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Lipids in Health and Disease

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Lipid droplet accumulation in microglia and their potential roles

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Abstract
Microglia are the resident immune cells of the central nervous system (CNS), where lipid metabolism is critical for maintaining homeostasis. In response to various external stimuli, they demonstrate a range of phenotypic expressions and lipid metabolic reprogramming. Lipid droplets (LDs) are dynamic organelles that function beyond energy storage, actively participating in neuropathological progress. Recent investigations have identified a subset of microglia characterized by the accumulation of LDs, referred to as "lipid-droplet-accumulating microglia" (LDAM). This review aims to investigate the processes involved in LD formation and degradation, the factors that modulate them, focusing particularly on the function of LDAM and their implications for CNS disorders. By synthesizing current evidence, we clarify the biological significance of LDs in these cells and their therapeutic targeting potential, providing new directions for future research.

Keywords Lipid droplets, Microglia, Central nervous system, Neurological disorders, Lipid metabolism

Background

Microglia phenotypes

Surveilling microglia

Microglia, the central nervous system (CNS)-resident immune cells, tasked with the maintenance of homeostasis in the neural microenvironment [1]. In 2005, the application of non-invasive two-photon in vivo imaging demonstrated that these cells exhibit very dynamic without pathological challenges [2]. Characterized by a small soma with highly ramified branches (Fig. 1). This unique morphology allows single microglia to monitor large volumes of its surrounding via specialized receptors, which can identify complement fragments, immunoglobulins, adhesion molecules, and others [3]. It reveals that microglia exhibit significant activity in physiological states, overturning the traditional concept of "resting microglia". Consequently, the cells in their normal physiological states are now more appropriately termed "surveilling microglia" [4].

Reactive microglia

Microglia have gained significant attention since the 1990s, with mounting evidence demonstrating their involvement in most neurological disorders. Microglia influence α-synuclein cell-to-cell transfer in a mouse model of Parkinson's disease (PD) [5] and respond to malaria-induced extracellular vesicles in human [6]. Quantitative analyses of microglia reveal diverse morphologic responses in the rat cortex after diffuse brain injury [7]. Progression of Alzheimer's disease (AD), Multiple Sclerosis (MS), traumatic encephalopathy and seizure are associated with microglial dysfunction and their mediated neuroinflammation [8–11]. These microglia

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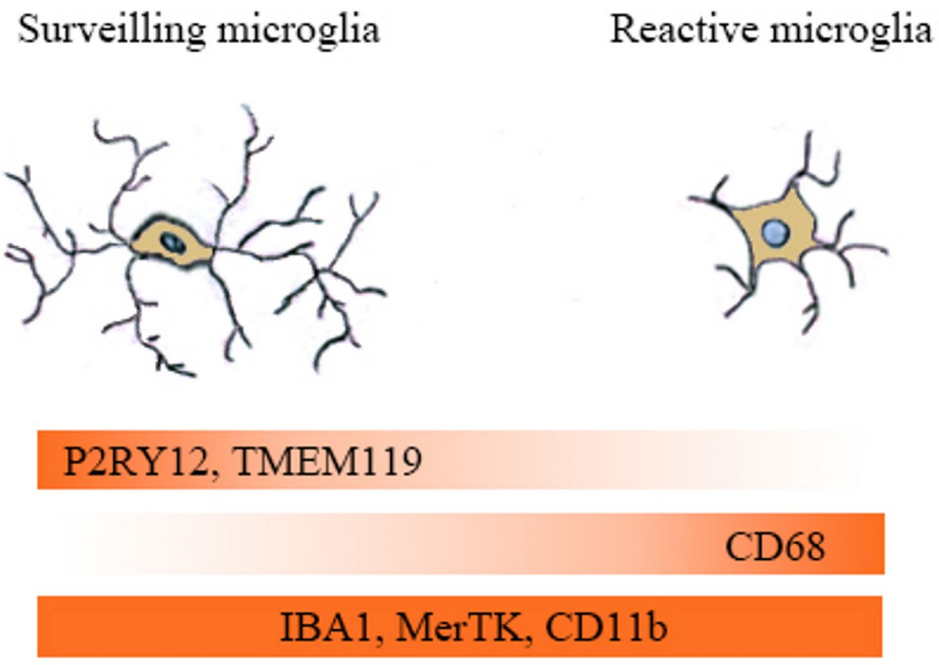

Fig. 1 Schematic representation of microglial markers in two different states. P2RY12 and TMEM119 are strongly expressed in surveilling microglia but exhibit dramatic downregulation in reactive microglia. Conversely, CD68 shows minimal expression in surveilling state yet becomes significantly upregulated in reactive state. IBA1, MerTK and CDl1b are expressed in both phenotypic states

have hypertrophic somata and retracted processes. The cellular phenotypic transformation, characterized by rapid proliferation, and significant alterations in functional properties, is designated as "reactive microglia " (Fig. 1) [3]. Distinct surface markers differentiate these two states. Reactive microglia exhibit high expression of CD68, while surveilling microglia show high expression of P2RY12 and TMEM119 (Fig. 1) [3, 4, 12].

Recent advancements in single-cell transcriptomics have illuminated various subtypes and states of microglia associated with pathologies [13]; "neurodegenerative microglia", characterized by a dysfunctional phenotype [14]; "proliferative region-associated microglia" that emerge during development [15]; "lipid-droplet-accumulating microglia" (LDAM), showing phagocytic impairment, reactive oxygen species overproduction, and pro-inflammatory cytokine release [16]. A series of studies have demonstrated that microglia accumulate lipid droplets (LDs) in response to inflammation, high-fat diet (HFD), excitotoxicity in neurons, lead exposure, and neurodegenerative diseases [17–24]. In stroke and MS, white matter damage generates myelin debris (with additional cellular debris in stroke cases). Microglial clearance of these debris disrupts lipid homeostasis, driving LD formation. This LDAM phenotype initiates pro-inflammatory responses, thereby exacerbating disease progression [21, 25].

The structure and functions of lds

LDs are dynamic lipid stores, comprising a monolayer phospholipid (PL) membrane interspersed with proteins enveloping triacylglycerols (TAG), cholesterol esters (CEs), and other lipids [26]. Beyond energy storage, LDs participate in several vital physiological processes including cell signaling, metabolic regulation and the composition of cellular membranes. These organelles exhibit remarkable environmental adaptability, and are involved in the storage of vitamins, the provision of signaling lipid precursors, the alleviation of endoplasmic reticulum (ER) stress and lipotoxicity, the restoration of mitochondrial damage, as well as the maturation, storage, and turnover of proteins [27–31]. However, microglial LD overload triggers oxidative stress and pro-inflammatory states that propagate damage to neighboring neurons, astrocytes, and oligodendrocytes, ultimately leading to disease exacerbation [16, 19, 32].

Content of the review

This review describes LD biogenesis and degradation, alterations in microglia during LD accumulation, and their contributions to neurological disorders. By synthesizing emerging evidence, we highlight therapeutic opportunities through microglial lipid metabolic reprogramming and outline novel directions for future investigation.

Synthesis of lds

LD formation is a complex biological process that encompasses lipid aggregation and membrane reorganization. It initiates with ER-mediated neutral lipid synthesis, followed by nascent LD budding and fusion-mediated expansion. Newly synthesized neutral lipids phase-separate from ER PLs, forming lens-shaped structures within ER bilayer leaflets. Progressive expansion drives them protrude into the cytoplasm from the ER membrane. A PL monolayer envelops the spherical lipid bodies, forming LDs. It subsequently incorporates additional lipids to form these droplets through budding [33].

LD formation and stability require both CEs and TAG. CEs sequestration in LDs depends on enough TAG levels to maintain structural integrity. A diminishment in TAG levels may alter LD biophysical properties, as demonstrated by polarized light microscopy showing a transition from isotropy to anisotropy. The physical state of LDs is correlated with the hydrolysis of CEs and the reduced rate of cholesterol efflux, ultimately compromising LD stability [34].

Key enzymes related to LD formation

TAG synthesis in LDs occurs through two principal pathways. The *de novo* TAG synthesis pathway, operating in most cell types, involves four enzymatic steps: glycerol-3-phosphate acyltransferase (GPAT), acylglycerol phosphate acyltransferase (AGPAT), phosphatidic acid phosphatase (PAP), and diacylglycerol acyltransferase (DGAT) sequentially catalyze these reactions (Fig. 2) [35]. The alternative pathway converts monoacylglycerol and fatty acids (FAs) into TAG by monoacylglycerol acyltransferase and DGAT. In addition, two other enzymes are also quite significant: fatty acid synthase (FASN) and acyl CoA long chain synthase (ACSL) (Fig. 2). FASN is involved in the synthesis of FAs, while ACSL primarily

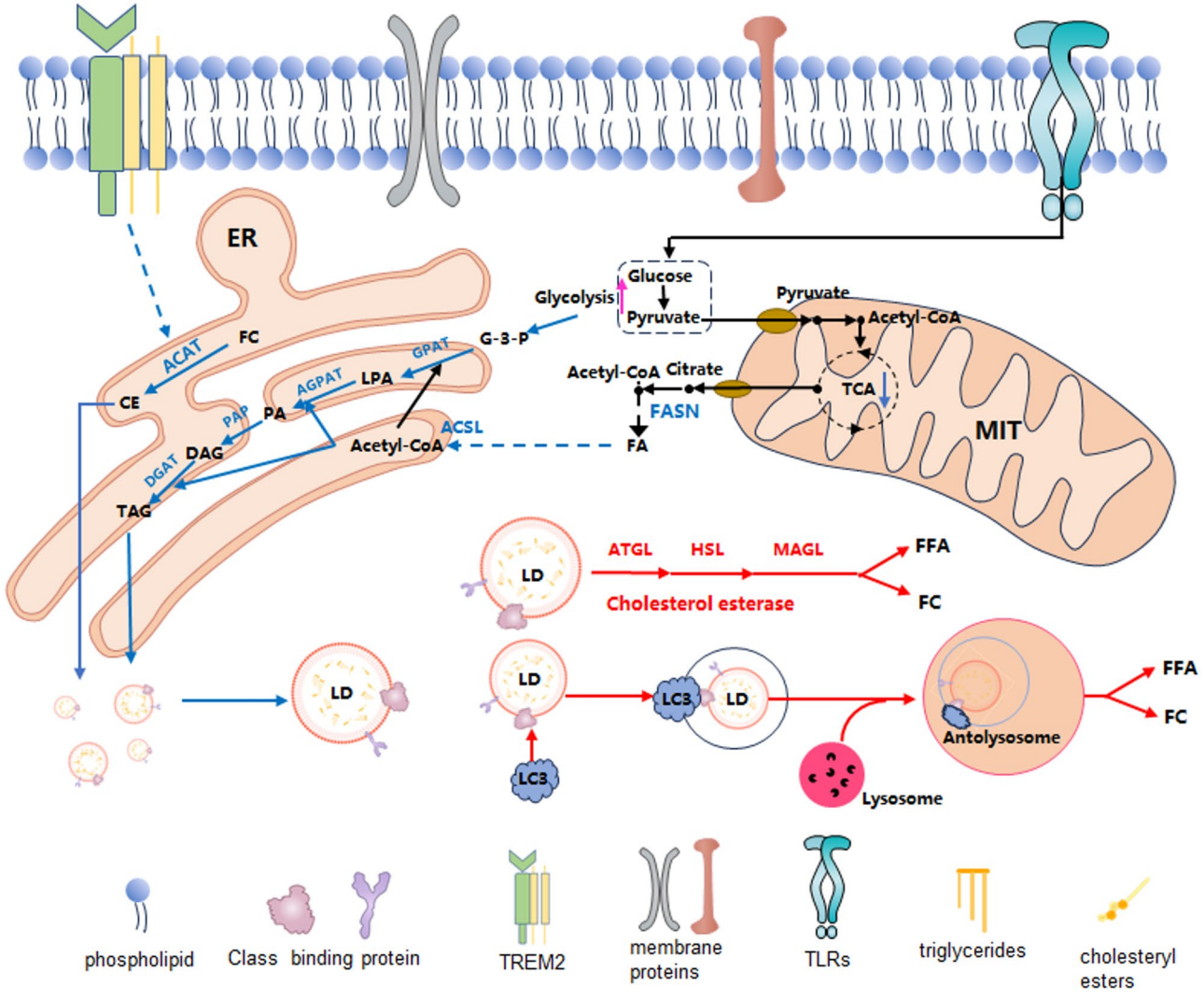

Fig. 2 The biogenesis and degradation of LDs in reactive microglia

participates in the activation of long-chain FAs, furnishing the essential substrates for TAG synthesis. CEs in LDs are synthesized from FAs and cholesterol by acyl-CoA cholesterol acyl transferase (ACAT) [36].

GPAT

TAG biosynthesis initiates in the ER through GPAT3 or GPAT4-catalyzed rate-limiting reactions. These isoforms catalyze lysophosphatidic acid formation from glycerol-3-phosphate and fatty acyl-CoA [37, 38]. GPAT3 is more easily induced by external stimuli and notably regulated by various factors such as the activation of peroxisome proliferator-activated receptor γ activation, genetic obesity, and nutritional status, establishing it as the inducible isoform. But GPAT4 remains relatively unaffected by these conditions and is regarded as a constitutive isoform [39]. Beyond lipid biosynthesis, GPAT3 repairs damaged biofilms in cerebrum nerves and restores normal physiological functions [40]. Evidence suggests that within 30 min of oleic acid supplementation, GPAT4 localizes in ER domains adjacent to sites of LD formation. By 3 h, GPAT4 is detected in domains that are continuous with yet distinct from the ER. Upon LD induction, a substantial proportion of GPAT4 is observed within the LD fraction. Furthermore, LDs devoid of *GPAT4* maintain a consistent diameter, whereas those containing *GPAT4* continue to expand [41]. In macrophages that accumulate LDs, the knockout of *GPAT3* and *GPAT4* results in a diminished overall area of LDs and leads to the formation of multiple smaller droplets. Thus, these observations highlight the pivotal roles of GPAT3 and GPAT4 in the growth of LDs.

