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Lipid droplets in central nervous system and functional profiles of brain cells containing lipid droplets in various diseases

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Abstract

Lipid droplets (LDs), serving as the convergence point of energy metabolism and multiple signaling pathways, have garnered increasing attention in recent years. Different cell types within the central nervous system (CNS) can regulate energy metabolism to generate or degrade LDs in response to diverse pathological stimuli. This article provides a comprehensive review on the composition of LDs in CNS, their generation and degradation processes, their interaction mechanisms with mitochondria, the distribution among different cell types, and the roles played by these cells—particularly microglia and astrocytes—in various prevalent neurological disorders. Additionally, we also emphasize the paradoxical role of LDs in post-cerebral ischemia inflammation and explore potential underlying mechanisms, aiming to identify novel therapeutic targets for this disease.

Keywords Lipid droplet, Inflammation, Lipid metabolism, Stroke, Stress

Background

The lipids are crucial small molecule compounds that play essential roles in brain function and homeostasis. They not only serve as structural components of cell membranes and provide fuel for energy metabolism, but also act as vital signaling molecules involved in cellular communication [1].

The lipid droplets (LDs) are recognized as dynamic intracellular organelles that play a crucial role in the storage, metabolism, and distribution of lipids [2]. The are spherical cellular organelles, primarily consisting of two hydrophobic core lipids, triacylglycerol (TAG) and cholesterol ester (CE), enclosed by a phospholipid monolayer and serving as the primary storage site for neutral lipids in neurons, glia cells, and other cells within the CNS (cerebral nervous system) [3, 4]. LDs exhibit a wide range of sizes, spanning from nanometers to microns, and demonstrate highly dynamic properties, as they may undergo changes in size, shape, and composition under stress conditions [5]. LDs play a role in various cellular processes, such as providing substrates for cellular energy metabolism, promoting cell proliferation, responding to metabolic stress, and releasing inflammatory mediators [6–11]. However, the formation mechanisms, composition, biological effects, etc. of LDs triggered by different stimuli vary significantly and may even exhibit contrasting characteristics across various diseases, pathological stages, and cell types.

In this review, we provide a comprehensive review of the biogenesis and degradation processes of LDs in the nervous system, along with an exploration of the diverse roles and regulatory mechanisms governing LD-containing cells in aging, neurodegenerative diseases, cerebral

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ischemia, and glioma. The objective of this review is to enhance our understanding of the involvement of LDs in both physiological and pathological processes within the nervous system.

The composition of LDs

The predominant neutral lipids within the LDs core are CEs and TAGs, with their relative proportions varying according to cell types [12]. For instance, the LD core of adipocytes is predominantly composed of TAGs, whereas that of macrophages primarily consists of CEs [13]. In certain specialized cell types, the LD core may also encompass retinyl esters, waxes, ether lipids, and other lipophilic compounds such as fat-soluble vitamins [14, 15]. These lipids are encased by a polar, amphipathic phospholipid monolayer. In the LDs of mammalian cells, phosphatidylcholine (PC) serves as the predominant surface lipid and is crucial for the emulsification of LDs, functioning as a surfactant for LDs and playing a crucial role in lipid emulsification, regulating morphology and expansion of LD [16]. The following compounds are phosphatidyl ethanolamine (PE) and phosphatidyl inositol (PI). However, compared to other biological membranes, LDs lack phosphatidylserine (PS) and phosphatidic acid (PA) [3, 17, 18].

In addition to the neutral lipid core containing cholesterol esters and triglycerides, the phospholipid monolayer on the surface of LDs also encompasses several proteins involved in lipid metabolism [15, 19–21]. During the process of LD formation, distinct protein groups regulate their development, maturation, and degradation [22, 23]. These proteins can be categorized into two groups based on their origin: Class I proteins are situated in the endoplasmic reticulum (ER) and translocate from the ER to LD during the process of LD formation. Subsequently, they accumulate at the surface of LD via the ER-LD pathway. Class II proteins are localized in the cytoplasm and are directed to the surface of LDs from the cytoplasm as required for development or cellular metabolism [24].

Seipin, a Class I protein primarily localized within the internal membrane tubules of the ER, is involved in the early stages of LD formation by stabilizing TAG clusters and facilitating their recruitment, thereby promoting local aggregation of lipid crystals. Changes in Seipin expression may result in abnormal shapes and quantities of LDs [25–27]. In addition, fat storage-inducing transmembrane protein 2 (FIT2), which is localized within the enrichment regions of ER tubules, not only modulates the morphology of the ER but also interacts with diacylglycerol (DAG) and TAG, leading to their accumulation. Subsequently, FIT2 engages with ER tubule-forming proteins and the cytoskeletal protein septin7 to modulate the curvature of oil lens and facilitates the emergence of nascent LDs [28]. Recently, there has been a report on the phosphatase activity of FIT2, suggesting its involvement in maintaining the balance of phospholipids between the cytosol and the luminal side of the ER membrane [29].

The Perilipin family members (PLIN1 to PLIN5) are additional representative proteins found on the surface of LD categorized as a type II protein, which are considered to be a crucial regulator of LDs [30]. They play a role in the generation, transportation, and circulation of LDs, can shield LDs from lipase-induced dissolution, and contribute to the movement and intercellular signal communication of LDs [31–33].

Each perilipin demonstrates a distinct expression pattern and serves various essential functions: Perilipin 1 (PLIN1) is predominantly expressed in adipocytes and macrophages. PLIN1 can inhibit the activation of Adipose triglyceride lipase (ATGL), thus preventing the hydrolysis of triglycerides, and it plays a crucial role in the biogenesis, stabilization, and maturation of LDs in adipocytes [34]. Meanwhile, PLIN1 predominates and envelops large LDs in macrophages, resulting in the downregulation of lipid efflux proteins ATP-binding cassette transporter A Member 1 (ABCA1) and ATP Binding Cassette Subfamily G Member 1 (ABCG1), a critical process for constraining the development of macrophage inflammatory phenotype and providing protection against atherosclerotic lesions [35].

Perilipin 2 (PLIN2) and Perilipin 3 (PLIN3) exhibit widespread expression in non-adipose tissues [3]. Due to its consistent association with the surface of LDs, PLIN2 accumulation hinders the mobilization of fatty acids for fat breakdown and lipid digestion, thereby safeguarding LDs from degradation. As a result, it is regarded as an indicator of LDs content [36–38]. Accumulation of LDs decorated with PLIN2 occurs during the aging process of the brain. This occurrence may function as an early indication and initial stage of inflammation, early tauopathy, or neurodegenerative conditions such as Alzheimer's disease (AD) [32]. Additionally, PLIN2 has been shown to enhance microglial activation in mice and promote inflammatory responses, as well as nucleotide-binding oligomerization domainlike receptor pyrin domain containing 3 (NLRP3) inflammasome activation, contributing to the pathological process of Oxygen–glucose deprivation/Reperfusion (OGD/R) injury [39].

