such as α-Syn aggregation, neuroinflammation, and mitochondrial dysfunction. Therefore, elucidating the mechanisms underlying abnormal LPL metabolism in PD is crucial for understanding its pathogenesis, developing early diagnostic markers, and devising new therapeutic strategies.

3.5. Cholesterol metabolism: From membrane rigidity to α-Syn aggregation

Cholesterol is a crucial steroid component abundant in nerve tissues, particularly in the brain.[135,136] While primarily synthesized in the ER, cholesterol is rapidly translocated to various organelles.[90] It plays a key role in maintaining plasma membrane stability and fluidity, participating in the synthesis of steroid hormones, and regulating cell signaling. Cholesterol metabolism includes synthesis, modification, transportation, and excretion processes, and its dysregulation alters cholesterol levels, contributing to various diseases, including cardiovascular diseases and neurodegenerative diseases.[137]

Cholesterol metabolism in PD is dysregulated in both the CNS and peripheral systems.[135] Furthermore, fibroblasts from PD patients also exhibit reduced cholesterol biosynthesis due to decreased 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase activity.[138] Statins inhibit HMG-CoA reductase, thereby reducing endogenous cholesterol synthesis and modulating neuronal integrity, synaptic plasticity, and neurotransmitter release.[139,140]

Moreover, cholesterol metabolism critically regulates α-Syn conformation/aggregation through multiple mechanisms, as evidenced by the presence of isopentenyl diphosphate isomerase (a cholesterol biosynthesis enzyme) in Lewy bodies.[141] Experimental evidence demonstrates that the cholesterol 24-hydroxylase (CYP46A1) promotes α-Syn pathology in PD, with clinical studies further showing elevated levels of both CYP46A1 and its enzymatic product 24-hydroxycholesterol (24-OHC, a brain-specific oxysterol) in PD patients—a pathological process potentially mediated through stimulation of the X-box binding protein 1–lymphocyte-activation gene 3 (LAG3) axis.[142] Targeting the CYP46A1–24-OHC axis and LAG3 may represent promising disease-modifying strategies for PD. Furthermore, the incorporation of oxidized cholesterol metabolites (e.g., 24-OHC and 27-OHC) into neuronal membrane lipid rafts potently promotes the conversion of α-Syn from α-helix to β-sheet conformation and enhances its aggregation propensity.[143,144]

4. Discussion

This review systematically outlines the mechanisms by which lipid metabolism dysregulation acts as a central hub in PD pathogenesis, integrating lipid–organelle interactions, abnormalities in key lipid pathways (FAs, phospholipids, sphingolipids, etc.), and the tripartite interplay between lipid metabolic networks and core PD pathological mechanisms (e.g., α-Syn aggregation, mitochondrial dysfunction, and neuroinflammation).

In PD, lipid–organelle communication is disrupted primarily through successive breakdown of MCS, particularly those between mitochondria and LDs, MAMs, and lysosomes and LDs. This impairs targeted transport of FAs, phospholipids, and calcium ions, resulting in abnormal LD aggregation, mitochondrial dysfunction, and autophagy impairment.[41] LD accumulation stems from impaired lipophagy (e.g., α-Syn-mediated PLD1 inhibition and PLIN4–α-Syn interaction).[19,48,50] PLIN5 dysfunction disrupts mitochondria–LD contact, triggering an energy crisis through reduced FA transport to mitochondria.[28] MAMs, critical for ER-mitochondria lipid exchange, are structurally disrupted by pathological α-Syn, reducing

PE/PS transport, impairing CL synthesis, and triggering mitochondrial apoptosis.[29] *GBA1* mutations (a major PD risk factor) reduce GCase activity, causing GlcCer accumulation in lysosomes. GlcCer inhibits the V-ATPase proton pump, raising lysosomal pH, inactivating LAL, and impairing lipophagy while disrupting α-Syn's tetramer–monomer balance to promote aggregation.[26] In addition, LPC activates the GPR35–ERK pathway, disrupting Golgi structure and blocking GCase transport to lysosomes, exacerbating GlcCer accumulation.[131]

Lipid metabolism dysregulation involves multiple pathogenic pathways: FA imbalance (e.g., PUFA reduction and SCFA-mediated inflammation), phospholipid remodeling (e.g., CL/PC/PE dysfunction), sphingolipid disruption (e.g., Cer/GlcCer accumulation), and cholesterol metabolite-driven α-Syn aggregation.[59,144-146] These abnormalities form a complex network: reduced PUFAs impair membrane fluidity and neuroprotection; CL deficiency disrupts mitochondrial respiration and α-Syn stability;[88,145] PC/PE imbalance promotes α-Syn aggregation;[96,97] and GlcCer accumulation triggers a "lysosomal damage–α-Syn aggregation–neuroinflammation" cycle.[107] Furthermore, SCFAs link gut dysbiosis to neuroinflammation through TLR4/NF-κB activation, while LPC imbalance exacerbates inflammation and α-Syn pathology through GPR35–ERK signaling.[131] In addition, as discussed in Section 3.3.2, gangliosides GM1 and GM3 play pivotal roles in PD pathogenesis, with GM1 acting as a neuroprotective agent and GM3 promoting pathological progression.[116-118] Disruptions in their expression levels or metabolic equilibrium directly contribute to dopaminergic neuron loss and abnormal α-Syn aggregation, thereby accelerating disease progression.