AGPAT

The second step in *de novo* TAG synthesis is catalyzed by AGPAT. This reaction generates phosphatidic acid — a key precursor for TAG and PL biosynthesis [42]. During rat development, *AGPAT2* and *AGPAT5* mRNA upregulation correlates with elevated AGPAT activity, which is important for forming the skin permeability barrier. Barrier impairment triggers the expression of *AGPAT1*, *AGPAT2*, and *AGPAT3*, indicating that AGPATs may play a role in synthesizing PLs or TAG, which are necessary for the restoration of skin permeability [43]. *AGPAT4*, exhibiting the highest mRNA expression in the brain, is believed to be with high selectivity for polyunsaturated fatty acyl-CoA, especially DHA-CoA, and play an important role in sustaining DHA within the nerve membranes [44].

PAP

The third step of TAG synthesis involves the dephosphorylation of phosphatidic acid, catalyzed by PAP, resulting in the production of DAG [42]. DAG serves as the direct precursor for TAG, phospholipids phosphatidylethanolamine and phosphatidylcholine [45]. DAG generation represents the first committed step in TAG biosynthesis, highlighting the critical role of PAP activity in the modulation of TAG or membrane PL biosynthesis [46]. This enzymatic activity is conferred by the lipin protein family [47]. Pah1 is the yeast PAP enzyme, when utilized, can reduce DAG production, thereby diminishing LD formation and lipid storage. It alleviates α-synuclein-mediated toxicity and leads to a decrease in the formation of α-synuclein inclusion bodies [48].

DGAT

The terminal critical step in TAG biosynthesis is facilitated by DGAT [49]. DGAT1 and DGAT2, both located within the ER, are responsible for the conversion of DAG into TAG, thereby playing an essential role in preventing lipotoxicity, protecting against mitochondrial dysfunction and ER stress during lipolysis [26, 50]. DGAT2 is also co-localized with mitochondria and LDs, where it facilitates the synthesis and storage of TAG within LDs [51]. Recent studies on targeted TAG metabolism reveal that LD accumulation can be inhibited by either suppressing DGAT1 activity or enhancing the expression of adipose triacylglycerol lipase (ATGL) [52, 53]. Mice deficient in the *DGAT1* gene exhibit a lean phenotype and demonstrate resistance to diet-induced obesity, diabetes, and hepatic steatosis [54, 55]. Conversely, mice devoid of the *DGAT2* gene die shortly after birth, presumably due to lipid imbalances in the skin that impair its barrier function [56]. Furthermore, DGAT2 can esterify ceramide into acyl ceramide, which is subsequently stored in LDs [57]. It's even more interesting that inhibiting DGAT allows FAs, initially used to create neutral lipids, to be redirected towards PL synthesis, thereby promoting axons regeneration in neurons following injury [58].

FASN

FASN primarily catalyzes the biosynthesis of FAs [59]. In mammals, FASN typically exists in a dimeric form and performs multiple catalytic functions, facilitating the conversion of acetyl-CoA and malonyl-CoA into both saturated and unsaturated FAs [60]. FASN activity is modulated by a variety of factors, including nutritional status, hormonal influences, and metabolic demands. Under nutrient-replete conditions, there is a marked elevation in both the expression and enzymatic activity of FASN, which in turn promotes the synthesis and storage of FAs, triggering LD biogenesis through excessive lipid accumulation [61, 62].

ACAT

ACAT comprises of two isoforms, ACAT1 and ACAT2, which are expressed in microglia [63, 64]. Their primary

function is to catalyze the conversion of cholesterol into CEs, which are subsequently either stored in LDs or integrated into lipoproteins [65, 66]. Studies demonstrated elevated cholesterol concentrations in the brains of individuals diagnosed with AD and in familial AD transgenic mouse models [67–69]. ACAT inhibitor (e.g., avasimibe) or *ACAT*-knock out mice, has shown a reduction in AD-like pathology and alterations in amyloid precursor protein processing within familial AD transgenic mice [70]. Additionally, tissue-specific ACAT2 inhibition in hepatic or intestinal systems reduces CEs accumulation, effectively preventing hypercholesterolemia [71].

ACSL

The ACSL family is responsible for the conversion of long-chain FAs into acyl-CoA derivatives. Through single-nucleus RNA sequencing of brain tissue, it is determined that ACSL1$^+$ microglia are found to be most abundant in AD patients. In vitro experiments have demonstrated that amyloid-beta (Aβ) induces the expression of ACSL1, the synthesis of TAG and the accumulation of LD in human induced pluripotent stem cell-derived microglia [72]. Notably, ACSL3 is identified as a protein associated with LDs that is essential for the formation, expansion, and maturation of LDs. In the initial stage of LD biogenesis, ACSL3 is translocated to LDs [73]. In vitro, lipopolysaccharides (LPS)-stimulated microglia upregulate *ACSL4* expression, while *ACSL4* knockdown attenuates proinflammatory cytokine production. In an acute 1-methyl,4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) model, *ACSL4* knockdown is found to mitigate neuroinflammation [74].

Degradation of LDs

Mechanism of LD mobilization and degradation

LD degradation is not merely a simple breakdown of lipids, it involves intricate cellular regulatory mechanisms and enzymatic reactions. This process encompasses lipolysis and autophagy. The mobilization of LDs is regulated by various signaling molecules and hormones, which modulate the degradation pathways by either activating or inhibiting specific enzymes [75]. LD degradation is related to specific enzymes, such as ATGL, hormone-sensitive lipase (HSL), monoacylglycerol lipase (MAGL), cholesterol esterase (Fig. 2). Autophagy also plays a pivotal role in LD degradation, particularly under conditions of cellular stress, by facilitating the breakdown of droplets to supply energy and metabolic substrates [76]. The interplay of these mechanisms allows cells to adjust to changes in energy demand and maintain metabolic homeostasis. The precise way cells determine the utilization of lipolysis or autophagy for the turnover of LDs remains undetermined. However, it is plausible that significant intercommunication exists between these two pathways [77].

Key enzymes related to LD degradation

ATGL

ATGL belongs to the nine-member patatin-like phospholipase domain-containing protein A family and is the only robust triglyceride hydrolase within the family. It specifically catalyzes the hydrolysis of the initial ester bond in TAG, resulting in the production of DAG [78, 79]. Furthermore, research indicates that the autophagosome marker, microtubule-associated proteins 1 light chain 3 (LC3), is mechanistically linked to ATGL-mediated lipolysis, as ATGL contains LC3-interacting region motifs. Mutations in a single LC3-interacting region motif on ATGL can disrupt its interaction with LDs, thereby impairing lipolytic activity [80].

HSL

HSL is tasked with the hydrolysis of TAG and DAG, and its activity is regulated by hormones such as glucagon and adrenaline. These hormones induce HSL phosphorylation by activating the signaling pathways of AMP-activated protein kinase and protein kinase [81]. Additionally, the expression and activity of HSL are influenced by nutritional status, inflammatory responses, and a variety of metabolic factors, making HSL a crucial player in the balance of energy metabolism and fat storage [82]. Investigations indicate that HSL activity affect the lipid metabolism of microglia, which may, in turn, impact neuroinflammation and neurodegenerative diseases [83]. Consequently, the modulation of HSL activity can present new approaches for treating related neurological disorders.

MAGL

MAGL catalyzes monoacylglycerol into glycerol and free fatty acids (FFA). This is the final stage in lipid catabolism and critically regulates both lipid metabolism and endocannabinoid homeostasis [84]. 2-arachidonoylglycerol is the most abundant endocannabinoid, while MAGL serves as the primary enzyme that degrades 2-arachidonoylglycerol in the brain. By inactivating MAGL, it exerts anti-inflammatory and neuroprotective effects in neurodegenerative diseases [85]. Studies have shown that the inactivation of MAGL leads to significant changes in the expression of immune- and inflammation-related genes in microglia and astrocytes. Notably, in mice with *MAGL* deficiency in astrocytes, the upregulation of chemokine expression is more pronounced in microglia [86].

Cholesterol esterase

Cholesterol esterase primarily functions to hydrolyze CEs to free cholesterol, a fundamental component of

membrane assembly. Consequently, its enzymatic activity has a direct influence on cellular functions. Research indicates that the expression and activity of cholesterol esterase are associated with various pathological states, such as atherosclerosis and metabolic syndrome [87, 88]. It may be regulated by various factors, including dietary components and hormone levels, highlighting its significance in maintaining lipid homeostasis within the organism [89].

The relationship between autophagy and LD degradation

Research has identified a specific autophagic process, termed "lipophagy", which selectively targets LDs. This process involves the formation of autophagosomes that encapsulate LDs, transporting them to lysosomes for degradation (Fig. 2). Autophagy is intricately linked to cellular energy requirements, nutritional status, and responses to stress [76]. Certain studies have indicated a synergistic relationship wherein lipolysis acts upon larger LDs, resulting in the production of smaller droplets that are either reduced in size or newly synthesized, thereby becoming susceptible to lipophagic uptake [90]. This indicates that lipophagy predominantly targets smaller LDs within the cell and is less effective on larger droplets [91].

The role of autophagosomes in LD degradation

Studies have found that autophagosomes engage with LDs via specific receptors, thereby facilitating their degradation. For instance, LC3 labels LDs, promoting their encapsulation by autophagosomes for subsequent conveyance to lysosomes. Autophagosomes fuse with lysosomal vesicles, which encompass early and late endosomes as well as lysosomes, to form autolysosomes. Within the lysosomal environment, lysosomal acid lipase exhibits optimal functionality at a pH range of 4.5-5, showing the capacity to hydrolyze TAG, DAG and CEs, producing FAs, free cholesterol and glycerol [78, 91–94]. Moreover, the genesis and maturation of autophagosomes are closely associated with dynamic alterations in LDs. Certain autophagy-related proteins, including ATG9A, ATG14, and ORP8, assist in transporting and degrading these droplets [95–97]. In conditions like metabolic syndrome, a decrease in autophagosome function can lead to LD accumulation, worsening lipid metabolism disorders [98]. Consequently, enhancing autophagosome function may also be a new treatment strategy.

The regulatory role of lds on autophagosomes

Beyond serving as substrates for degradation by autophagosomes, LDs play an important role in regulating autophagosome functions. They influence the genesis and function of autophagosomes by releasing FAs and various signaling molecules. Studies have demonstrated that the presence of LDs promotes the synthesis of autophagosomes and enhances autophagic activity by modulating autophagy-related gene expression [99]. Moreover, the interplay between LDs and autophagosomes can markedly impact metabolic processes and energy status within the cell. For example, degradation products of LDs can provide energy for the formation of autophagosomes [100]. Hence, a comprehensive understanding of the regulatory mechanisms by which LDs modulate autophagosome functions is crucial for elucidating the complex metabolic processes in cells.

The enzymes mentioned above play a crucial role in the synthesis and degradation of LDs. They also serve as potential targets for intervention across disease states. Additionally, these enzymes have received increasing attention in CNS cells, as delineated in Table 1. Surveilling microglia do not form significant LDs. Under pathological conditions, they undergo significant alterations in their lipid metabolism, leading to the formation of LDs (Fig. 2) [32, 33].

During the progression of neurological disorders, microglia transition from "surveilling microglia" to "reactive microglia" while triggering receptor expressed on myeloid cells 2 (TREM2) or toll-like receptors (TLRs) are triggered. In the CNS, microglia are the only cell type that expresses TREM2, which is involved in regulating lipid metabolism in response to various stimuli, including cell debris, myelin debris, APOE and peripheral lipoprotein particles [32, 113]. TLRs, localized to membrane lipid rafts, are triggered by pathogen-associated molecules (expressed by microbial invaders, such as bacterial flagellin, lipoteichoic acid and LPS) and damage-associated molecules (derived from tissue damage, such as α-synuclein, Aβ, and heat shock proteins) [114, 115]. Under pathological conditions, microglia may exhibit a metabolic shift characterized by enhanced glycolysis and disruption of the TCA cycle, resulting in the accumulation of glucose-derived citrate. Excess citrate is transported to the cytosol and converted into acetyl-CoA, supplying the raw materials for FFA production. Glucose-derived G-3-P is utilized for neutral lipid synthesis in the ER, initiating LD biogenesis. Newly formed small LDs rapidly coalesce into larger LDs. The lipolysis of LDs is mainly to FFAs by ATGL, HSL and MAGL. In addition, LC3, a protein closely related to the autophagy process, recognizes autophagy receptors on LDs, and promotes the attachment of ATGL to LDs to form autophagosomes by interacting with the structural domain of the LC3 interacting region of ATGL. The autophagosomes subsequently fuse with the lysosomes to form autolysosomes, which further degrade LDs to FFAs and FCs.