Perilipin (PLIN3) is the most widely expressed endogenous protein involved in the initial stage of LDs synthesis and serves as a marker for newly formed LDs. This protein is localized in the cytoplasm and promptly accumulates in the newly formed LDs following TAG nucleation, safeguarding TAG aggregates from lipolysis. Deficiency of PLIN3 results in reduced cellular TAG content [40–43]. The Y232 site of PLIN2 and the Y251 site of PLIN3

can undergo phosphorylation by Choline kinase alpha 2 (CHKa2). Phosphorylated PLIN2/3 dissociate from LDs and undergo degradation via autophagy facilitated by 70 kDa heat shock cognate protein (HSC70), thereby facilitating lipid degradation, fatty acid oxidation, and proliferation of the brain tumor [44].

Perilipin 4 (PLIN4) has the capability to interact with the LD membrane and establish a protective barrier, thus safeguarding the LDs from degradation by lipolytic enzymes. This contributes significantly to maintaining the stability of LDs within the cell [45]. Neurons depend on PLIN4 to facilitate the utilization of LDs by mitochondria for β-oxidation during periods of inflammation and oxidative stress [46, 47]. Studies have demonstrated that PLIN4 is upregulated in the brains of toxin-induced Parkinson's disease models, leading to the promotion of LD formation. Additionally, it has been found that a dysfunctional PLIN4/LD/mitochondrial autophagy axis is implicated in the pathological progression of Parkinson's disease, suggesting that PLIN4-LD could potentially serve as both a biomarker and therapeutic target for the condition [47]. In a distinct investigation, the researchers uncovered that SH2B1, operating as an adapter protein, enhanced the interaction between HSC70 and PLIN4, thereby promoting PLIN4's degradation. This mechanism effectively alleviated LD accumulation and oxidative stress in neurons, providing defense against methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonian neurodegenerative disease [48]. Furthermore, PLIN4 represents a crucial target for the probiotic cell extract therapy of Alzheimer's disease [49].

Perilipin 5 (PLIN5) functions as a scaffold for lipases, including ATGL and hormone-sensitive lipase (HSL), thereby stabilizing LDs by inhibiting the interaction of these lipases and suppressing LD hydrolysis. Simultaneously, it reduces the levels of saturated palmitic acid that can be detrimental to mitochondria. When energy demand increases, PLIN5 promotes LD lipolysis through its interaction with lipase enzymes, leading to the production of fat acids (FAs) that are subsequently utilized for mitochondrial β-oxidation [50–52]. Additionally, PLIN5 possesses a unique structure comprising an N-terminal domain homologous to other Perilipin proteins and a distinctive C-terminal region that facilitates recruitment of mitochondria onto the surface of LDs [53–55]. PLIN5 extends beyond its involvement in LD formation and stability, encompassing various pathological processes. Notably, the absence of PLIN5 can induce insulin resistance in muscle cells, provoke heightened ER stress and inflammatory response in the liver, contribute to cardiac dysfunction and impact the progression of conditions such as ischemia–reperfusion injury, atherosclerosis [53, 56–60]. For instance, PLIN5 exerts a protective effect on neuronal OGD/R injury by modulating the nuclear factor erythroid 2-related factor 2 (Nrf2)- protein kinase B (Akt)- Glycogen synthase kinase 3 β (GSK-3β) pathway, decreasing oxidative stress levels such as reactive oxygen species (ROS) and malondialdehyde (MDA), and attenuating the release of pro-inflammatory mediators such as nuclear factor kappa-B (NF-κB) activation. Consequently, the upregulation of PLIN5 represents a survival strategy for neurons under ischemic injury [61].

The biosynthesis of LDs

The formation of LDs can be delineated as a sequential four-stage progression, encompassing nucleation, expansion, budding, and detachment [7].

The contact sites between LDs and ERs in glial cells may play an essential role in the biogenesis of nascent LDs [62, 63]. In glial cells, free fat acids (FFAs) are synthesized de novo within the lipid bilayers of the ER to form LDs. The final step of neutral lipid TAG synthesis is catalyzed by Diacylglycerol O-Acyltransferase 1 (DGAT1) and DGAT2 enzymes, while neutral lipid CEs are synthesized by acyl-CoA cholesterol acyltransferases (ACAT1 and ACAT2) [13, 33, 55]. When the concentration of neutral lipids exceeds their critical level, phase separation occurs, leading to the formation of lens-shaped structures (with a diameter of 20–60 μm) between the ER bilayers [64]. Due to the distinct composition of the dual-membrane cavity surface of the ER compared to the cytoplasmic face, it is possible that asymmetry in monolayer tension plays a role in regulating the direction of LD budding [65]. The reduction of cytoplasm surface tension leads to an increase in the contact angle between developing LDs and the ER, thereby promoting the budding of LDs [66]. After the process of germination, LDs have the capacity to engage in interactions with other cellular organelles, thereby supplying nearby TAGs and fatty acids. Additionally, they may increase in size by merging with other LDs or through lipid synthesis [14].

Degradation of LDs

Similar to other cellular organelles, LDs undergo a biogenesis and degradation cycle, contributing to the maintenance of LD stability [7].

When necessary, FAs are primarily mobilized from LDs through two distinct mechanisms: lipolysis or lipophagy. The process of lipolysis involves the breakdown of neutral lipids in LDs by lipase and certain cofactors [67]. Furthermore, LDs can be engulfed by autophagosomes and then transported to lysosomes, where they undergo hydrolysis into FFAs. This process, known as "lipophagy" [68, 69].

Lipolysis

The regulation of lipolysis involves the interaction between PLINs and lipases, wherein PLINs assume different roles depending on their state [70, 71]. They can either recruit and activate lipases or act as a formidable barrier to prevent lipases from accessing LDs and reduce interactions with lipase coactivators [67, 71–73]. There are three primary enzymes responsible for catalyzing lipolysis [73, 74]: (1) ATGL catalyzes the initial step of lipolysis, and its activity is regulated by coactivator comparative gene identification-58 (CGI-58) and repressor protein G0S2 to fully exert hydrolase activity, thereby converting TAGs into DAGs and FFAs [73, 75, 76]. Patatin-like phospholipase domain containing 2 (Pnpla2) encodes the gene responsible for ATGL. The expression of ATGL is stimulated by various factors, including proliferator-activated receptor (PPAR) agonists, mammalian target of rapamycin complex 1 (mTORC1) inhibition, and forkhead box O 1 (FOXO1) activation [77–79]. Interestingly, the correlation between ATGL activity and mRNA expression levels is not always positive, which may be attributed to post-translational modifications. Furthermore, it should be noted that ATGL modification occurs independently of protein kinase A (PKA) [73, 80]. (2) PKA-responsive lipase E/hormone-sensitive lipase (LIPE/HSL) contains multiple crucial phosphorylation sites that can be targeted by various kinases, particularly PKA, thereby leading to an augmentation of its enzymatic activity [77, 81]. Furthermore, β-adrenergic stimulation could induce HSL enzyme activity, whereas insulin exerts inhibitory effects on both HSL expression and phosphorylation [82, 83]. Subsequently, phosphorylated HSL translocate to LDs, which subsequently facilitate the hydrolysis of DAGs into monoacylglycerol (MAG) and FFAs. (3) Monoglyceride lipase (MGLL/MGL) catalyzes the final step of lipolysis, and transfers MAG into glycerol and FA. The coordinated activity of these three enzymes in the fatty acid pathway results in the production of glycerol and FAs [73, 84].