Despite these insights, key questions remain: the causal timeline of lipid abnormalities (whether initiator or consequence of PD) requires longitudinal validation, and cell-type specificity in lipid metabolism (e.g., neuronal vs. glial differences) needs elucidation through single-cell approaches. Translational challenges, such as BBB

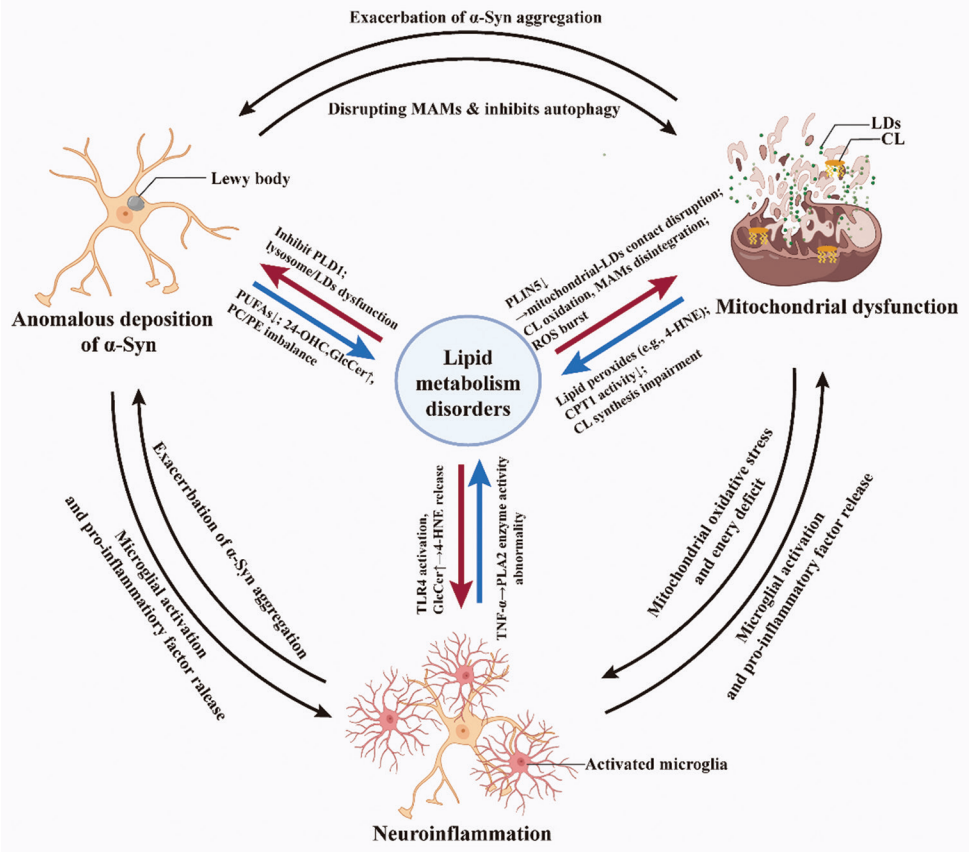

Figure 1. Tripartite interplay between lipid dysregulation and the core pathological hallmarks of Parkinson's disease: α-synuclein aggregation, mitochondrial dysfunction, and neuroinflammation

Abbreviations: α-Syn: α-synuclein; LDs: Lipid droplets; CL: Cardiolipin; MAMs: Mitochondria-associated ER membranes; PLIN5: Perilipin-5; CPT1: Palmitoyltransferase 1; ROS: Reactive oxygen species; PUFAs: polyunsaturated fatty acids; 24-OHC: 24-hydroxycholesterol; GlcCer: Glucosylceramide; PC/PE: Phosphatidylcholine/Phosphatidylethanolamine; TLR4: Toll-like receptor 4; 4-HNE: 4-hydroxynonenal; TNF-α: Tumor necrosis FActor-α;PLA2: Phospholipase A2; PLD1: Phospholipase D1.

penetration for lipid-targeted drugs, also warrant further investigation. From a therapeutic perspective, targeting lipid metabolism offers multiple avenues: restoring MCS function to normalize lipid transport, enhancing lipophagy through ATG14 activation or PLD1 inhibition, modulating key enzymes (e.g., CRLS1, GCase, and CYP46A1), and regulating SCFA levels through gut microbiota modulation. Figure 1 summarizes these mechanisms, highlighting lipid metabolism as a unifying target for stabilizing energy metabolism, reducing oxidative stress, and inhibiting α-Syn aggregation in PD.

Disorders of sphingolipid metabolism are centered on Cer, and GlcCer accumulates due to defective GCase function, forming a vicious cycle with α-Syn aggregation by impairing V-ATPase function.[26] Abnormal lipid metabolism also triggers neuroinflammation through multiple pathways. For example, a bidirectional LPC imbalance in PD impedes GCase transport and induces leukocyte extravasation and elevation of pro-inflammatory mediators, exacerbating neuroinflammation.

5. Conclusion

Lipid metabolism dysregulation activates microglia, triggering excessive inflammation, which, synergistically with oxidative stress, mitochondrial dysfunction, α-Syn aggregation, and aberrant organelle communication, forms a mutually reinforcing pathological loop. Clarifying these mechanisms will advance PD therapeutics by identifying lipid-centric targets to break this cycle and preserve neuronal function.

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Conflict of interest

Sheng-Xi Wu is an Associate Editor of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

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