Table 1 Relevant literature on enzymes involved in LD synthesis and lipolysis in the nervous system disorders. Includes studies using in vitro and/or in vivo models

	Name	Subtype	In vitro and/or in vivo model	Type of cell	Region of interest in vivo model	References
Key enzymes related to LD formation	GPAT	GPAT1/GPAT4	hypothalamic neurons exposed to excess lipids	neuron	hypothalamus	[101]
		GPAT4	HFD mouse model	neuron	hippocampus	[102]
	AGPAT	AGPAT1	transgenic Huntington's disease rat	N	hypothalamus	[103]
		AGPAT3	Familial intellectual disability and retinal dystrophy	neuron	cortex	[104]
	DGAT	DGAT1/DGAT2	astrocytes exposed to metabolic stress (nutrient deprivation, excess of extracellular FFAs and lactate) or hypoxic stress	astrocyte	N/A	[53]
		DGAT2	human AD and the 5x familial AD transgenic mouse model	microglia	hippocampus	[105]
	FASN	FASN	the cognitive enhancement and hippocampal neurogenesis induced by mice voluntary running	N	subgranular zone of the dentate gyrus	[106]
		FASN	spinal cord injury mouse model	microglia	spinal cord	[107]
	ACAT	ACAT1	AD	neuron and microglia	N	[108]
		ACAT1	LPS-induced cell and acute neuroinflammation mouse model	microglia	hippocampus and cortex	[64]
		ACAT2	BV-2 murine microglial cell line	microglia	N/A	[63]
	ACSL	ACSL1	AD-APOE3/3 and AD-APOE4/4 postmortem human brain tissue	microglia	frontal cortex	[72]
		ACSL3	anxiety and depression in 3x AD transgenic mice	neuron	hippocampus and cortex	[109]
		ACSL4	ischemic stroke	neuron and microglia	cortex	[110]
		ACSL4	LPS- and MPTP-induced neuroinflammation model	microglia	substantia nigra	[74]
Key enzymes related to LD degradation	MAGL	MAGL	primary hippocampal neuron culture	neuron	hippocampus	[85]
		MAGL	cell type-specific *MAGL* knockout mice	microglia and astrocyte	hippocampus and cortex	[86]
	ATGL	ATGL	LPS-induced cell and the microglial ATGL KO mouse model	microglia	hypothalamus, cortex and hippocampus	[111]
			ischemic stroke	microglia	infarct regions	[112]

LD Lipid droplet, GPAT glycerol-3-phosphate acyltransferase, HFD high-fat diet, AGPAT acyl-glycerol phosphate acyltransferase, DGAT diacylglycerol acyltransferase, FASN fatty acid synthase, ACAT acyl-CoA cholesterol acyl transferase, ACSL acyl CoA long chain synthetase, MAGL monoacylglycerol lipase, ATGL adipose triglyceride lipase, AD Alzheimer's disease, APOE apolipoprotein E, LPS lipopolysaccharides, MPTP 1-methyl, 4-phenyl-1,2,3,6 tetrahydropyridine, N/A not available, N no description

LD regulatory proteins

LD regulatory proteins are specifically involved in the regulation of the formation, maturation, and turnover of LDs [41, 116]. A variety of proteins are essential for these processes, and extensive research has been dedicated to proteins such as seipin, perilipin, FIT proteins, and ER shaping proteins, including atlastin, receptor expression-enhancing protein 1, Pex30, and Nexins protein family. These ER shaping proteins not only sustain the structure of ER but are also implicated in the formation of specialized LD sites [117, 118] (see Table 2).

Main functional changes in LDAM

LD is an adaptable organelle essential for cellular signaling, lipid metabolism, membrane transport, and the synthesis and release of inflammatory mediators [144]. As the primary immune cells in the CNS, microglia possess a multitude of receptors that are sensitive to changes in lipid composition [145, 146]. The accumulation of LDs in microglia indicates pathological conditions and adversely impacts their functions, including polarization, phagocytosis, and immune defense capabilities.

Pro-inflammatory

Under normal conditions, leukocytes, epithelial cells, hepatocytes and other non-adipocytic cells typically do not form LDs. However, in the presence of infectious, neoplastic, inflammatory responses, there is a dramatic expansion in both the size and number of LDs in those cells. Consequently, LDs are frequently regarded as indicators of inflammation [144, 147]. Excessive lipid storage can lead to LD accumulation, which in turn may provoke

Table 2 Relevant literatures on LD regulatory proteins and their discovery involved in LD synthesis and degradation

Name	location	subtype	Found and conclusion	References
Seipin	ER transmembrane proteins	N/A	Seipin serves as a vital link between the ER and LDs that supports the standard growth of LDs. The deficiency of *Seipin* leads to irregular sized LDs, larger or smaller.	[119–122]
PLIN	LD surface proteins	PLIN 1/2	PLIN1 and PLIN2 are LD structural proteins. PLIN1 inhibits the activation of ATGL, preventing the lipolysis of TAG. PLIN2 is used as a marker for LDs and the overexpression of PLIN2 protects LDs from autophagy.	[123–125]
		PLIN 3/4	PLIN3 and PLIN4 induce the formation of LDs. PLIN3 is a marker for small or newly formed LDs. It probably promotes LD formation by stabilizing the ER structural domain. PLIN4 can promote LD formation in the brains of models of toxin-induced PD.	[126–130]
		PLIN5	PLIN5 is crucial for energy balance by regulating TAG storage and lipolysis.	[131]
FIT	ER-localized protein	N/A	FIT proteins are responsible for storing TAG in LDs and promote the budding of LDs from the ER by regulating DAG levels at their biogenesis sites.	[132–134]
Atlastin	ER-localized protein	N/A	Atlastin is related to the morphology of the ER and can regulate the size of LDs.	[135]
REEPs	ER-localized protein	N/A	REEPs maintain the structure of the ER by stabilizing the high curvature.	[136, 137]
Pex30	ER-localized protein	N/A	Pex30 helps maintain the structure of the ER and is concentrated in forming LD sites of ER.	[138–140]
Mdm1	ER-localized protein	N/A	Mdm1 are proteins in the ER that combine with LDs, overexpression of which promotes LD formation. *Mdm1* mutants display defects in ER structure and TAG accumulation, leading to increased susceptibility to lipotoxicity.	[141–143]

ER endoplasmic reticulum, LD Lipid droplet, PLIN Perilipin, ATGL adipose triglyceride lipase, TAG triacylglycerol, FIT fat storage-inducing transmembrane, REEPs receptor expression-enhancing proteins, PD Parkinson's disease, N/A not available

inflammatory responses [148]. Ischemia/reperfusion injuries in the brain have been linked to LD accumulation in microglia, and subsequent neuroinflammation within the CNS. TGF-β overexpression attenuates LD accumulation and lowers the levels of inflammatory factors [149]. Conversely, *PLIN2* deficiency enhances lipolysis and lipid efflux, resulting in a phenotype associated with diminished inflammation [150]. These findings establish microglial LD overload as a driver of pro-inflammatory activation (Fig. 3).

Phagocytosis

Lipoprotein lipase mediates the hydrolysis of TAG and the uptake of lipoproteins by binding to their receptors [151]. These processes contribute to tissue repair and are closely associated with the PL balance and triggering receptor expressed on myeloid cells 2 (TREM2), which influences the phagocytic activity of microglia [152–154]. The phagocytic capability of cells also depends on lipase-driven FA release from intracellular stores. ATGL deficiency blocks TAG hydrolysis, resulting in decreased intracellular FFA concentrations and an increased accumulation of LDs. As a result, there is a reduction in intracellular ATP levels, which impairs phagocytic function [155, 156]. In a demyelination model, aged mice display phagocytic cells with an excessive accumulation of myelin debris, which subsequently lead to the formation of cholesterol crystals and rupture phagolysosomal membranes. In this context, cholesterol originating from myelin is converted into LDs [157]. Thus, LD formation reflects cellular lipid overload, overwhelming phagocytic thresholds. Aging microglia exhibit defective cholesterol clearance, resulting in an accumulation of cholesterol-rich myelin debris. This accumulation promotes crystal formation, further impairing the phagocytic efficacy of microglia (Fig. 3), thereby exacerbating the advancement of aging and MS [25, 157, 158].

Signal transduction

LDs function as pivotal signaling platforms that modulate the metabolism and immune responses of phagocytic cells [159]. LDs consist of neutral lipids encased in a monolayer of PLs, which can be converted into arachidonic acid [35]. Upon activation of phagocytes, the release of arachidonic acid initiates signaling cascades that provoke inflammatory responses, consequently leading to the generation of lipid mediators. Eicosanoids, which are synthesized from arachidonic acid, are primarily produced in LDs [160]. These signaling lipids are important in both physiological and pathological conditions, such as tissue homeostasis, host defense, and the inflammatory response. Lipid overload activates various lipid response pathways, such as the liver X receptor and peroxisome proliferator-activated receptor pathways, which aid in the remodeling of microglia, promoting the proliferation and their ability to clear debris [161, 162]. Microglia recognize and internalize myelin debris through the coordinated action of multiple receptors on their surface, including Axl, TREM2, Gas6 and LRP1 [163–166].

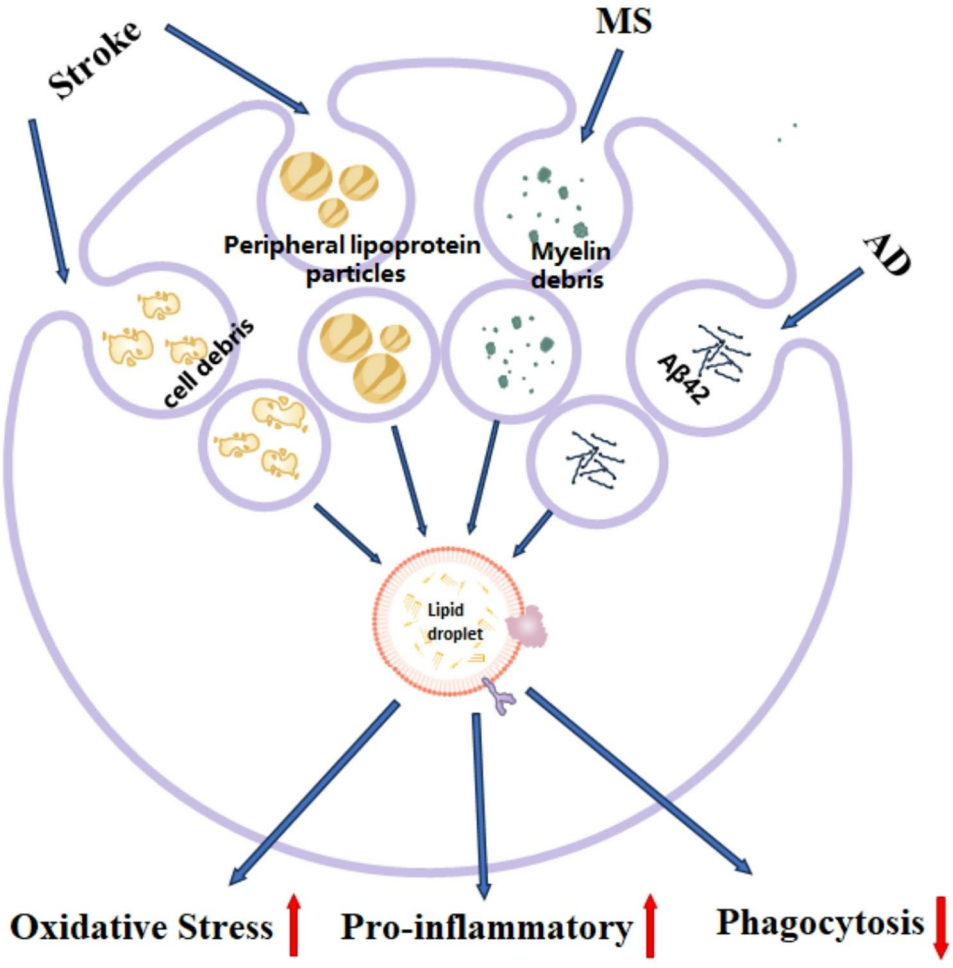

Fig. 3 The accumulation of LDs in microglia

LDAM in different periods

LDAM during developmental stage

Park et al. (2023) [167] reported the presence of PLIN2$^+$ LDAM in the embryonic brains of both mice and humans. Subsequent studies, using induced pluripotent stem cell-derived microglia to emulate microglia during brain development, reveal that these cells exhibit elevated lipid metabolism, notably in cholesterol, and contain abundant PLIN2$^+$ LDs. These droplets export the cholesterol and its esters, which are taken up by neuronal progenitor cells, contributing to neurogenesis. In the adult brain, astrocytes are the primary cells that produce cholesterol required for neuritogenesis and synaptogenesis. However, astrocytes are absent in the embryonic brain [168, 169]. Thus, during the nascent phases of brain development, microglia might play a crucial role in the production and exportation of requisite cholesterol to sustain neuronal cells.

LDAM during childhood and adolescence

HFD

HFD has emerged as a high-risk factor for various neurodegenerative and debilitating mental disorders, such as depression and anxiety [170–172]. Adolescents preferentially overconsume palatable HFD, exhibiting susceptible to mental health issues [173, 174]. A 2024 study revealed that in HFD-fed mice, microglia in the hippocampal region exhibited excessive activation and LD accumulation. This indicates that the depression and anxiety-like behaviors observed in the mice, along with structural changes in hippocampal neurons and myelin, may be associated with microglial involvement in HFD. The study further demonstrated that suppression of microglial overactivation through minocycline alleviated the abnormal behaviors and hippocampal structural changes in mice, although it did not reduce LD accumulation in hippocampal microglia. However, in vitro experiments demonstrated that reducing LD accumulation can inhibit the excessive microglial overactivation triggered by serum from mice with HFD [175]. These experimental

results raise the question of whether the formation of LDAM induced by HFD occurs before and contributes to disease progression. If so, therapeutic strategies targeting the inhibition of LD synthesis or promotion of their degradation could potentially ameliorate the pro-inflammatory effects of microglia and alleviate disease symptoms.

Niemann-Pick type C (NPC) disease

Inborn errors in lipid metabolism can cause severe damage to cells, especially neurons, driving rare but often fatal disorders. NPC exemplifies disrupted lipid homeostasis, predominantly caused by *NPC1* gene mutations. These mutations trigger abnormal endosomal/lysosomal lipid storage, ultimately leading to premature death due to progressive neurodegeneration [176]. A study in 2021 revealed that the transport of lipids to lysosomes in $Npc1^{-/-}$ microglia was impaired, leading to significant LD accumulation, despite intact lysosomal degradation function [177]. This study suggests that NPC pathogenesis involves mutation-driven LD accumulation, generating neuroinflammatory milieus that exacerbate neurodegeneration. Consequently, promoting the breakdown of LDs may help in treating the disease. Despite the unimpaired lysosomal function, the observed LD accumulation indicates impaired lipophagic degradation pathways. This raises critical questions about the targeting of lipolysis and the identification of specific LD-degrading enzymes could constitute potential therapeutic strategies.

LDAM during aging

Age-related changes in CNS microglia include hypertrophy of the cell body, reduced branching, and shortened processes, accompanied by elevated secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). These cells become overreaction and dysfunction during immune responses, promoting the formation of LDs (Fig. 3) [158, 178, 179]. Ultrastructural analyses reveal that LDs are prevalent in 20-month-old mice but scarce in 3-month-old ones. Histological staining of $TMEM119^{+}$ microglia with BODIPY shows preferential LD accumulation within microglia versus other neural cells [16]. Notably, this type of microglia, characterized by a compromised phagocytic capacity, represents a substantial indicator of aging [178, 180]. Studies show that in the hippocampus of aging mice, LDAM exhibits an increased immune response involving the lysosomal-associated protein CD68. Three-dimensional imaging reconstructions demonstrate that $CD68^{+}$ signals are frequently clustered around LDs, suggesting a link to phagocytic dysfunction and a pro-inflammatory state [16]. Additionally, other studies propose that LDs co-localized with LC3 may be degraded through lipophagy [180]. Given the age-related decline in autophagy, diminished lipophagy could drive progressive LD accumulation during aging. Furthermore, microglia gradually become dysfunctional, their capabilities declining, characterized by heightened oxidative stress, defective phagocytosis, and elevated pro-inflammatory signals (Fig. 3). All these alterations are linked to the accumulation of LDs in microglia [178].