Lipophagy

In the process of lipid autophagy, double membrane autophagosomes engulf either entire or partial LDs, transport them to lysosomes, and merge with lysosomes containing acid hydrolase enzymes. These enzymes degrade LDs into FFAs, providing energy for the organism and maintaining lipid homeostasis within the cell [69].

Chaperone-mediated autophagy

HSPA8/HSC70 is a homologue of the HSP70 family that is constitutively expressed and serves as an intriguing partner protein. HSP70 fulfills a conserved role in various cellular functions by collaborating with its co-chaperones, including clathrin-mediated endocytosis, protein folding, and regulation of chaperone-mediated autophagy (CMA) [85, 86].

Moreover, PLIN2 and PLIN3, along with the recently identified PLIN5, serve as substrates for lysosomal degradation through the CMA pathway [37, 87]. The CMA process involves the recognition of a five-peptide motif (KFERQ or related sequences) within proteins, leading to the formation of a specific protein subpopulation that is targeted for degradation in the lysosome. During this process, the HSC70 identifies, binds to, and transports the protein to the inner membrane of lysosome-associated membrane protein 2A (LAMP-2A), forming a multimeric complex that facilitates transport of unfolded proteins containing the KFERQ motif into the lysosomal lumen for degradation [86]. Five peptides associated with CMA have been identified in PLIN-2 (LDRLQ) and PLIN-3 (SLKVQ), which undergo degradation via CMA prior to ATGL-dependent lipolysis and lipophagy. Hence, CMA plays a pivotal role in LD degradation [37, 87].

Macrolipophagy

Autophagy-mediated lipolysis, also referred to as macroautophagy of LDs, represents one of the cellular degradation pathways for LDs [68, 69, 73, 88]. Autophagosomes are vesicles with a double membrane that have the ability to encapsulate and transport LDs to the lysosome for degradation.

LDs contribute to autophagosome formation by supplying lipids via enzymes such as PNPLA5 [89]. The autophagy related (ATG) 8 family proteins microtubule-associated protein 1 light chain 3 (MAP1LC3/LC3) or GABARAPs serve as the primary ligands on phagosomes, binding to cargo receptors containing LC3-interacting region (LIR) motifs, however, they do not play a role in LD localization [90]. ATG3 facilitates the binding of ATG8 (LC3) to PE on the autophagosome membrane, which is a crucial step in autophagosome formation. Additionally, the ATG3 protein is also capable of facilitating the binding and esterification of LC3 with LDs, where esterified LC3B recruits autophagosomes through interaction with LC3 on these structures. Autophagosomes expand and engulf complete or partial LDs, which subsequently fuse with lysosomes for degradation into FFAs by acid lipases within lysosomes [91–93].

The recruitment of LDs by lysosomes is also under the regulation of RAB7 [94]. Rab7 is a small guanosine triphosphatase (GTPase) that orchestrates intracellular membrane transport processes and is one of the numerous RAB proteins located on the LD surface. Additionally, it serves as a crucial component of various, degradative compartments, including lysosomes

and multivesicular bodies, playing an essential role in the transport and maturation within the late endocytic pathway [95–98]. As a significant regulator of lipid autophagy, Rab7 becomes activated in diverse degradative organelles under nutrient stress conditions, facilitating the transport of multivesicular bodies and lysosomes to the LD surface through microtubule-mediated regulation, thereby enhancing the degradative metabolism of LDs [94, 99].

Lipolysis and lipophagy may operate as synchronized processes working in conjunction [100]. Interestingly, the role of lipophagy may necessitate the presence of LDs that meet specific size requirements. Smaller LDs can be directly engulfed, while larger LDs exceed the encapsulation capacity of phagocytic vesicles. The reduction in LD size through ATGL-mediated lipolysis is essential. Simultaneously, newly synthesized FFAs are incorporated into small LDs via the ER and subsequently degraded through lipophagy [101]. This phenomenon may be attributed to increased surface tension and membrane curvature induced by the monolayer structure of LDs [102, 103]. The size of LDs targeted by lipidophagy typically falls within the micrometer range or smaller [90].

The three mechanisms of LD degradation are illustrated in Fig. 1.

Interaction between LDs and mitochondria

In addition to lysosomes, LDs can also closely interact with various organelles such as mitochondria and peroxisomes [104]. In fact, LDs have interactions with nearly all organelles, and the directional migration of LDs may depend on the necessity of transporting them to different organelles [105]. Mitochondria, which are crucial for the hydrolytic and oxidative degradation of FAs, play a key role as the primary source of intracellular ATP production [106]. Mitochondrial dysfunction can result in intracellular lipid accumulation, leading to lipid toxicity, lipid peroxidation, and a series of pathological processes that ultimately cause further mitochondrial fragmentation, dysfunction, and even cell death [47, 48]. However, LDs can serve as a buffering mechanism to sequester excess lipids in order to prevent mitochondrial damage [107, 108]. On the other hand, as cellular reserve energy sources LDs transport FAs released from degradation to mitochondria for β-oxidation and ATP production through their interaction during nutrient stress [109]. This process requires colocalization along microtubules followed by directional proximity facilitated by molecular motors between LDs and mitochondria [110–112]. The docking proteins (mainly Perilipins, such as PLIN4 and PLIN5) promote adhesion and interaction between LDs and mitochondria [47, 55, 105, 110, 113]. Mitochondria closely associated with LDs are referred to as peridroplet