Neurological disorders associated with LDAM

Microglial LD accumulation occurs in multiple CNS disorders [20, 181, 182]. Depending on the mechanisms of LD formation and their influence on these diseases, the reversal of LDAM may represent viable therapeutic targets in these conditions (Fig. 3).

AD

AD is primarily characterized by the deposition of Aβ plaques and the formation of neurofibrillary tangles made up of hyperphosphorylated tau [183]. Disruptions in lipid metabolism are closely linked to AD pathogenesis. In the CNS, apolipoprotein (APOE) mediates the transport of cholesterol to neurons, supporting axonal development and synaptic plasticity essential for learning, memory formation, and neuronal repair [184, 185]. It has three main alleles: *APOE2*, *APOE3* and *APOE4*. Research has found that *APOE4* is significantly associated with an increased risk of developing AD [186]. AD pathogenesis extends beyond neurons, with astrocytes, microglia and oligodendrocytes actively contributing to disease progression [187–189]. Abnormal lipid metabolism induced by the *APOE4* genotype in microglia has been found to lead to excessive accumulation of LDs, which not only affects the phagocytic and clearance abilities of microglia, but also influences their interaction with neurons, leading to disorders at the neuronal network level and neurodegenerative changes [190, 191]. Therefore, dysfunctional microglia may serve as a contributing factor to the pathological accumulation of abnormal protein aggregates in the brain [192].

In animal models of AD, LDs emerge before amyloid plaque and neurofibrillary tangle formation, suggesting lipid dysregulation drives AD progression [193]. Both human AD brains and 5xFAD mouse models show microglia LD formation upon Aβ exposure (Fig. 3), with droplet density increasing with proximity to amyloid plaques. Microglia with LD accumulation exhibit reduced Aβ phagocytic capacity [105]. The experimental results indicate a reciprocal promotion between microglial LD accumulation and Aβ production. Regardless of the causal sequence, ACAT inhibitor treatment in AD mouse models, achieved 86% brain CE reduction with parallel 88–99% Aβ decrease [194]. *ACAT* knockout enhances the microglia's ability to phagocytose Aβ and promotes its lysosomal degradation [195]. Studies demonstrate an inverse relationship between microglial LD levels and phagocytic activity in AD models. Therefore,

the induced amyloid precursor protein-KI/Fit2i Delta M phi transgenic mouse model, specifically designed to reduce microglial LDs, demonstrates consistent enhancement of phagocytic capacity and significant Aβ deposition reduction [196].

MS

MS, a neuroinflammatory disorder characterized by CNS demyelination and neurodegeneration [197]. During disease progression, both microglia and infiltrating macrophages exhibit enhanced phagocytic capacity [198]. Microglial phagocytic activity, which is vital for the clearance of cellular debris and apoptotic cells, is essential for myelin regeneration [199]. In LPS-induced demyelination models, LD accumulation not only compromises phagocytic function but triggers excessive production of pro-inflammatory mediators (e.g., inducible nitric oxide synthase, NLR family pyrin domain containing 3, cluster of differentiation 16, nitric oxide synthase 2, and interleukin 12), thereby impeding the effective clearance of myelin debris [200, 201]. Recent research has demonstrated that microglia, via TREM receptors, promote the phagocytosis of myelin debris and clearance of apoptotic cells, thus supporting tissue repair and regeneration processes. Nevertheless, overactivation or dysfunction of microglia, mediated by TREM receptors, may lead to the release of pro-inflammatory cytokines and neurotoxic factors, exacerbate MS neuropathology [25]. Myelin, which is rich in lipids, particularly cholesterol, poses a challenge in demyelinated areas where phagocytic cells are incapable of removing cholesterol-rich myelin remnants, leading to the formation of cholesterol crystals that contribute to the intracellular accumulation of LDs (Fig. 3) [202]. This LD-driven microglial dysfunction induces pro-inflammatory responses, further damages oligodendrocytes and exacerbating demyelination [157, 200, 201, 203, 204]. Studies have demonstrated that enhancing myelin-derived lipid efflux from LDAM restores microglial phagocytic capacity while providing oligodendrocytes with substrates for remyelination [203, 205]. Targeting lipid homeostasis thus emerges as a promising therapeutic strategy for enhancing remyelination capacity [200].

Stroke

Ischemic stroke, the most prevalent form of stroke, results from cerebral hypoperfusion. Glutamate-induced excitotoxicity serves as a well-established driver of cell death in ischemic stroke [206]. This neurotoxic cascade involves calcium overload, increased production of reactive oxygen species, mitochondrial dysfunction, ER stress, and ferroptosis [207–211]. Most of these factors can induce LD accumulation [212]. In the oxygen and glucose deprivation model, microglia display enhanced levels of LD accumulation and elevated expression patterns of PLIN2. In the middle cerebral artery occlusion stroke model, the formation of LD in microglia is induced [213]. The occurrence of LDs after a stroke may be attributed to multiple mechanisms. These include the swift demise of cells within a relatively brief timeframe, resulting in microglia phagocytosing the deceased cells and subsequently forming LDs. An additional potential mechanism may be the disruption of the blood-brain barrier, allowing the penetration of peripheral lipoprotein particles (Fig. 3) [214, 215]. Several studies have shown that by minimizing LD accumulation, it is possible to suppress autophagy, enhance cerebral blood flow, reduce brain injury, and promote neurological recovery [216, 217].

PD

PD manifests through progressive degeneration of dopaminergic neurons in the substantia nigra, clinically presenting with tremors, rigidity, and bradykinesia [218]. Its main pathological feature is the intracellular accumulation of α-synuclein aggregates, leading to the formation of Lewy bodies [219, 220]. Numerous studies have demonstrated LD accumulation in the neurons of PD patients. The pathogenesis of PD has been associated with lysosomal dysfunction and abnormal lipid metabolism in neurons, resulting in α-synuclein aggregation [219, 221, 222]. α-synuclein can bind to the monolayer of PLs on the surface of LDs, shielding them from lipolysis and thereby promoting their accumulation [223, 224]. The presence of LDs containing neutral lipids may function as an early indicator of neurodegeneration, coexisting with α-synuclein overexpression [225]. Whether LDs also present in the glial cells of PD-affected brain? A 2020 study using a fluorescent probe (BODIPY) labeling LDs revealed substantial LD accumulation in dopaminergic neurons and microglia, but not astrocytes, in PD substantia nigra [226]. However, this study concentrated on neurons and did not delve into presence of LDs in microglia in PD or their connection to the disease's pathological processes.

Neuropathic pain

As previously stated, LDs are emerging as key inflammatory mediators. Microglial-driven inflammation constitutes a central pathogenic mechanism in neurological disorders [227]. This response is also crucial in the development of chronic neuropathic pain [228, 229]. This raises a pivotal question: How LDs in microglia correlate with neuropathic pain and what specific roles they may fulfill in this context? In 2021, Navia-Pelaez JM et al. conducted a study that demonstrated in a mouse model of chemotherapy-induced peripheral neuropathy, there was a notable alteration in the expression of lipid metabolism

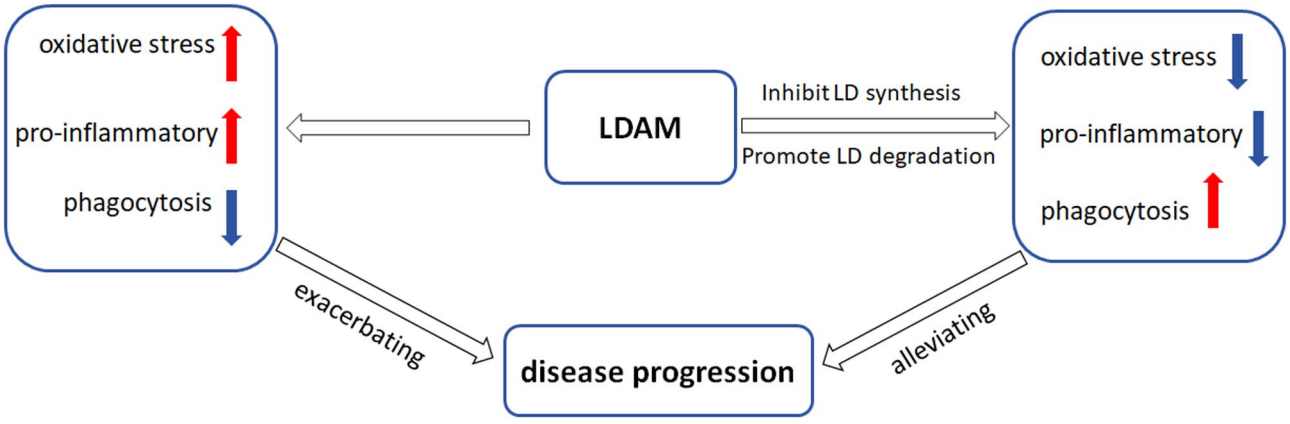

Fig. 4 Schematic representation illustrating the link between LDAM, the function and disease progression

genes and the accumulation of LDs in spinal cord microglia. Moreover, an intrathecal injection of apoA-I binding protein, which promotes cholesterol depletion in spinal cord microglia, correspondingly reduced LD accumulation and alleviated neuropathic pain [230]. These outcomes underscore the potential therapeutic implications of targeting LDs in the management of neuropathic pain. However, it is not yet determined whether pain triggers the accumulation of LDs in spinal cord microglia or if the initial event is the appearance of LDAM, which releases inflammatory factors that induce neuropathic pain; the causal relationship and specific mechanisms remains enigmatic (Fig. 3).

Lipids in LDAM are derived from multiple sources during various disease states, including cell debris, myelin debris, peripheral lipoprotein particles, Aβ, among others. LDAM are characterized by increased oxidative stress, a pro-inflammatory state, and reduced phagocytic capacity.

Discussion

Summary

Recent experimental advancements have offered novel insights into the role of lipid metabolism in regulating microglial biology. While debates persist regarding microglial subtype classification, these cells exhibit stimulus-dependent activation states [4]. Lipids in LDAM originate from several key sources, such as the uptake of apoptotic cells [14], myelin debris [153, 157], lipoprotein particles [231] and neuronal-derived lipids [190, 192].

Considering the multiplicity of lipid sources contributing to droplet formation, is there heterogeneity in LD composition among distinct pathological states? In aging, LD accumulation is predominantly characterized by increased levels of TAG [16]. In contrast, in AD and cisplatin-induced conditions, the primary accumulation of cholesteryl esters is observed within LDs. These differences imply that microglia have distinct mechanisms for forming and accumulating LDs during different conditions. Consequently, LDs play several important roles in cells. They serve as energy storage depots, inflammation markers, lipid signaling centers, and protective waste storage for overactive neurons, and they result from lysosomal dysfunction. In addition, LDAM is linked to various neurological disorders [19].

Future perspectives and challenges

The researches on LDAM during development [167] highlight significant lipids functions in brain maturation, particularly regulating myelination, neurite growth, and synaptogenesis. Lipids are known to influence the proliferation of neural progenitor cells and neurogenesis [232–235].Therapeutic strategies targeting LD dynamics (through formation inhibition or degradation acceleration) may confer multiple benefits: attenuate pro-inflammatory responses and oxidative stress; restore phagocytic capacity to alleviate disease progression (Fig. 4). The liberation of lipids from LDs might also contribute to myelin/neurite repair. Notably, enhanced neural progenitor cell proliferation in mature brains offer the possibility of replacing neurons lost in various pathological states. Current interventions demonstrate efficacy in normalizing lipid metabolism, reducing inflammation and slowing disease progression. For example, ACAT is the key enzyme for converting cholesterol into CE. In the AD animal model, inhibiting ACAT can reduce the level of CE in the brain, thereby reducing the accumulation of LDs in microglia, restoring the phagocytic ability, and facilitating the clearance of Aβ [194, 195]. Nonetheless, some challenges persist. This review summarizes the key synthetic enzymes, degradative enzymes, and regulatory proteins involved in the dynamics of LDs. While some of these have been investigated in studies, many remain uninvestigated and thus represent potential targets for future research and therapeutic development. However, as these enzymes are not microglia-specific, necessitating

a careful assessment of potential adverse effects. Additionally, several critical questions remain unresolved: what are the specific triggering factors and lipid metabolic processes underlying LD accumulation in microglia under different pathological conditions? While the stages and severity of specific diseases can be ascertained, the exact timing of LD formation in microglia and their evolution across different disease stages remains indistinct. Consequently, determining the optimal timing for intervention poses a significant challenge.

Addressing these challenges necessitates the implementation of advanced high-resolution technologies to investigate temporal and spatial alterations in microglial lipid profiles. The enhanced resolution of confocal microscopy, coupled with the evolution of sophisticated analytical mapping tools, has facilitated comprehensive analysis of LDs, enabling detailed examination of their number, dimension, localization, and dynamic properties [26, 236]. The label-free coherent anti-stokes Raman scattering microscopy is a nonlinear imaging technique that detects the vibrational characteristics of specific chemical bonds, allowing for label-free visualization of molecular structures without phototoxicity [237]. This technique enables the acquisition of higher-resolution and high-throughput lipid structural data. For instance, it can be utilized to quantify the acyl chains constituting TAG within LDs [238, 239]. Mass spectrometry imaging represents a physics-based surface analytical method that can be employed for single-cell resolution lipidomics and even proteomics on brain tissue Sects. [240, 241]. Advanced high-throughput mass spectrometry methodologies further decode specific cell type and secreted lipid profiles, establishing an essential foundation for elucidating lipid-mediated regulatory processes in microglia [242].