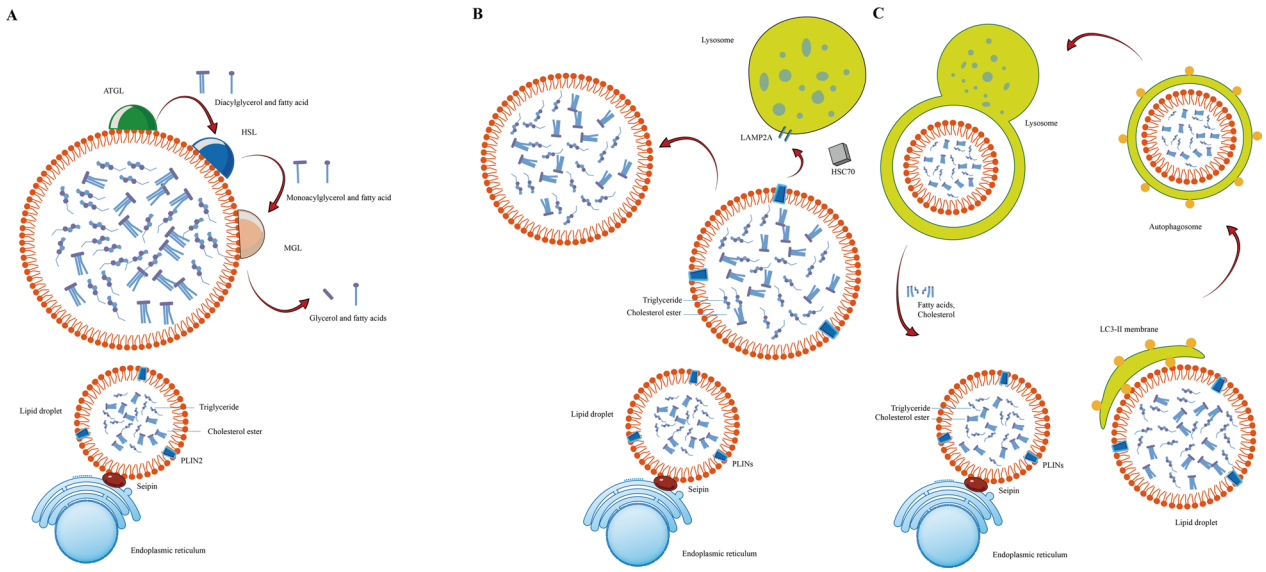

Fig. 1 Three Mechanisms of Lipid Droplet Degradation. **A**. Lipolysis: Triglycerides within lipid droplets are hydrolyzed into glycerol and free fatty acids through the action of three cytosolic lipases: adipose triglyceride lipase ATGL/HSL/MGL. **B**. Chaperone-mediated autophagy: HSC70 identifies a specific sequence in perilipin located on the surface of lipid droplets and facilitates its translocation to lysosomes for degradation. **C**. Macrolipophagy: LC3, functioning as a structural protein of the autophagosome, is conjugated to phosphatidylethanolamine (PE) to form the membrane-bound form LC3-II. The autophagosomes subsequently expand and engulf lipid droplets, which are then transported to lysosomes for degradation. *ATGL* adipose triglyceride lipase, *HSL*: hormone-sensitive lipase, *MGL* monoglyceride lipase, *PLIN2* perilipin 2, *LAMP2A* lysosome-associated membrane protein 2A, *HSC70* heat shock cognate protein, *LC3* microtubule-associated protein 1 light chain 3

mitochondria (PDM) [106]. The significance of PDM lies in establishing a direct FAs transport channel from reservoir LDs to β-oxidation site mitochondria which not only rapidly provides sufficient energy for cells but also limits lipotoxicity caused by excessive release of FFAs from LDs [114].

A potential association between LDs and mitophagy has been proposed. Ionizing radiation induces the accumulation of LDs in close proximity to mitochondria and facilitates the targeted transportation of FAs to mitochondria. However, due to mitophagy, lysosomes engulf mitochondria that interact with LDs and release FFAs into the cytoplasm. However, FFAs within cytoplasm are susceptible to peroxidation, ultimately leading to ferroptosis. Inhibition of mitochondrial engulfment significantly decreases the accumulation of LDs around mitochondria and reduces the level of FFAs under radiation-induced stress. Interestingly, when mitophagy is inhibited, DGAT1 remains highly expressed following exposure to ionizing radiation and may specifically transport FAs released from lysosomes, resulting in a substantial increase in nascent LDs [115].

Certain molecules or pathways with dual roles in lipid metabolism and mitochondrial activity are pivotal in establishing the link between LDs and mitochondria.

Under nutrients restriction, both Sirtuins (sirt) and 5'-prime-AMP-activated protein kinase (AMPK) are activated, thereby triggering the activation of Peroxisome Proliferator-Activated Receptor Gamma, Coactivator 1 Alpha (PGC-1α) through deacetylation or phosphorylation mechanisms, respectively [116–121]. Consequently, this leads to an upregulation in the expression of molecules related to mitochondrial oxidative phosphorylation (OxPhos) via the downstream Nuclear Respiratory Factor-1/2 (NRF1/2)—Transcription Factor A, Mitochondrial (TFAM) pathway [117–120, 122–125]. The loss of TFAM in astrocytes results in impaired mitochondrial OxPhos function, leading to enhanced fat accumulation, reduced FAs degradation, and increased production of ROS [104, 126]. In addition, the regulation of mitophagy by AMPK is mediated through various metabolic pathways in response to intracellular energy fluctuations [127–129].

As a microglia-specific subtype of hexokinase (HK), HK2 plays a dual regulatory role in energy metabolism and mitochondrial function [130]. On one hand, as the rate-limiting enzyme of glycolysis, HK2 promotes energy production to maintain microglial movement, proliferation, and effector functions. On the other hand, HK2 binds to voltage-dependent anion channels (VDACs) on the outer mitochondrial membrane (OMM) to regulate normal membrane potential and permeability while preventing cytochrome C release from mitochondria that would neutralize continuous ROS generation within them [131–133]. Inhibiting HK2 increases lipid metabolism levels while suppressing glycolysis leading to increased mitochondrial ROS levels and accumulation of toxic intermediates that enhance phagocytic function and inflammation levels in microglia [130, 134, 135]. Developing drugs that specifically target kinase activity or the interaction between HK2 and OMM may help selectively modulate HK2 function in microglia cells and potentially have therapeutic implications in disease [130].

The cell types that contain LDs in CNS

LDs have been identified in various types of brain cells, including neurons, astrocytes, oligodendrocytes (OLs), microglia, and ependymal cells [136]. LDs can be formed under a variety of environmental and cellular conditions, such as heightened extracellular lipid concentration, inflammatory events, increased levels of ROS, and alterations in intracellular metabolism [109, 137]. Nevertheless, under physiological conditions, the presence of LDs in the brain is minimal [138]. It is noteworthy that ependymal cells represent the exclusive cell type in the brain capable of generating substantial LDs under non-pathological conditions, even though their quantities are lower in young organisms and escalate with age [139, 140].

Neuron

Apart from cultured neurons found in certain areas like the hippocampus [141], dorsal root ganglion [142], striatum [143], hypothalamus [144], neurons in vivo typically do not gather LDs [142, 145, 146]. The reason is that due to the active oxidative glucose/lactic acid metabolism of neurons during intense activity, neurons accumulate ROS, which may result in ROS-mediated lipid peroxidation of the membrane [141, 147]. Nonetheless, neurons display a restricted antioxidant defense system, and their mitochondria show a diminished capacity for metabolizing FFAs [141]. The β-oxidation of FFAs, in comparison to glucose metabolism, results in a higher quantity of superoxide, which acts as a precursor for most other ROS [145]. This renders neurons particularly susceptible to periods of heightened activity, and neuron death could be induced via apoptosis and neurodegeneration unless neurons eliminate the oxidized FAs by transferring them to glial cells [141, 148]. Furthermore, the neuronal biological membrane can undergo degradation via autophagy and be transformed into FAs, which are then stored as neutral lipids in LDs or lipoprotein particles before being transferred to astrocytes [141].

Astrocyte

Astrocytes, as the most prevalent cell type in CNS, play a crucial role in the regulation of numerous essential brain functions [149, 150].

Astrocyte processes surround blood vessels and neuronal synapses, allowing them to take up FFAs from the bloodstream and extracellular space [151, 152]. FFAs can diffuse into astrocytes and can also be transported across the plasma membrane by fatty acid transporters (FATP) from the solute carrier protein (SLC27) family, such as FATP1 and FATP4 [9]. Additionally, fatty acid binding proteins (FABP), including FABP7, play a role in their uptake [153, 154]. Subsequently, these FFAs are stored within the cells as LDs [155, 156]. Research has indicated that primary astrocytes and astrocytes derived from rat brain tissue can uptake and store excessive exogenous FFAs, such as oleic acid, in LDs [[156, 157]].

Additionally, they function as a pivotal regulator of energy metabolism and provide direct metabolic and antioxidant support to neurons within the central nervous system [158, 159]. Neuronal oxidative stress can induce adjacent astrocytes to form LDs through mediators such as apolipoproteins. Astrocytes increase the breakdown of LDs by responding to neuronal activity and transferring the released FAs into mitochondria as a source of fuel for oxidative phosphorylation to consume FFAs [141, 160]. Furthermore, in contrast to neurons, astrocytes are equipped with a plentiful reservoir of antioxidants, enabling them to effectively mitigate the oxidative stress induced by the β-oxidation of FAs [141, 161–163]..

Astrocytes remain the predominant cellular population that facilitates β-oxidation of FFAs, despite their primary reliance on glycolysis for energy production [94, 164, 165]. Mitochondria within astrocytes play a pivotal role in fatty acid metabolism and exhibit heightened sensitivity to FAs load [104].

Microglia

Microglia serve as the primary immune cells and play a crucial role in safeguarding brain function [130]. Under physiological conditions, resting microglia in CNS exhibit a highly branched morphology and continuously monitor danger signals to maintain brain homeostasis [166]. When exposed to pathological conditions, activated microglia undergo dynamic processes that result in the formation of different response phenotypes based on various signal stimulations [167–169]. These changes are accompanied by alterations in morphology, gene expression, and function, enabling microglia to participate in a diverse range of cell signaling cascades that contribute to either protective or injurious roles [170].

When activated, they alter their transcriptional profile, assume new functions, and may accumulate LDs [171–173]. Activation of inflammation and the phagocytosis of cell/myelin fragments can both contribute to the generation of LDs in microglia [174]. Lipoprotein particles and lipid particles originating from neurons also play a significant role in the generation of LDs in microglia [141, 175].

During the process of aging, age-related inflammatory factors may result in the progressive activation and dysfunction of microglia. This represents a novel detrimental state of microglia characterized by impaired phagocytosis, neuroinflammation, elevated levels of ROS, as well as alterations in lipid metabolism, referred to as 'lipid droplet-accumulating microglia' (LDAM) [172, 176, 177]. This specific subset of activated microglia is also observed in neurodegenerative models and has been proposed as a potential biomarker for early-stage neurodegeneration [162]. Furthermore, it involves certain specific genetic modifiers and is believed to be associated with inherited forms of neurodegenerative diseases [162].

Oligodendrocyte

Oligodendrocyte can produce myelin—a multilayered membrane rich in lipids, particularly cholesterol—that wraps around the axon to facilitate rapid neural signal transmission [178]. OLs are able to utilize both endogenously synthesized cholesterol and exogenously synthesized cholesterol from neighboring cell types for the production of myelin [179]. Immature OLs could synthesize LDs within ER. However, with the assistance of Sigma-1 receptor (Sig-1R), ER-synthesized galactosylceramides (GalCer) and cholesterol are transported to the myelin membrane for completing OLs differentiation and integrating LDs into the myelin sheath [180]. In the context of aging or neurodegenerative conditions, degradation of myelin results in the temporary storage of fatty acids from myelin in LDs within oligodendrocytes. Subsequently, these fatty acids are transferred to astrocytes, where they undergo β-oxidation to produce ketone bodies as an alternative energy source for neurons [181].

Ependymal cell

Unlike other types of glial cells, ependymal cells possess the ability to uptake lipid particles in cerebrospinal fluid via CD36 and Low Density Lipoprotein Receptor-Related Protein (LRP), thereby accumulating LDs under normal physiological conditions. [182–184]. However, the presence of LDs within ependymal cells can also be augmented during aging, obesity and Alzheimer's disease. [139, 140, 185–187]. The involvement of LDs in the functioning of ependymal cells requires further investigation in the future.

The Role of LDs in Neuroinflammation

Inflammation plays a crucial role in the formation of LDs

Lipopolysaccharide (LPS) can activate the TLR4, a pattern recognition receptor on the surface of microglia. This activation subsequently triggers the downstream signaling cascade involving TGFβ-activated kinase 1 (TAK1), mitogen-activated protein kinase kinases (MKKs), and phosphorylated p38 mitogen-activated protein kinases (p38 MAPKs), culminating in the activation of the transcription factor activator protein-1 (AP-1). Additionally, LPS promotes the expression of PLIN2, a crucial surface protein that safeguards neutral lipids within LDs from lipolysis, thereby playing a significant role in the increased number and size of LDs. Furthermore, LPS can upregulate PLIN2 expression via the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway [173].

The components of LDs play a role in the process of neuroinflammation

LDs can engage in various inflammatory signaling pathways by transforming their constituent lipids into active lipid mediators. This process primarily consists of three stages: the presence of precursors for active lipid mediators, the enzymatic conversion of these precursors into active lipid mediators, and the interaction of active lipid mediators with receptors on target cells [188]. Fatty acids, which are esterified and stored within LDs, can be categorized into three primary types: saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs). Notably, PUFAs serve as precursors for the biosynthesis of two major classes of bioactive mediators: pro-inflammatory eicosanoids, primarily derived from ω-6 PUFAs (with the exception of prostaglandin E2 and lipoxins, which exhibit anti-inflammatory properties), and specialized pro-resolving mediators (SPMs), predominantly originating from ω-3 PUFAs [189].

The precursors of these active mediators are distributed in two distinct reservoirs of biological activity: the phospholipid pool and the triglyceride pool. These pools correspond to the monolayer phospholipid shell in the fundamental structure of the LD and the neutral lipid in its core, respectively [190–192]. The former process necessitates the action of phospholipase A2, typically calcium-dependent cytosolic phospholipase A2 alpha (cPLA2α), at the sn-2 position of glycerophospholipids, resulting in the production of lysophospholipids and polyunsaturated fatty acids, including arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) [193, 194]. TAG in ATGL and HSL can undergo the lipolysis pathway to generate the corresponding PUFAs [195, 196]. Cyclooxygenases (COX), Lipoxygenases (LOX), and Cytochrome P450 (CYP) epoxygenases generate both pro-inflammatory eicosanoids and SPMs with anti-inflammatory properties [189]. These lipid mediators can function as ligands for PPARs, G protein-coupled receptors (GPCRs), and TLRs, eliciting inflammatory and immune responses in target cells through autocrine or paracrine signaling mechanisms [189, 197].

In the study conducted by Armen Khatchadourian and colleagues, the co-localization of cPLA2α with induced LDs was observed in microglia activated by LPS [173]. In the research conducted by Huiya Li et al., it has been demonstrated that inhibiting ATGL activity can decrease the secretion of proinflammatory cytokines from microglia in the OGD/R model, thereby enhancing neurological function in a cerebral ischemia–reperfusion in vivo model [174]. The study by Josephine Louise Robb et al. also elucidates the role of ATGL in mediating the breakdown of TAG within LDs, thereby contributing to acute neuroinflammation [198].

The ratio of ω-6 to ω-3 PUFAs might influence the equilibrium of downstream proinflammatory and anti-inflammatory lipid mediators, potentially impacting the overall inflammatory status [199, 200]. Aging can result in chronic modifications to brain lipid metabolism, including a reduction in ω-3 PUFA levels, which may be linked to chronic neuroinflammation associated with the aging process [201]. We hypothesize that the reduction in ω-3 PUFA levels may also manifest in alterations to the lipid composition of LDs in lipid-laden cells within the aging brain. The study conducted by Julia Marschallinger et al. demonstrated minimal changes in the lipid composition of LDs in both young and aged microglia [172]. However, their study does not delve into the more detailed compositional changes within various lipid fractions in LDs, such as alterations in the fatty acid species esterified with TAG. Future research should prioritize this area.