During the early 21st century, lipidomics emerged as a distinct research field, which allows for comprehensive qualitative and quantitative analysis of a diverse array of lipids within cells [243, 244]. Through systems biology, it becomes feasible to integrate lipidomics, metabolomics, and proteomics using mathematical approaches, enabling visualization and prediction of complex interactions and characteristics, such as metabolic pathways and networks, disease initiation and progression, as well as pharmaceutical interventions [245]. Future researches ought to further leverage lipidomic and proteomic technologies to investigate subtle compositional changes in LDs across different pathological stages and spatial locations, as well as their corresponding functional variations.

Current understanding of lipid metabolism in microglia is still at a nascent stage. Comprehensive studies focusing on LDs and their metabolic processes are essential for enhancing our understanding of CNS metabolism and the mechanisms underlying disease development.

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Y.X. Li. and Q. Z. drafted the main manuscript; Y. W. prepared the figures; W.Y. Du. prepared the tables; R.Y. Yang. integrated the relevant literature; J. W. and Y. L. provided the core topic and revised the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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References

1. Yin J, Valin KL, Dixon ML, Leavenworth JW. The role of microglia and macrophages in CNS homeostasis, autoimmunity, and Cancer. J Immunol Res. 2017;2017:5150678.
2. Tremblay M. The role of microglia at synapses in the healthy CNS: novel insights from recent imaging studies. Neuron Glia Biol. 2011;7(1):67–76.
3. Green TRF, Rowe RK. Quantifying microglial morphology: an insight into function. Clin Exp Immunol. 2024;216(3):221–9.
4. Paolicelli RC, Sierra A, Stevens B, Tremblay ME, Aguzzi A, Ajami B, et al. Microglia states and nomenclature: A field at its crossroads. Neuron. 2022;110(21):3458–83.
5. George S, Rey NL, Tyson T, Esquibel C, Meyerdirk L, Schulz E, et al. Microglia affect α-synuclein cell-to-cell transfer in a mouse model of parkinson's disease. Mol Neurodegener. 2019;14(1):34.
6. Mbagwu SI, Lannes N, Walch M, Filgueira L, Mantel PY. Human microglia respond to Malaria-Induced extracellular vesicles. Pathogens. 2019;9(1).
7. Morrison H, Young K, Qureshi M, Rowe RK, Lifshitz J. Quantitative microglia analyses reveal diverse morphologic responses in the rat cortex after diffuse brain injury. Sci Rep. 2017;7(1):13211.
8. Jurga AM, Paleczna M, Kuter KZ. Overview of general and discriminating markers of differential microglia phenotypes. Front Cell Neurosci. 2020;14:198.
9. Poniatowski ŁA, Cudna A, Kurczych K, Bronisz E, Kurkowska-Jastrzębska I. Kinetics of serum brain-derived neurotrophic factor (BDNF) concentration levels in epileptic patients after generalized tonic-clonic seizures. Epilepsy Res. 2021;173:106612.
10. Olczak M, Poniatowski ŁA, Siwińska A, Kwiatkowska M, Chutorański D, Wierzba-Bobrowicz T. Elevated serum and urine levels of progranulin (PGRN) as a predictor of microglia activation in the early phase of traumatic brain injury: a further link with the development of neurodegenerative diseases. Folia Neuropathol. 2021;59(1):81–90.
11. Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. Nat Neurosci. 2018;21(10):1359–69.
12. Lier J, Streit WJ, Bechmann I. Beyond activation: characterizing microglial functional phenotypes. Cells. 2021;10(9).
13. Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, et al. A unique microglia type associated with restricting development of alzheimer's disease. Cell. 2017;169(7):1276–e12901217.

14. Krasemann S, Madore C, Cialic R, Baufeld C, Calcagno N, El Fatimy R, et al. The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. Immunity. 2017;47(3):566–e581569.
15. Li Q, Cheng Z, Zhou L, Darmanis S, Neff NF, Okamoto J, et al. Developmental heterogeneity of microglia and brain myeloid cells revealed by deep Single-Cell RNA sequencing. Neuron. 2019;101(2):207–e223210.
16. Marschallinger J, Iram T, Zardeneta M, Lee SE, Lehallier B, Haney MS, et al. Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. Nat Neurosci. 2020;23(2):194–208.
17. Teixeira V, Maciel P, Costa V. Leading the way in the nervous system: lipid droplets as new players in health and disease. Biochim Biophys Acta Mol Cell Biol Lipids. 2021;1866(1):158820.
18. Foley P. Lipids in alzheimer's disease: A century-old story. Biochim Biophys Acta. 2010;1801(8):750–3.
19. Farmer BC, Walsh AE, Kluemper JC, Johnson LA. Lipid droplets in neurodegenerative disorders. Front Neurosci. 2020;14:742.
20. Tamosaityte S, Galli R, Uckermann O, Sitoci-Ficici KH, Koch M, Later R, et al. Inflammation-related alterations of lipids after spinal cord injury revealed by raman spectroscopy. J Biomed Opt. 2016;21(6):61008.
21. Guan X, Wu J, Geng J, Ji D, Wei D, Ling Y, et al. A novel hybrid of telmisartan and borneol ameliorates neuroinflammation and white matter injury in ischemic stroke through ATF3/CH25H Axis. Transl Stroke Res. 2024;15(1):195–218.
22. Hu M, Zhang J, Wu J, Su P. Lead exposure induced lipid metabolism disorders by regulating the lipophagy process in microglia. Environ Sci Pollut Res Int. 2023;30(60):125991–6008.
23. Victor MB, Leary N, Luna X, Meharena HS, Scannail AN, Bozzelli PL, et al. Lipid accumulation induced by APOE4 impairs microglial surveillance of neuronal-network activity. Cell Stem Cell. 2022;29(8):1197–e12121198.
24. Zhuang H, Yao X, Li H, Li Q, Yang C, Wang C, et al. Long-term high-fat diet consumption by mice throughout adulthood induces neurobehavioral alterations and hippocampal neuronal remodeling accompanied by augmented microglial lipid accumulation. Brain Behav Immun. 2022;100:155–71.
25. Farzan M, Saberi-Rounkian M, Asadi-Rizi A, Heidari Z, Farzan M, Fathi M, Aghaei A, Azadegan-Dehkordi F, Bagheri N. The emerging role of the microglia triggering receptor expressed on myeloid cells (TREM) 2 in multiple sclerosis. Exp Neurol. 2025;384:115071.
26. Olzmann JA, Carvalho P. Dynamics and functions of lipid droplets. Nat Rev Mol Cell Biol. 2019;20(3):137–55.
27. Beller M, Herker E, Füllekrug J. Grease on-Perspectives in lipid droplet biology. Semin Cell Dev Biol. 2020;108:94–101.
28. Welte MA, Gould AP. Lipid droplet functions beyond energy storage. Biochim Biophys Acta Mol Cell Biol Lipids. 2017;1862(10 Pt B):1260–72.
29. Roberts MA, Olzmann JA. Protein quality control and lipid droplet metabolism. Annu Rev Cell Dev Biol. 2020;36:115–39.
30. Dierge E, Debock E, Guilbaud C, Corbet C, Mignolet E, Mignard L, et al. Peroxidation of n-3 and n-6 polyunsaturated fatty acids in the acidic tumor environment leads to ferroptosis-mediated anticancer effects. Cell Metab. 2021;33(8):1701–e17151705.
31. Chen B, Cheng C, Wu Y, Li S, Han M, Zhen L, et al. PGC-1α-mediated imbalance of mitochondria-lipid droplet homeostasis in neomycin-induced ototoxicity and nephrotoxicity. Acta Pharm Sin B. 2024;14(10):4413–30.
32. Yamamoto S, Masuda T. Lipid in microglial biology - from material to mediator. Inflamm Regen. 2023;43(1):38.
33. Ralhan I, Chang CL, Lippincott-Schwartz J, Ioannou MS. Lipid droplets in the nervous system. J Cell Biol. 2021;220(7).
34. Lada AT, Willingham MC, St Clair RW. Triglyceride depletion in THP-1 cells alters cholesteryl ester physical state and cholesterol efflux. J Lipid Res. 2002;43(4):618–28.
35. Walther TC, Chung J, Farese RV. Jr. Lipid droplet biogenesis. Annu Rev Cell Dev Biol. 2017;33:491–510.
36. Islimye E, Girard V, Gould AP. Functions of Stress-Induced lipid droplets in the nervous system. Front Cell Dev Biol. 2022;10:863907.
37. Cao J, Li JL, Li D, Tobin JF, Gimeno RE. Molecular identification of microsomal acyl-CoA:glycerol-3-phosphate acyltransferase, a key enzyme in de novo triacylglycerol synthesis. Proc Natl Acad Sci U S A. 2006;103(52):19695–700.
38. Nagle CA, Vergnes L, Dejong H, Wang S, Lewin TM, Reue K, Coleman RA. Identification of a novel sn-glycerol-3-phosphate acyltransferase isoform, GPAT4, as the enzyme deficient in Agpat6-/- mice. J Lipid Res. 2008;49(4):823–31.
39. Shan D, Li JL, Wu L, Li D, Hurov J, Tobin JF, Gimeno RE, Cao J. GPAT3 and GPAT4 are regulated by insulin-stimulated phosphorylation and play distinct roles in adipogenesis. J Lipid Res. 2010;51(7):1971–81.
40. Chen XR, Besson VC, Beziaud T, Plotkine M, Marchand-Leroux C. Combination therapy with fenofibrate, a peroxisome proliferator-activated receptor alpha agonist, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, on experimental traumatic brain injury. J Pharmacol Exp Ther. 2008;326(3):966–74.
41. Krahmer N, Hilger M, Kory N, Wilfling F, Stoehr G, Mann M, Farese RV Jr., Walther TC. Protein correlation profiles identify lipid droplet proteins with high confidence. Mol Cell Proteom. 2013;12(5):1115–26.
42. Santoshi M, Bansia H, Hussain M, Jha AK, Nagaraja V. Identification of a 1-acyl-glycerol-3-phosphate acyltransferase from Mycobacterium tuberculosis, a key enzyme involved in triacylglycerol biosynthesis. Mol Microbiol. 2024;121(6):1164–81.
43. Takeuchi K, Reue K. Biochemistry, physiology, and genetics of GPAT, AGPAT, and lipin enzymes in triglyceride synthesis. Am J Physiol Endocrinol Metab. 2009;296(6):E1195–1209.
44. Eto M, Shindou H, Shimizu T. A novel lysophosphatidic acid acyltransferase enzyme (LPAAT4) with a possible role for incorporating docosahexaenoic acid into brain glycerophospholipids. Biochem Biophys Res Commun. 2014;443(2):718–24.
45. Reue K, Brindley DN. Thematic review series: glycerolipids. Multiple roles for lipins/phosphatidate phosphatase enzymes in lipid metabolism. J Lipid Res. 2008;49(12):2493–503.
46. Crotta Asis A, Savoretti F, Cabruja M, Gramajo H, Gago G. Characterization of key enzymes involved in triacylglycerol biosynthesis in mycobacteria. Sci Rep. 2021;11(1):13257.
47. Reue K, Zhang P. The lipin protein family: dual roles in lipid biosynthesis and gene expression. FEBS Lett. 2008;582(1):90–6.
48. Soste M, Charmpi K, Lampert F, Gerez JA, van Oostrum M, Malinovska L, et al. Proteomics-Based monitoring of pathway activity reveals that blocking diacylglycerol biosynthesis rescues from Alpha-Synuclein toxicity. Cell Syst. 2019;9(3):309–e320308.
49. Shockey JM, Gidda SK, Chapital DC, Kuan JC, Dhanoa PK, Bland JM, Rothstein SJ, Mullen RT, Dyer JM. Tung tree DGAT1 and DGAT2 have nonredundant functions in triacylglycerol biosynthesis and are localized to different subdomains of the endoplasmic reticulum. Plant Cell. 2006;18(9):2294–313.
50. Chitraju C, Mejhert N, Haas JT, Diaz-Ramirez LG, Grueter CA, Imbriglio JE, et al. Triglyceride synthesis by DGAT1 protects adipocytes from Lipid-Induced ER stress during lipolysis. Cell Metab. 2017;26(2):407–e418403.
51. McFie PJ, Banman SL, Kary S, Stone SJ. Murine diacylglycerol acyltransferase-2 (DGAT2) can catalyze triacylglycerol synthesis and promote lipid droplet formation independent of its localization to the endoplasmic reticulum. J Biol Chem. 2011;286(32):28235–46.
52. Nakajima S, Gotoh M, Fukasawa K, Murakami-Murofushi K, Kunugi H. Oleic acid is a potent inducer for lipid droplet accumulation through its esterification to glycerol by diacylglycerol acyltransferase in primary cortical astrocytes. Brain Res. 2019;1725:146484.
53. Smolič T, Tavčar P, Horvat A, Černe U, Halužan Vasle A, Tratnjek L, et al. Astrocytes in stress accumulate lipid droplets. Glia. 2021;69(6):1540–62.
54. Chen HC, Farese RV. Jr. Inhibition of triglyceride synthesis as a treatment strategy for obesity: lessons from DGAT1-deficient mice. Arterioscler Thromb Vasc Biol. 2005;25(3):482–6.
55. Smith SJ, Cases S, Jensen DR, Chen HC, Sande E, Tow B, et al. Obesity resistance and multiple mechanisms of triglyceride synthesis in mice lacking dgat. Nat Genet. 2000;25(1):87–90.
56. Stone SJ, Myers HM, Watkins SM, Brown BE, Feingold KR, Elias PM, Farese RV. Jr. Lipopenia and skin barrier abnormalities in DGAT2-deficient mice. J Biol Chem. 2004;279(12):11767–76.
57. Senkal CE, Salama MF, Snider AJ, Allopenna JJ, Rana NA, Koller A, Hannun YA, Obeid LM. Ceramide is metabolized to acylceramide and stored in lipid droplets. Cell Metab. 2017;25(3):686–97.
58. Yang C, Wang X, Wang J, Wang X, Chen W, Lu N, Siniossoglou S, Yao Z, Liu K. Rewiring neuronal glycerolipid metabolism determines the extent of axon regeneration. Neuron. 2020;105(2):276–e292275.
59. Luan J, Yu M, Gu Q, Zhou X, Shao Y, Chen T, et al. Fatty acid synthase inhibition improves hypertension-induced erectile dysfunction by suppressing oxidative stress and NLRP3 inflammasome-dependent pyroptosis through activating the Nrf2/HO-1 pathway. Front Immunol. 2024;15:1532021.
60. Jones SF, Infante JR. Molecular pathways: fatty acid synthase. Clin Cancer Res. 2015;21(24):5434–8.
61. Günenc AN, Graf B, Stark H, Chari A. Fatty acid synthase: structure, function, and regulation. Subcell Biochem. 2022;99:1–33.