In addition to their role in the synthesis of eicosanoid acids and SPMs, other metabolites derived from these compounds are also implicated in inflammatory processes. For instance, when FA overload occurs in astrocytes, it not only induces the formation of LDs but also results in an excess of acetyl-CoA, an intermediate product of FA metabolism. This surplus of acetyl-CoA surpasses the OxPhos capacity of mitochondria, leading to its detachment from the mitochondria and subsequent acetylation of signal transducer and activator of transcription 3 (STAT3). Consequently, this process mediates the formation of reactive astrocytes and promotes the release of pro-inflammatory cytokines, which in turn activate microglia [104]. Comparable outcomes were observed in the study conducted by Yoon-Hee Kwon

et al. [202]. Another instance, in aged microglia, which exhibit reduced efficiency in clearing myelin debris, cholesterol accumulation within lysosomes results in impaired lysosomal function and the activation of inflammasomes [203].

In addition to the lipid component of LDs, the protein component has also been associated with neuroinflammation in multiple studies. The findings by Xu-Ying Liu et al. demonstrated that PLIN2 can be upregulated in both in vitro and in vivo models of cerebral ischemia–reperfusion injury, thereby exacerbating the inflammatory response and activating the NLRP3 inflammasome [39]. The up-regulation of PLIN2 and pro-inflammatory factors in human brain tissues has been associated with aging and neurodegenerative diseases [32]. Nevertheless, these findings do not entirely preclude the potential impact of lipid components of LDs on inflammatory processes. In the study conducted by Melanie Loix et al., it was found that PLIN2 expression was upregulated by macrophages in a demyelinating disease model of the CNS via the uptake of myelin and activation of the PPARγ pathway. The knockout of PLIN2 not only facilitated the enzymatic lipolysis of LDs in foam macrophages but also mitigated the inflammatory phenotype of these cells [204]. This finding contrasts with the previously mentioned results, which indicate that the ATGL/HSL pathway can generate proinflammatory mediators. We hypothesize that the variation in lipid ligands across distinct disease models may contribute to this phenomenon.

In the demyelination model, cholesterol-rich myelin serves as the primary lipid ligand responsible for the formation of phagocyte LDs. Consequently, it does not supply the active lipid mediator precursors that TAGs provide in the lipolytic pathway induced by PLIN2 knockout. Conversely, cholesteryl esters within LDs are likely to generate inflammatory lipid mediators predominantly via the lipophagy-lysosomal acid lipase (LAL) pathway [205]. Melanie Loix et al. further elucidated that the knockout of PLIN2 did not impact the lipophagy pathway. Notably, their research also demonstrated that the absence of PLIN2 led to a decrease in phospholipid components during LD degradation, suggesting that PLIN2 plays a role in maintaining the phospholipid abundance of LDs. This maintenance is crucial for providing precursors for cPLA2α to facilitate arachidonate production, an effect that was negated by the knockout of PLIN2.This may elucidate that in the disease model of CNS demyelination, the upregulation of PLIN2 sustains the inflammatory phenotype of foam phagocytes, whereas PLIN2 knockdown diminishes this inflammatory phenotype, thus facilitating remyelination following demyelination. However, in the study conducted by Huiya Li et al., cell debris generated through the repeated freeze–thaw cycles of HT22 cell lines in the OGD/R model inadequately represented the substantial quantity of myelin debris produced following ischemic injury. Furthermore, based on the quantitative polymerase chain reaction (qPCR) analysis of genes associated with cholesterol and triglyceride synthesis/metabolism in the in vivo model, the researchers concluded that TAG, rather than cholesterol, constitutes the primary neutral lipid component within LDs during cerebral ischemia–reperfusion injury [174]. This may elucidate that inhibiting ATGL activity in the cerebral ischemia–reperfusion injury model decreases the enzymatic hydrolysis of PUFA from TAG within LDs, consequently diminishing the release of the pro-inflammatory lipid mediator eicanoic acid.

LDs in CNS under various pathological conditions

During the process of brain development and aging, or in pathological conditions such as exposure to detrimental agents, neurodegenerative diseases, and cancer, LDs frequently emerge within the brain [206–210]. Impairment of fatty acid storage in LDs or dysregulation of lipid degradation metabolism in LDs may precipitate the onset of disease [55, 197].

Cerebral ischemic stroke

Inflammatory mechanism

Cerebral ischemic stroke is a critical pathological condition characterized by inflammation and various cellular stress responses, including oxidative stress [61, 136]. The development of LDs in stroke conditions may arise from the synergistic action of various mechanisms [211].

Neuroinflammation serves as a crucial indicator of secondary cellular damage in ischemic stroke [212–214]. The altered post-stroke environment, characterized by ionic imbalance, disruption of crucial neuron-microglia interactions, diffuse depolarization, rapid and widespread acute cell death releasing danger signals and generating substantial tissue debris, as well as necrotic cells releasing their contents into the extracellular environment leading to a robust inflammatory response, induces morphological and phenotypic changes in microglia. This causes them to adopt proinflammatory properties and enhances their phagocytic activity against lipid-rich damaged tissue debris such as myelin/cell debris [215, 216]. These changes may lead to the formation of massive LDs during stroke in response to the disorder caused by ischemia and efforts to restore lost homeostasis [217, 218].

Furthermore, inflammation triggers metabolic changes that promote glycolysis, pentose-phosphate pathway activation, and lipid biosynthesis. These modifications, in conjunction with lipid absorption, drive the formation of LDs, support synthesis metabolism, and facilitate the proliferation of microglia cells. Proliferating microglia

release trophic factors that contribute to the protection and repair [217]. Triggering Receptor Expressed On Myeloid Cells 2 (TREM2), a transmembrane protein responsible for lipid transport [219, 220], is thought to act as a lipid sensor in microglial cells and may link lipid metabolism with microglia-mediated inflammatory progression [172]. In the ischemic stroke model, TREM2 can attenuate inflammation, enhance cholesterol metabolism, inhibit cholesterol conversion into cholesteryl ester through various signaling pathways, thereby inhibiting the formation of CEs-rich LDs [221].

Another potential mechanism involves the disruption of the blood–brain barrier due to inflammation following a stroke, which permits peripheral lipoprotein particles to penetrate the ischemic brain tissue. This process provides essential materials for the formation of LDs [222].

The timing of LD formation during the progression of stroke varies among different studies. In one study, evident LDs were observed in microglia 3 days after middle cerebral artery occlusion (MCAO) surgery [174], whereas Arbaizar-Rovirosa M et al. reported the presence of lipid-laden microglia on the first day after MCAO [223]. Furthermore, an additional study indicated elevated levels of LDs 7 days after stroke induction [211]. A time-dependent investigation of LDs during the 72-h re-oxygenation period following OGD revealed that the initial rise in LD count was transient. Following a peak at 24 h of re-oxygenation treatment, the number of LDs declined. It was suggested that this decline might be attributed to the sustained upregulation of the anti-inflammatory factor Transforming Growth Factor Beta 1 (TGF-β1), which exerts its effects in an autocrine manner [224].