62. Paiva P, Medina FE, Viegas M, Ferreira P, Neves RPP, Sousa JPM, Ramos MJ, Fernandes PA. Animal fatty acid synthase: A chemical nanofactory. Chem Rev. 2021;121(15):9502–53.
63. Rimmerman N, Juknat A, Kozela E, Levy R, Bradshaw HB, Vogel Z. The non-psychoactive plant cannabinoid, cannabidiol affects cholesterol metabolism-related genes in microglial cells. Cell Mol Neurobiol. 2011;31(6):921–30.
64. Li H, Huynh TN, Duong MT, Gow JG, Chang CCY, Chang TY. ACAT1/SOAT1 blockade suppresses LPS-Mediated neuroinflammation by modulating the fate of Toll-like receptor 4 in microglia. Int J Mol Sci. 2023;24(6).
65. Chang TY, Chang CC, Lin S, Yu C, Li BL, Miyazaki A. Roles of acyl-coenzyme a:cholesterol acyltransferase-1 and– 2. Curr Opin Lipidol. 2001;12(3):289–96.
66. Lin S, Lu X, Chang CC, Chang TY. Human acyl-coenzyme a:cholesterol acyltransferase expressed in chinese hamster ovary cells: membrane topology and active site location. Mol Biol Cell. 2003;14(6):2447–60.
67. Picard C, Julien C, Frappier J, Miron J, Théroux L, Dea D, Breitner JCS, Poirier J. Alterations in cholesterol metabolism-related genes in sporadic Alzheimer's disease. Neurobiol Aging. 2018;66:180.e181-180.e189.
68. Feringa FM, van der Kant R. Cholesterol and alzheimer's disease; from risk genes to pathological effects. Front Aging Neurosci. 2021;13:690372.
69. Chan RB, Oliveira TG, Cortes EP, Honig LS, Duff KE, Small SA, Wenk MR, Shui G, Di Paolo G. Comparative lipidomic analysis of mouse and human brain with alzheimer disease. J Biol Chem. 2012;287(4):2678–88.
70. Valencia-Olvera AC, Balu D, Faulk N, Amiridis A, Wang Y, Pham C, et al. Inhibition of ACAT as a therapeutic target for alzheimer's disease is independent of ApoE4 lipidation. Neurotherapeutics. 2023;20(4):1120–37.
71. Ohshiro T, Matsuda D, Sakai K, Degirolamo C, Yagyu H, Rudel LL, Omura S, Ishibashi S, Tomoda H. Pyripyropene A, an acyl-coenzyme a:cholesterol acyltransferase 2-selective inhibitor, attenuates hypercholesterolemia and atherosclerosis in murine models of hyperlipidemia. Arterioscler Thromb Vasc Biol. 2011;31(5):1108–15.
72. Haney MS, Pálovics R, Munson CN, Long C, Johansson PK, Yip O, et al. APOE4/4 is linked to damaging lipid droplets in alzheimer's disease microglia. Nature. 2024;628(8006):154–61.
73. Kassan A, Herms A, Fernández-Vidal A, Bosch M, Schieber NL, Reddy BJ, et al. Acyl-CoA synthetase 3 promotes lipid droplet biogenesis in ER microdomains. J Cell Biol. 2013;203(6):985–1001.
74. Zhou X, Zhao R, Lv M, Xu X, Liu W, Li X, et al. ACSL4 promotes microglia-mediated neuroinflammation by regulating lipid metabolism and VGLL4 expression. Brain Behav Immun. 2023;109:331–43.
75. Corbo JH, Chung J. Mechanisms of lipid droplet degradation. Curr Opin Cell Biol. 2024;90:102402.
76. Xu C, Fan J. Links between autophagy and lipid droplet dynamics. J Exp Bot. 2022;73(9):2848–58.
77. Cohen S. Lipid droplets as organelles. Int Rev Cell Mol Biol. 2018;337:83–110.
78. Zechner R, Madeo F, Kratky D. Cytosolic lipolysis and lipophagy: two sides of the same coin. Nat Rev Mol Cell Biol. 2017;18(11):671–84.
79. Zimmermann R, Strauss JG, Haemmerle G, Schoiswohl G, Birner-Gruenberger R, Riederer M, et al. Fat mobilization in adipose tissue is promoted by adipose triglyceride lipase. Science. 2004;306(5700):1383–6.
80. Martinez-Lopez N, Garcia-Macia M, Sahu S, Athonvarangkul D, Liebling E, Merlo P, Cecconi F, Schwartz GJ, Singh R. Autophagy in the CNS and periphery coordinate lipophagy and lipolysis in the brown adipose tissue and liver. Cell Metab. 2016;23(1):113–27.
81. Nagaroor V, Gummadi SN. An overview of mammalian and microbial hormone-sensitive lipases (lipolytic family IV): biochemical properties and industrial applications. Biotechnol Genet Eng Rev. 2023;39(2):281–310.
82. Recazens E, Mouisel E, Langin D. Hormone-sensitive lipase: sixty years later. Prog Lipid Res. 2021;82:101084.
83. Olichwier A, Sowka A, Balatskyi VV, Gan AM, Dziewulska A, Dobrzyn P. SCD1-related epigenetic modifications affect hormone-sensitive lipase (Lipe) gene expression in cardiomyocytes. Biochim Biophys Acta Mol Cell Res. 2024;1871(1):119608.
84. Tisi A, Scipioni L, Carozza G, Di Re L, Cimino G, Di Meo C, et al. Alterations of endocannabinoid signaling and microglia reactivity in the retinas of AD-like mice precede the onset of hippocampal β-amyloid plaques. J Neurochem. 2025;169(2):e16256.
85. Song Y, Zhang J, Chen C. Fine-tuning of synaptic upscaling at excitatory synapses by endocannabinoid signaling is mediated via the CB1 receptor. Sci Rep. 2015;5:16257.
86. Zhu D, Zhang J, Hashem J, Gao F, Chen C. Inhibition of 2-arachidonoylglycerol degradation enhances glial immunity by single-cell transcriptomic analysis. J Neuroinflammation. 2023;20(1):17.
87. Traver MS, Bartel B. The ubiquitin-protein ligase MIEL1 localizes to peroxisomes to promote seedling oleosin degradation and lipid droplet mobilization. Proc Natl Acad Sci U S A. 2023;120(29):e2304870120.
88. Huang F, Dai Q, Zheng K, Ma Q, Liu Y, Jiang S, Jiang W, Yan X. Exploring the inhibitory potential of KPHs-AL-derived GLLF peptide on pancreatic lipase and cholesterol esterase activities. Food Chem. 2024;439:138108.
89. Yoshida K, Konishi K, Magana-Mora A, Rougny A, Yasutake Y, Muramatsu S, et al. Production of recombinant extracellular cholesterol esterase using consistently active promoters in Burkholderia stabilis. Biosci Biotechnol Biochem. 2019;83(10):1974–84.
90. Schott MB, Weller SG, Schulze RJ, Krueger EW, Drizyte-Miller K, Casey CA, McNiven MA. Lipid droplet size directs lipolysis and lipophagy catabolism in hepatocytes. J Cell Biol. 2019;218(10):3320–35.
91. Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, Czaja MJ. Autophagy regulates lipid metabolism. Nature. 2009;458(7242):1131–5.
92. Sheriff S, Du H, Grabowski GA. Characterization of lysosomal acid lipase by site-directed mutagenesis and heterologous expression. J Biol Chem. 1995;270(46):27766–72.
93. Warner TG, Dambach LM, Shin JH, O'Brien JS. Purification of the lysosomal acid lipase from human liver and its role in lysosomal lipid hydrolysis. J Biol Chem. 1981;256(6):2952–7.
94. Grumet L, Eichmann TO, Taschler U, Zierler KA, Leopold C, Moustafa T, et al. Lysosomal acid lipase hydrolyzes retinyl ester and affects retinoid turnover. J Biol Chem. 2016;291(34):17977–87.
95. Pu M, Zheng W, Zhang H, Wan W, Peng C, Chen X, et al. ORP8 acts as a lipophagy receptor to mediate lipid droplet turnover. Protein Cell. 2023;14(9):653–67.
96. Mailler E, Guardia CM, Bai X, Jarnik M, Williamson CD, Li Y, Maio N, Golden A, Bonifacino JS. The autophagy protein ATG9A enables lipid mobilization from lipid droplets. Nat Commun. 2021;12(1):6750.
97. Shatz N, Chohan Y, Klionsky DJ. ATG14 and STX18: gatekeepers of lipid droplet degradation and the implications for disease modulation. Autophagy. 2024;20(8):1697–9.
98. Ishimaru K, Yoshioka K, Kano K, Kurano M, Saigusa D, Aoki J, et al. Sphingosine kinase-2 prevents macrophage cholesterol accumulation and atherosclerosis by stimulating autophagic lipid degradation. Sci Rep. 2019;9(1):18329.
99. Drizyte-Miller K, Schott MB, McNiven MA. Lipid droplet contacts with autophagosomes, lysosomes, and other degradative vesicles. Contact (Thousand Oaks). 2020;3:1–13.
100. Zhen Y, Stenmark H, Autophagosome Biogenesis. Cells. 2023;12(4).
101. McFadden JW, Aja S, Li Q, Bandaru VV, Kim EK, Haughey NJ, Kuhajda FP, Ronnett GV. Increasing fatty acid oxidation remodels the hypothalamic neurometabolome to mitigate stress and inflammation. PLoS ONE. 2014;9(12):e115642.
102. Huang YQ, Wang Y, Hu K, Lin S, Lin XH. Hippocampal Glycerol-3-Phosphate acyltransferases 4 and BDNF in the progress of Obesity-Induced depression. Front Endocrinol (Lausanne). 2021;12:667773.
103. Cong WN, Cai H, Wang R, Daimon CM, Maudsley S, Raber K, Canneva F, von Hörsten S, Martin B. Altered hypothalamic protein expression in a rat model of huntington's disease. PLoS ONE. 2012;7(10):e47240.
104. Malik MA, Saqib MAN, Mientjes E, Acharya A, Alam MR, Wallaard I, et al. A loss of function variant in AGPAT3 underlies intellectual disability and retinitis pigmentosa (IDRP) syndrome. Eur J Hum Genet. 2023;31(12):1447–54.
105. Prakash P, Manchanda P, Paouri E, Bisht K, Sharma K, Wijewardhane PR et al. Amyloid β Induces Lipid Droplet-Mediated Microglial Dysfunction in Alzheimer's Disease. bioRxiv. 2023.
106. Chorna NE, Santos-Soto IJ, Carballeira NM, Morales JL, de la Nuez J, Cátala-Valentin A, Chornyy AP, Vázquez-Montes A, De Ortiz SP. Fatty acid synthase as a factor required for exercise-induced cognitive enhancement and dentate gyrus cellular proliferation. PLoS ONE. 2013;8(11):e77845.
107. Jian H, Wu K, Lv Y, Du J, Hou M, Zhang C, Gao J, Zhou H, Feng S. A critical role for microglia in regulating metabolic homeostasis and neural repair after spinal cord injury. Free Radic Biol Med. 2024;225:469–81.
108. Alavez-Rubio JS, Juarez-Cedillo T. ACAT1 as a therapeutic target and its genetic relationship with alzheimer's disease. Curr Alzheimer Res. 2019;16(8):699–709.
109. Wu CY, Zhang Y, Howard P, Huang F, Lee RH. ACSL3 is a promising therapeutic target for alleviating anxiety and depression in Alzheimer's disease. Geroscience. 2024.