This variation can be attributed to the disparity in the age of mice and the methodology employed for LD identification [174]. The majority of LD formation in cerebral ischemia occurs during the acute phase of the stroke. One potential explanation for this phenomenon is that, at this stage, microglia exhibit their highest level of phagocytic activity. Research indicates that on the first day after focal cerebral ischemia, microglia undergo a morphological transformation into an amoeboid shape, acquire phagocytic properties, and engulf neuron fragments. Following this, microglia continue to proliferate during the initial two weeks and exhibit their highest phagocytic activity in the two days after stroke [225]. Moreover, Li et al. revealed stable levels of LDs at day 14 but a marked reduction by day 30 post-stroke. Therefore, they postulated that the LDs within microglia gradually diminished or were potentially transferred to neighboring cells during the chronic phase of stroke [174].

LDs not only function as a passive lipid reservoir within microglia during stroke, but also serve as a crucial hub for integrating inflammatory signaling and lipid metabolism due to the distinct roles played by different lipid mediators in the inflammatory response. Saturated FAs can activate Toll Like Receptor 2/4 (TLR2/4), triggering an inflammatory response [226]. Hypoxia has been shown to result in the accumulation of saturated FAs, including toxic ceramides and acylcarnitines, as well as activation of the NF-κB transcription factor [227]. Depending on the type of PUFAs present, they can generate corresponding lipid derivatives with either anti-inflammatory or pro-inflammatory properties. These lipid mediators can act as ligands for PPARs, GPCRs, and TLR2/4 respectively, participating in inflammatory signaling pathways [189]. The derivatives derived from unsaturated long chain n-6 FAs generally exhibit pro-inflammatory effects; however, unsaturated long chain n-3 FAs inhibit TLR2/4 expression while activating PPARs to suppress NF-κB transcription and dampen the inflammatory response [226]. As a dynamic buffer for these lipids and their derivatives, LDs have the ability to modulate signal transduction effects accordingly.

Several studies have demonstrated that LDs in certain peripheral blood cells play a crucial role as an inflammation regulator in various disease processes. As previously mentioned, ATGL and HSL are the two primary enzymes involved in the process of lipolysis. In the peripheral blood, deficiency of ATGL can result in impaired macrophage phagocytosis, reduced migration and infiltration capacity, accompanied by the attenuation of inflammatory mediators such as Prostaglandin E 2 (PGE2) and Interleukin 6 (IL-6), thereby exhibiting an anti-inflammatory phenotype [228, 229]. Within mast cells, LD serves as the primary bioactive reservoir of endogenous arachidonate and provides an active site for enzymes involved in arachidonic acid oxidative metabolism. Meanwhile, ATGL facilitates the release of these inflammatory lipid mediators through lipolysis [230, 231]. Additionally, ATGL and its coactivators also participate in modulating inflammatory signaling by regulating the availability of these inflammatory lipid precursors within other leukocytes [196].

The activation of HSL within adipocytes in response to isoproterenol can enhance lipolysis. Subsequently, the FAs produced by HSL stimulate the upregulation of COX2, a crucial pro-inflammatory molecule, through the activation of JNK/NF-κB pathway. This leads to the recruitment of monocytes/macrophages via monocyte chemoattractant protein-1 (MCP-1) and subsequent immune infiltration [232]. Activation of the sphingosine kinase 1 and JNK signaling pathways, which are dependent on HSL, can also activate the β-adrenergic signaling pathway, resulting in upregulation of pro-inflammatory genes such as IL-6 [233].

Within the confines of the central nervous system, the inhibition of ATGL leads to significant enhancements in neurological function in MCAO mice, indicating that LDs exert a neuroprotective effect during the acute phase of cerebral ischemia [174]. However, the findings of other studies, present a contrasting perspective. The research conducted by Lin et al. demonstrated that LDs significantly accumulated in microglia within the OGD model, accompanied by an elevation in the production of inflammatory cytokines. The suppression of LDs formation markedly diminished both the infarct size and the motor function deficits in rats subjected to cerebral ischemia [234]. Similarly, the research conducted by Pan et al. demonstrated that the silencing of NEAT1 significantly inhibited LD formation and enhanced neuronal viability, consequently mitigating ischemic brain injury in MCAO mice [211]. It remains to be elucidated whether LD is a causative factor of inflammation, a consequence thereof, or if both elements exert mutual influence on one another [224].

After an ischemic event, microglia in aged mice demonstrate a higher presence of LDs compared to young mice. The re-proliferation of microglia leads to a reduction in the accumulation of LDs in newly generated microglia and contributes to the enhancement of motor function in aged mice following ischemic events [223]. It is evident that the cell division necessary for microglia regeneration utilizes LDs, potentially resulting in pro-repair phenotypes linked to microglial proliferation [8]. Instead, the persistent accumulation of lipids by microglial cells may lead to long-term functional dysregulation similar to that observed in foam cells [217].

The latest findings reveal a strong association between lipid peroxidation and ferroptosis, with lipid phagocytosis playing a crucial role in providing substrates for lipid peroxidation during the process of ferroptosis. Additionally, it initiates lipid release and subsequent lipid peroxidation, ultimately worsening the condition of patients with cerebral ischemia [235,236].

Stress response mechanisms

In addition to inflammation, the accumulation of LDs is also linked to various stress stimuli [136]. Common stressors include metabolic stress (resulting from nutrient deprivation, excessive exogenous FFAs or l-lactate), hypoxic stress, and the central nervous system's stress response activated by norepinephrine through the activation of alpha-2- and beta-adrenergic receptors (α2-AR/β-AR). These stressors are frequently encountered in various pathologies of the central nervous system, resulting in astrocytes accumulating LDs under these challenging conditions (Fig. 2) [156].

Starvation and hypoxia are the most immediate stressors during ischemic stroke, which may act as stimuli for the accumulation of LDs in astrocytes to shield neurons from stress-induced lipid toxicity.

The cellular nutritional state exerts a paradoxical influence on LD formation. As the predominant glial cells in CNS, astrocytes function as metabolic sensors and exhibit rapid responses to exogenous nutrient levels, accumulating LDs in conditions of obesity or diabetes characterized by elevated fatty acid concentrations [202, 237, 238]. Conversely, LDs can also develop in the absence of nutrients [109, 239, 240]. With the prolonged duration of starvation, starved cells can enhance autophagy activity to facilitate the degradation of cellular membranes and the recycling of FAs into LDs, thereby increasing both the number and volume of LDs. This dynamic process has been validated by Angelika S. Rambold et al. through the utilization of a fluorescent FA probe technique [109]. This mechanism effectively mitigates lipid toxicity induced by elevated FFAs while simultaneously priming substrates for subsequent mitochondrial metabolism [108, 109,157, 241, 242]. During periods of nutrient deprivation, astrocytes undergo a metabolic shift towards lipid metabolism to prioritize the remaining glucose for neurons, thereby enhancing neuronal vitality [243]. During extended periods of glucose deprivation, the stored free FFAs in astrocyte LDs can undergo conversion into ketones. These ketones serve as an alternative energy source that can be transported to neurons, thereby enhancing neuronal vitality in the absence of glucose [244, 245].