110. Cui Y, Zhang Y, Zhao X, Shao L, Liu G, Sun C, Xu R, Zhang Z. ACSL4 exacerbates ischemic stroke by promoting ferroptosis-induced brain injury and neuroinflammation. Brain Behav Immun. 2021;93:312–21.
111. Robb JL, Boisjoly F, Machuca-Parra AI, Coursan A, Manceau R, Majeur D, et al. Blockage of ATGL-mediated breakdown of lipid droplets in microglia alleviates neuroinflammatory and behavioural responses to lipopolysaccharides. Brain Behav Immun. 2025;123:315–33.
112. Li H, Liu P, Deng S, Zhu L, Cao X, Bao X, Xia S, Xu Y, Zhang B. Pharmacological upregulation of microglial lipid droplet alleviates neuroinflammation and acute ischemic brain injury. Inflammation. 2023;46(5):1832–48.
113. Qin Q, Teng Z, Liu C, Li Q, Yin Y, Tang Y. TREM2, microglia, and alzheimer's disease. Mech Ageing Dev. 2021;195:111438.
114. Ma M, Jiang W, Zhou R. DAMPs and DAMP-sensing receptors in inflammation and diseases. Immunity. 2024;57(4):752–71.
115. Heidari A, Yazdanpanah N, Rezaei N. The role of Toll-like receptors and neuroinflammation in parkinson's disease. J Neuroinflammation. 2022;19(1):135.
116. Bersuker K, Peterson CWH, To M, Sahl SJ, Savikhin V, Grossman EA, Nomura DK, Olzmann JA. A proximity labeling strategy provides insights into the composition and dynamics of lipid droplet proteomes. Dev Cell. 2018;44(1):97–e112117.
117. Klemm RW, Norton JP, Cole RA, Li CS, Park SH, Crane MM, et al. A conserved role for atlastin gtpases in regulating lipid droplet size. Cell Rep. 2013;3(5):1465–75.
118. Renvoisé B, Malone B, Falgairolle M, Munasinghe J, Stadler J, Sibilla C, Park SH, Blackstone C. Reep1 null mice reveal a converging role for hereditary spastic paraplegia proteins in lipid droplet regulation. Hum Mol Genet. 2016;25(23):5111–25.
119. Rao MJ, Goodman JM. Seipin: harvesting fat and keeping adipocytes healthy. Trends Cell Biol. 2021;31(11):912–23.
120. Zoni V, Khaddaj R, Lukmantara I, Shinoda W, Yang H, Schneiter R, Vanni S. Seipin accumulates and traps diacylglycerols and triglycerides in its ring-like structure. Proc Natl Acad Sci U S A. 2021;118(10).
121. Wang H, Becuwe M, Housden BE, Chitraju C, Porras AJ, Graham MM et al. Seipin is required for converting nascent to mature lipid droplets. Elife. 2016;5.
122. Jackson CL. Lipid droplet biogenesis. Curr Opin Cell Biol. 2019;59:88–96.
123. Yamaguchi T, Omatsu N, Matsushita S, Osumi T. CGI-58 interacts with perilipin and is localized to lipid droplets. Possible involvement of CGI-58 mislocalization in Chanarin-Dorfman syndrome. J Biol Chem. 2004;279(29):30490–7.
124. Brasaemle DL, Barber T, Wolins NE, Serrero G, Blanchette-Mackie EJ, Londos C. Adipose differentiation-related protein is an ubiquitously expressed lipid storage droplet-associated protein. J Lipid Res. 1997;38(11):2249–63.
125. Tsai TH, Chen E, Li L, Saha P, Lee HJ, Huang LS, Shelness GS, Chan L, Chang BH. The constitutive lipid droplet protein PLIN2 regulates autophagy in liver. Autophagy. 2017;13(7):1130–44.
126. Bulankina AV, Deggerich A, Wenzel D, Mutenda K, Wittmann JG, Rudolph MG, Burger KN, Höning. TIP47 functions in the biogenesis of lipid droplets. J Cell Biol. 2009;185(4):641–55.
127. Wolins NE, Skinner JR, Schoenfish MJ, Tzekov A, Bensch KG, Bickel PE. Adipocyte protein S3-12 coats nascent lipid droplets. J Biol Chem. 2003;278(39):37713–21.
128. Chung J, Wu X, Lambert TJ, Lai ZW, Walther TC, Farese RV. Jr. LDAF1 and seipin form a lipid droplet assembly complex. Dev Cell. 2019;51(5):551–e563557.
129. Khaddaj R, Stribny J, Cottier S, Schneiter R. Perilipin 3 promotes the formation of membrane domains enriched in diacylglycerol and lipid droplet biogenesis proteins. Front Cell Dev Biol. 2023;11:1116491.
130. Han X, Zhu J, Zhang X, Song Q, Ding J, Lu M, Sun S, Hu G. Plin4-Dependent lipid droplets hamper neuronal mitophagy in the MPTP/p-Induced mouse model of parkinson's disease. Front Neurosci. 2018;12:397.
131. Sztalryd C, Brasaemle DL. The perilipin family of lipid droplet proteins: gatekeepers of intracellular lipolysis. Biochim Biophys Acta Mol Cell Biol Lipids. 2017;1862(10 Pt B):1221–32.
132. Hayes M, Choudhary V, Ojha N, Shin JJ, Han GS, Carman GM, Loewen CJ, Prinz WA, Levine T. Fat storage-inducing transmembrane (FIT or FITM) proteins are related to lipid phosphatase/phosphotransferase enzymes. Microb Cell. 2017;5(2):88–103.
133. Choudhary V, Ojha N, Golden A, Prinz WA. A conserved family of proteins facilitates nascent lipid droplet budding from the ER. J Cell Biol. 2015;211(2):261–71.
134. Gross DA, Zhan C, Silver DL. Direct binding of triglyceride to fat storage-inducing transmembrane proteins 1 and 2 is important for lipid droplet formation. Proc Natl Acad Sci U S A. 2011;108(49):19581–6.
135. Bian X, Klemm RW, Liu TY, Zhang M, Sun S, Sui X, Liu X, Rapoport TA, Hu J. Structures of the atlastin gtpase provide insight into homotypic fusion of endoplasmic reticulum membranes. Proc Natl Acad Sci U S A. 2011;108(10):3976–81.
136. Björk S, Hurt CM, Ho VK, Angelotti T. REEPs are membrane shaping adapter proteins that modulate specific g protein-coupled receptor trafficking by affecting ER cargo capacity. PLoS ONE. 2013;8(10):e76366.
137. Park SH, Zhu PP, Parker RL, Blackstone C. Hereditary spastic paraplegia proteins REEP1, spastin, and atlastin-1 coordinate microtubule interactions with the tubular ER network. J Clin Invest. 2010;120(4):1097–110.
138. Joshi AS, Huang X, Choudhary V, Levine TP, Hu J, Prinz WA. A family of membrane-shaping proteins at ER subdomains regulates pre-peroxisomal vesicle biogenesis. J Cell Biol. 2016;215(4):515–29.
139. Wang S, Idrissi FZ, Hermansson M, Grippa A, Ejsing CS, Carvalho P. Seipin and the membrane-shaping protein Pex30 cooperate in organelle budding from the endoplasmic reticulum. Nat Commun. 2018;9(1):2939.
140. Joshi AS, Nebenfuehr B, Choudhary V, Satpute-Krishnan P, Levine TP, Golden A, Prinz WA. Lipid droplet and peroxisome biogenesis occur at the same ER subdomains. Nat Commun. 2018;9(1):2940.
141. Datta S, Liu Y, Hariri H, Bowerman J, Henne WM. Cerebellar ataxia disease-associated Snx14 promotes lipid droplet growth at ER-droplet contacts. J Cell Biol. 2019;218(4):1335–51.
142. Hariri H, Speer N, Bowerman J, Rogers S, Fu G, Reetz E, et al. Mdm1 maintains endoplasmic reticulum homeostasis by spatially regulating lipid droplet biogenesis. J Cell Biol. 2019;218(4):1319–34.
143. Henne WM, Zhu L, Balogi Z, Stefan C, Pleiss JA, Emr SD. Mdm1/Snx13 is a novel ER-endolysosomal interorganelle tethering protein. J Cell Biol. 2015;210(4):541–51.
144. Bozza PT, Viola JP. Lipid droplets in inflammation and cancer. Prostaglandins Leukot Essent Fat Acids. 2010;82(4–6):243–50.
145. Doens D, Fernández PL. Microglia receptors and their implications in the response to amyloid β for alzheimer's disease pathogenesis. J Neuroinflammation. 2014;11:48.
146. Hickman SE, Kingery ND, Ohsumi TK, Borowsky ML, Wang LC, Means TK, El Khoury J. The microglial sensome revealed by direct RNA sequencing. Nat Neurosci. 2013;16(12):1896–905.
147. Bozza PT, Magalhães KG, Weller PF. Leukocyte lipid bodies - Biogenesis and functions in inflammation. Biochim Biophys Acta. 2009;1791(6):540–51.
148. Zhao P, Zhao Z, Yu Z, Chen L, Jin Y, Wu J, Ren Z. Application of synthetic lipid droplets in metabolic diseases. Clin Transl Med. 2023;13(11):e1441.
149. Xin W, Pan Y, Wei W, Gerner ST, Huber S, Juenemann M et al. TGF-β1 decreases Microglia-Mediated neuroinflammation and lipid droplet accumulation in an in vitro stroke model. Int J Mol Sci. 2023;24(24).
150. Loix M, Wouters E, Vanherle S, Dehairs J, McManaman JL, Kemps H, et al. Perilipin-2 limits remyelination by preventing lipid droplet degradation. Cell Mol Life Sci. 2022;79(10):515.
151. Bruce KD, Gorkhali S, Given K, Coates AM, Boyle KE, Macklin WB, Eckel RH. Lipoprotein lipase is a feature of Alternatively-Activated microglia and may facilitate lipid uptake in the CNS during demyelination. Front Mol Neurosci. 2018;11:57.
152. Beisiegel U, Weber W, Bengtsson-Olivecrona G. Lipoprotein lipase enhances the binding of chylomicrons to low density lipoprotein receptor-related protein. Proc Natl Acad Sci U S A. 1991;88(19):8342–6.
153. Nugent AA, Lin K, van Lengerich B, Lianoglou S, Przybyla L, Davis SS, et al. TREM2 regulates microglial cholesterol metabolism upon chronic phagocytic challenge. Neuron. 2020;105(5):837–e854839.
154. Wei W, Zhang L, Xin W, Pan Y, Tatenhorst L, Hao Z, et al. TREM2 regulates microglial lipid droplet formation and represses post-ischemic brain injury. Biomed Pharmacother. 2024;170:115962.
155. Chandak PG, Radovic B, Aflaki E, Kolb D, Buchebner M, Fröhlich E, et al. Efficient phagocytosis requires triacylglycerol hydrolysis by adipose triglyceride lipase. J Biol Chem. 2010;285(26):20192–201.
156. Aflaki E, Radovic B, Chandak PG, Kolb D, Eisenberg T, Ring J, et al. Triacylglycerol accumulation activates the mitochondrial apoptosis pathway in macrophages. J Biol Chem. 2011;286(9):7418–28.
157. Cantuti-Castelvetri L, Fitzner D, Bosch-Queralt M, Weil MT, Su M, Sen P, et al. Defective cholesterol clearance limits remyelination in the aged central nervous system. Science. 2018;359(6376):684–8.
158. Shahidehpour RK, Higdon RE, Crawford NG, Neltner JH, Ighodaro ET, Patel E, Price D, Nelson PT, Bachstetter AD. Dystrophic microglia are associated with neurodegenerative disease and not healthy aging in the human brain. Neurobiol Aging. 2021;99:19–27.

159. Pereira-Dutra FS, Teixeira L, de Souza Costa MF, Bozza PT. Fat, fight, and beyond: the multiple roles of lipid droplets in infections and inflammation. J Leukoc Biol. 2019;106(3):563–80.
160. Bailey AP, Koster G, Guillermier C, Hirst EM, MacRae JI, Lechene CP, Postle AD, Gould AP. Antioxidant role for lipid droplets in a stem cell niche of Drosophila. Cell. 2015;163(2):340–53.
161. Bogie JF, Timmermans S, Huynh-Thu VA, Irrthum A, Smeets HJ, Gustafsson J, et al. Myelin-derived lipids modulate macrophage activity by liver X receptor activation. PLoS ONE. 2012;7(9):e44998.
162. Bogie JF, Jorissen W, Mailleux J, Nijland PG, Zelcer N, Vanmierlo T, et al. Myelin alters the inflammatory phenotype of macrophages by activating ppars. Acta Neuropathol Commun. 2013;1:43.
163. Weinger JG, Brosnan CF, Loudig O, Goldberg MF, Macian F, Arnett HA, Prieto AL, Tsiperson V, Shafit-Zagardo B. Loss of the receptor tyrosine kinase axl leads to enhanced inflammation in the CNS and delayed removal of myelin debris during experimental autoimmune encephalomyelitis. J Neuroinflammation. 2011;8:49.
164. Binder MD, Cate HS, Prieto AL, Kemper D, Butzkueven H, Gresle MM, et al. Gas6 deficiency increases oligodendrocyte loss and microglial activation in response to cuprizone-induced demyelination. J Neurosci. 2008;28(20):5195–206.
165. Gaultier A, Wu X, Le Moan N, Takimoto S, Mukandala G, Akassoglou K, Campana WM, Gonias SL. Low-density lipoprotein receptor-related protein 1 is an essential receptor for myelin phagocytosis. J Cell Sci. 2009;122(Pt 8):1155–62.
166. Poliani PL, Wang Y, Fontana E, Robinette ML, Yamanishi Y, Gilfillan S, Colonna M. TREM2 sustains microglial expansion during aging and response to demyelination. J Clin Invest. 2015;125(5):2161–70.
167. Park DS, Kozaki T, Tiwari SK, Moreira M, Khalilnezhad A, Torta F, et al. iPS-cell-derived microglia promote brain organoid maturation via cholesterol transfer. Nature. 2023;623(7986):397–405.
168. Ferris HA, Perry RJ, Moreira GV, Shulman GI, Horton JD, Kahn CR. Loss of astrocyte cholesterol synthesis disrupts neuronal function and alters whole-body metabolism. Proc Natl Acad Sci U S A. 2017;114(5):1189–94.
169. Mauch DH, Nägler K, Schumacher S, Göritz C, Müller EC, Otto A, Pfrieger FW. CNS synaptogenesis promoted by glia-derived cholesterol. Science. 2001;294(5545):1354–7.
170. Masana MF, Tyrovolas S, Kolia N, Chrysohoou C, Skoumas J, Haro JM et al. Dietary patterns and their association with anxiety symptoms among older adults: the ATTICA study. Nutrients. 2019;11(6).
171. Gubert C, Kong G, Renoir T, Hannan AJ. Exercise, diet and stress as modulators of gut microbiota: implications for neurodegenerative diseases. Neurobiol Dis. 2020;134:104621.
172. Ljungberg T, Bondza E, Lethin C. Evidence of the importance of dietary habits regarding depressive symptoms and depression. Int J Environ Res Public Health. 2020;17(5).
173. Ferschmann L, Bos MGN, Herting MM, Mills KL, Tamnes CK. Contextualizing adolescent structural brain development: environmental determinants and mental health outcomes. Curr Opin Psychol. 2022;44:170–6.
174. Nota MHC, Nicolas S, O'Leary OF, Nolan YM. Outrunning a bad diet: interactions between exercise and a Western-style diet for adolescent mental health, metabolism and microbes. Neurosci Biobehav Rev. 2023;149:105147.
175. Yao X, Yang C, Jia X, Yu Z, Wang C, Zhao J, et al. High-fat diet consumption promotes adolescent neurobehavioral abnormalities and hippocampal structural alterations via microglial overactivation accompanied by an elevated serum free fatty acid concentration. Brain Behav Immun. 2024;119:236–50.
176. Pfrieger FW. The Niemann-Pick type diseases - A synopsis of inborn errors in sphingolipid and cholesterol metabolism. Prog Lipid Res. 2023;90:101225.
177. Colombo A, Dinkel L, Müller SA, Sebastian Monasor L, Schifferer M, Cantuti-Castelvetri L, et al. Loss of NPC1 enhances phagocytic uptake and impairs lipid trafficking in microglia. Nat Commun. 2021;12(1):1158.
178. Mosher KI, Wyss-Coray T. Microglial dysfunction in brain aging and alzheimer's disease. Biochem Pharmacol. 2014;88(4):594–604.
179. Nakanishi H, Wu Z. Microglia-aging: roles of microglial lysosome- and mitochondria-derived reactive oxygen species in brain aging. Behav Brain Res. 2009;201(1):1–7.
180. Filipello F, You SF, Mirfakhar FS, Mahali S, Bollman B, Acquarone M, et al. Defects in lysosomal function and lipid metabolism in human microglia harboring a TREM2 loss of function mutation. Acta Neuropathol. 2023;145(6):749–72.
181. Churchward MA, Tchir DR, Todd KG. Microglial function during glucose deprivation: inflammatory and neuropsychiatric implications. Mol Neurobiol. 2018;55(2):1477–87.
182. Chali F, Milior G, Marty S, Morin-Brureau M, Le Duigou C, Savary E, Blugeon C, Jourdren L, Miles R. Lipid markers and related transcripts during excitotoxic neurodegeneration in kainate-treated mice. Eur J Neurosci. 2019;50(1):1759–78.
183. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. Cell. 2019;179(2):312–39.
184. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013;9(2):106–18.
185. Miao G, Zhuo D, Han X, Yao W, Liu C, Liu H, et al. From degenerative disease to malignant tumors: insight to the function of apoe. Biomed Pharmacother. 2023;158:114127.
186. Blumenfeld J, Yip O, Kim MJ, Huang Y. Cell type-specific roles of APOE4 in alzheimer disease. Nat Rev Neurosci. 2024;25(2):91–110.
187. Valles SL, Singh SK, Campos-Campos J, Colmena C, Campo-Palacio I, Alvarez-Gamez K, Caballero O, Jorda A. Functions of astrocytes under normal conditions and after a brain disease. Int J Mol Sci. 2023;24(9).
188. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in alzheimer's disease. Lancet Neurol. 2015;14(4):388–405.
189. Kedia S, Simons M. Oligodendrocytes in alzheimer's disease pathophysiology. Nat Neurosci. 2025;28(3):446–56.
190. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The Amyloid-β pathway in alzheimer's disease. Mol Psychiatry. 2021;26(10):5481–503.
191. Hu X, Ma YN, Xia Y. Association between abnormal lipid metabolism and alzheimer's disease: new research has revealed significant findings on the APOE4 genotype in microglia. Biosci Trends. 2024;18(2):195–7.
192. Wang S, Colonna M. Microglia in alzheimer's disease: A target for immunotherapy. J Leukoc Biol. 2019;106(1):219–27.
193. Hamilton LK, Dufresne M, Joppé SE, Petryszyn S, Aumont A, Calon F, et al. Aberrant lipid metabolism in the forebrain niche suppresses adult neural stem cell proliferation in an animal model of alzheimer's disease. Cell Stem Cell. 2015;17(4):397–411.
194. Hutter-Paier B, Huttunen HJ, Puglielli L, Eckman CB, Kim DY, Hofmeister A, et al. The ACAT inhibitor CP-113,818 markedly reduces amyloid pathology in a mouse model of alzheimer's disease. Neuron. 2004;44(2):227–38.
195. Shibuya Y, Chang CC, Huang LH, Bryleva EY, Chang TY. Inhibiting ACAT1/SOAT1 in microglia stimulates autophagy-mediated lysosomal proteolysis and increases Aβ1–42 clearance. J Neurosci. 2014;34(43):14484–501.
196. Wu X, Miller JA, Lee BTK, Wang Y, Ruedl C. Reducing microglial lipid load enhances β amyloid phagocytosis in an alzheimer's disease mouse model. Sci Adv. 2025;11(6):eadq6038.
197. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet. 2018;391(10130):1622–36.
198. Voss EV, Škuljec J, Gudi V, Skripuletz T, Pul R, Trebst C, Stangel M. Characterisation of microglia during de- and remyelination: can they create a repair promoting environment? Neurobiol Dis. 2012;45(1):519–28.
199. Neumann H, Kotter MR, Franklin RJ. Debris clearance by microglia: an essential link between degeneration and regeneration. Brain. 2009;132(Pt 2):288–95.
200. Zhou LQ, Dong MH, Hu ZW, Tang Y, Chu YH, Chen M, et al. Staged suppression of microglial autophagy facilitates regeneration in CNS demyelination by enhancing the production of linoleic acid. Proc Natl Acad Sci U S A. 2023;120(1):e2209990120.
201. Bogie JFJ, Grajchen E, Wouters E, Corrales AG, Dierckx T, Vanherle S et al. Stearoyl-CoA desaturase-1 impairs the reparative properties of macrophages and microglia in the brain. J Exp Med. 2020;217(5).
202. Ionescu RB, Nicaise AM, Reisz JA, Williams EC, Prasad P, Willis CM, et al. Increased cholesterol synthesis drives neurotoxicity in patient stem cell-derived model of multiple sclerosis. Cell Stem Cell. 2024;31(11):1574–e15901511.
203. Berghoff SA, Spieth L, Sun T, Hosang L, Schlaphoff L, Depp C, et al. Microglia facilitate repair of demyelinated lesions via post-squalene sterol synthesis. Nat Neurosci. 2021;24(1):47–60.
204. Bosch-Queralt M, Cantuti-Castelvetri L, Damkou A, Schifferer M, Schlepckow K, Alexopoulos I, et al. Diet-dependent regulation of TGFβ impairs reparative innate immune responses after demyelination. Nat Metab. 2021;3(2):211–27.
205. Vanherle S, Jorissen W, Dierckx T, Loix M, Grajchen E, Mingneau F, et al. The ApoA-I mimetic peptide 5A enhances remyelination by promoting clearance and degradation of myelin debris. Cell Rep. 2022;41(6):111591.
206. Belov Kirdajova D, Kriska J, Tureckova J, Anderova M. Ischemia-Triggered glutamate excitotoxicity from the perspective of glial cells. Front Cell Neurosci. 2020;14:51.

207. Aarts M, Iihara K, Wei WL, Xiong ZG, Arundine M, Cerwinski W, MacDonald JF, Tymianski M. A key role for TRPM7 channels in anoxic neuronal death. Cell. 2003;115(7):863–77.
208. Xiong ZG, Zhu XM, Chu XP, Minami M, Hey J, Wei WL, et al. Neuroprotection in ischemia: blocking calcium-permeable acid-sensing ion channels. Cell. 2004;118(6):687–98.
209. Yoshida S, Abe K, Busto R, Watson BD, Kogure K, Ginsberg MD. Influence of transient ischemia on lipid-soluble antioxidants, free fatty acids and energy metabolites in rat brain. Brain Res. 1982;245(2):307–16.
210. Owens K, Park JH, Gourley S, Jones H, Kristian T. Mitochondrial dynamics: cell-type and hippocampal region specific changes following global cerebral ischemia. J Bioenerg Biomembr. 2015;47(1–2):13–31.
211. Nakka VP, Gusain A, Raghubir R. Endoplasmic reticulum stress plays critical role in brain damage after cerebral ischemia/reperfusion in rats. Neurotox Res. 2010;17(2):189–202.
212. Gasparovic C, Rosenberg GA, Wallace JA, Estrada EY, Roberts K, Pastuszyn A, Ahmed W, Graham GD. Magnetic resonance lipid signals in rat brain after experimental stroke correlate with neutral lipid accumulation. Neurosci Lett. 2001;301(2):87–90.
213. Wei W, Lattau SSJ, Xin W, Pan Y, Tatenhorst L, Zhang L, et al. Dynamic brain lipid profiles modulate microglial lipid droplet accumulation and inflammation under ischemic conditions in mice. Adv Sci (Weinh). 2024;11(41):e2306863.
214. Doll DN, Hu H, Sun J, Lewis SE, Simpkins JW, Ren X. Mitochondrial crisis in cerebrovascular endothelial cells opens the blood-brain barrier. Stroke. 2015;46(6):1681–9.
215. Jackman K, Kahles T, Lane D, Garcia-Bonilla L, Abe T, Capone C, et al. Progranulin deficiency promotes post-ischemic blood-brain barrier disruption. J Neurosci. 2013;33(50):19579–89.
216. Pan Y, Xin W, Wei W, Tatenhorst L, Graf I, Popa-Wagner A, et al. Knockdown of NEAT1 prevents post-stroke lipid droplet agglomeration in microglia by regulating autophagy. Cell Mol Life Sci. 2024;81(1):30.
217. Arbaizar-Rovirosa M, Pedragosa J, Lozano JJ, Casal C, Pol A, Gallizioli M, Planas AM. Aged lipid-laden microglia display impaired responses to stroke. EMBO Mol Med. 2023;15(2):e17175.
218. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron. 2003;39(6):889–909.
219. Russo T, Riessland M. Lipid accumulation drives cellular senescence in dopaminergic neurons. Aging. 2024;16(14):11128–33.
220. Li Y, Yin Q, Wang B, Shen T, Luo W, Liu T. Preclinical reserpine models recapitulating motor and non-motor features of parkinson's disease: roles of epigenetic upregulation of alpha-synuclein and autophagy impairment. Front Pharmacol. 2022;13:944376.
221. Alecu I, Bennett SAL. Dysregulated lipid metabolism and its role in α-Synucleinopathy in parkinson's disease. Front Neurosci. 2019;13:328.
222. Casadio M. Lipid markers of neurodegeneration. Nat Cell Biol. 2022;24(7):1009.
223. Cole NB, Murphy DD, Grider T, Rueter S, Brasaemle D, Nussbaum RL. Lipid droplet binding and oligomerization properties of the parkinson's disease protein alpha-synuclein. J Biol Chem. 2002;277(8):6344–52.
224. Outeiro TF, Lindquist S. Yeast cells provide insight into alpha-synuclein biology and pathobiology. Science. 2003;302(5651):1772–5.
225. Alza NP, Conde MA, Scodelaro-Bilbao PG, Salvador GA. Neutral lipids as early biomarkers of cellular fate: the case of α-synuclein overexpression. Cell Death Dis. 2021;12(1):52.
226. Brekk OR, Honey JR, Lee S, Hallett PJ, Isacson O. Cell type-specific lipid storage changes in parkinson's disease patient brains are recapitulated by experimental glycolipid disturbance. Proc Natl Acad Sci U S A. 2020;117(44):27646–54.
227. Edison P, Brooks DJ. Role of neuroinflammation in the trajectory of alzheimer's disease and in vivo quantification using PET. J Alzheimers Dis. 2018;64(s1):S339–51.
228. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology. 2018;129(2):343–66.
229. Inoue K, Tsuda M. Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. Nat Rev Neurosci. 2018;19(3):138–52.
230. Navia-Pelaez JM, Choi SH, Dos Santos Aggum Capettini L, Xia Y, Gonen A, Agatisa-Boyle C et al. Normalization of cholesterol metabolism in spinal microglia alleviates neuropathic pain. J Exp Med. 2021;218(7).
231. Kunjathoor VV, Tseng AA, Medeiros LA, Khan T, Moore KJ. beta-Amyloid promotes accumulation of lipid peroxides by inhibiting CD36-mediated clearance of oxidized lipoproteins. J Neuroinflammation. 2004;1(1):23.
232. Scott-Hewitt N, Perrucci F, Morini R, Erreni M, Mahoney M, Witkowska A, et al. Local externalization of phosphatidylserine mediates developmental synaptic pruning by microglia. Embo J. 2020;39(16):e105380.
233. Knobloch M. The role of lipid metabolism for neural stem cell regulation. Brain Plast. 2017;3(1):61–71.
234. Driver AM, Kratz LE, Kelley RI, Stottmann RW. Altered cholesterol biosynthesis causes precocious neurogenesis in the developing mouse forebrain. Neurobiol Dis. 2016;91:69–82.
235. Knobloch M, Braun SM, Zurkirchen L, von Schoultz C, Zamboni N, Araúzo-Bravo MJ, et al. Metabolic control of adult neural stem cell activity by Fasn-dependent lipogenesis. Nature. 2013;493(7431):226–30.
236. Valm AM, Cohen S, Legant WR, Melunis J, Hershberg U, Wait E, et al. Applying systems-level spectral imaging and analysis to reveal the organelle interactome. Nature. 2017;546(7656):162–7.
237. Evans CL, Potma EO, Puoris'haag M, Côté D, Lin CP, Xie XS. Chemical imaging of tissue in vivo with video-rate coherent anti-Stokes raman scattering microscopy. Proc Natl Acad Sci U S A. 2005;102(46):16807–12.
238. Yu Y, Ramachandran PV, Wang MC. Shedding new light on lipid functions with CARS and SRS microscopy. Biochim Biophys Acta. 2014;1841(8):1120–9.
239. Paul A, Wang Y, Brännmark C, Kumar S, Bonn M, Parekh SH. Quantitative mapping of triacylglycerol chain length and saturation using broadband CARS microscopy. Biophys J. 2019;116(12):2346–55.
240. Gilmore IS, Heiles S, Pieterse CL. Metabolic imaging at the Single-Cell scale: recent advances in mass spectrometry imaging. Annu Rev Anal Chem (Palo Alto Calif). 2019;12(1):201–24.
241. Taylor MJ, Lukowski JK, Anderton CR. Spatially resolved mass spectrometry at the single cell: recent innovations in proteomics and metabolomics. J Am Soc Mass Spectrom. 2021;32(4):872–94.
242. Randolph CE, Manchanda P, Arora H, Iyer S, Saklani P, Beveridge C, Chopra G. Mass spectrometry-based single-cell lipidomics: advancements, challenges, and the path forward. TRAC Trends Anal Chem. 2023;169:117350.
243. Han X, Gross RW. Global analyses of cellular lipidomes directly from crude extracts of biological samples by ESI mass spectrometry: a bridge to lipidomics. J Lipid Res. 2003;44(6):1071–9.
244. Kishimoto K, Urade R, Ogawa T, Moriyama T. Nondestructive quantification of neutral lipids by thin-layer chromatography and laser-fluorescent scanning: suitable methods for lipidome analysis. Biochem Biophys Res Commun. 2001;281(3):657–62.
245. Hyötyläinen T, Orešič M. Systems biology strategies to study lipidomes in health and disease. Prog Lipid Res. 2014;55:43–60.

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