In ischemic diseases, hypoxia occurs in addition to glucose deprivation [246], leading to anaerobic metabolism and the accumulation of l-lactate through glycolysis. L-lactate is released from neurons and may build up in the extracellular space, which could induce LDs accumulation within astrocytes [156, 247, 248]. After an elevation in l-lactate levels within the brain, the activation of l-lactate receptors found on the surfaces of astrocytes and neurons, such as the Gi protein-coupled l-lactate-sensitive receptor GPR81, stimulates the accumulation of LDs. This activation results in a decrease in cAMP production, inhibition of cAMP-dependent lipolysis enzymes, and promotion of LDs accumulation [249–251]. L-lactate can also be transported into astrocytes via monocarboxylic acid transporters (MCTs) and lactate channels, where it can serve as a substrate for the re-synthesis of FFA [252]. This may induce the accumulation of LDs in astrocytes as a protective mechanism against the detrimental impact of excessive FFAs [9,141, 162, 163].

Under conditions of nutrient deprivation, astrocytes, which primarily metabolize lipids, exhibit an upregulation in the production of ROS precursors [145]. In

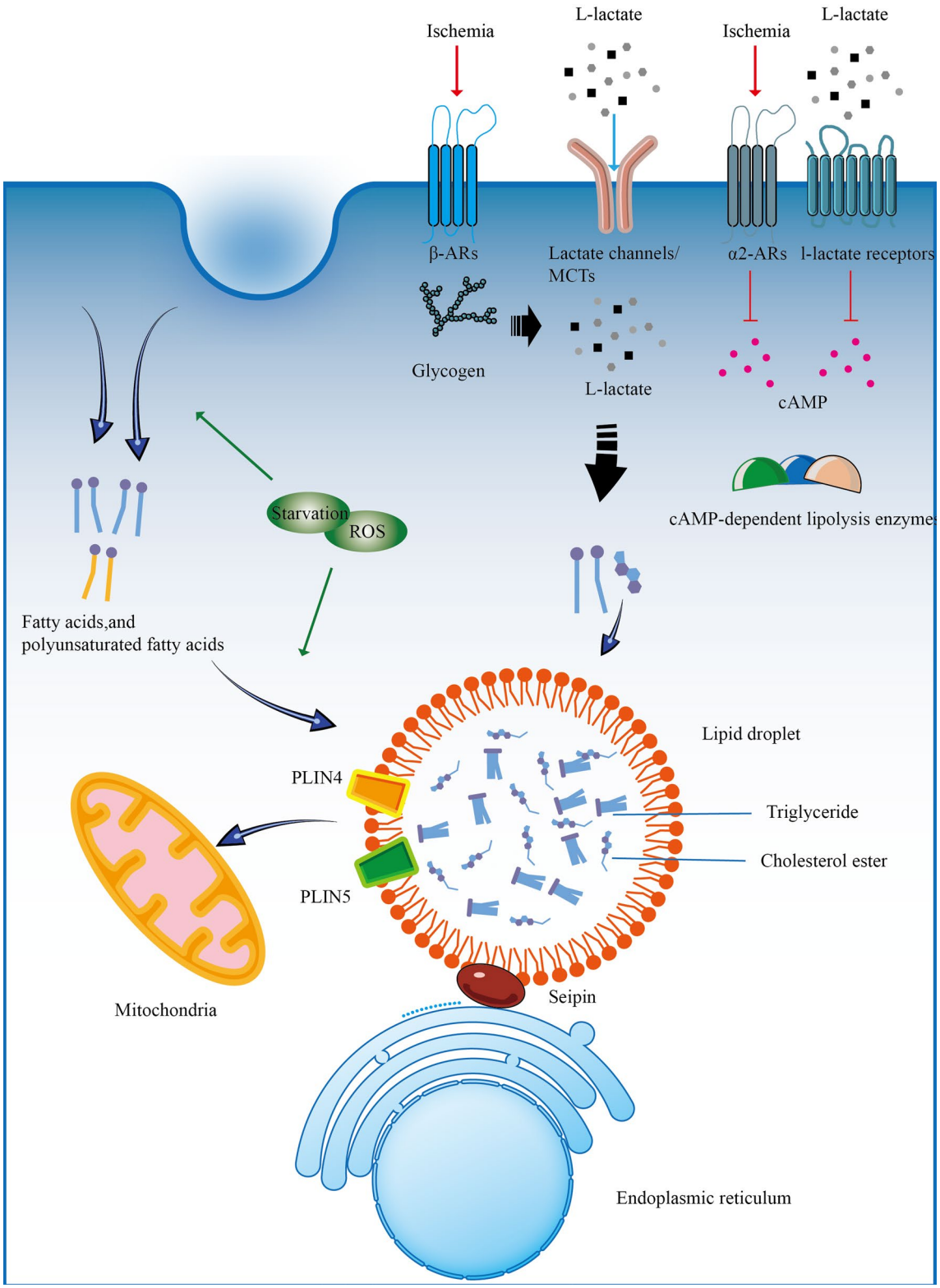

Fig. 2 Lipid droplets formation in astrocytes during cerebral ischemia. Astrocytes could accumulate lipid droplets under various stress stimuli such as nutrient deprivation, hypoxia, elevated ROS and activation of adrenergic receptors. *α2-AR* alpha-2-adrenergic receptors, *β-AR* beta-adrenergic receptor, *MCT* monocarboxylic acid transporter, *ROS* reactive oxygen species. *PLIN* perilipin

response to heightened ROS levels, astrocytes activate hypoxia-inducible factor 1/2 (HIF-1/2) pathways to facilitate the transfer of membrane PUFAs into LDs, thereby safeguarding them against peroxidation [163, 253].

The presence of norepinephrine stress is also observed in ischemia and reperfusion (I/R) [254, 255]. Norepinephrine can regulate lipid metabolism in astrocytes during ischemic stroke through the activation of β-adrenergic and α2-adrenergic receptors [156]. Stimulation of α2-AR inhibits cAMP-dependent lipolysis while promoting LD accumulation, whereas stimulation of β-AR enhances L-lactate production to promote LD formation [156,256,257].

Alzheimer's disease

In mouse models of Alzheimer's disease, LD accumulation precedes the development of the two primary hallmarks of the disease, namely β-amyloid plaques and tau protein-based neurofibrillary tangles [187, 258].

Neuroglia can shield neurons from lipid toxicity by uptaking lipids generated by neurons and forming LDs, with Apolipoprotein E (ApoE) playing a crucial role in this process [9,10]. ROS at elevated levels can trigger neurons to generate LDs. Unlike astrocytes, neurons are unable to efficiently utilize FFA as a source of energy due to their inability to regulate the excessive ROS production by mitochondria during the β-oxidation process [145, 160, 164]. The neuronal lipid transporters ABCA1 and ABCA7 are essential for the assembly of neuronal lipids and their integration into ApoE/D particles originating from astrocytes [259]. Lipoprotein particles are internalized by astrocytes through endocytosis, leading to the release of FFAs and their incorporation into LDs, thereby mitigating the detrimental effects of FFAs [141]. The research results of Mi et al. in the AD mouse model indicate that the formation of astrocyte LD functions as a primary protective mechanism against brain lipid toxicity, rather than triggering reactive neuroinflammation [104].

APOE4 represents the most significant genetic predisposing factor for AD [260]. The dysregulation of lipid homeostasis, characterized by an increase in lipid anabolism, was observed in ApoE4 microglia and astrocytes derived from induced pluripotent stem cells (iPSCs), potentially contributing to the accumulation of LDs in ApoE4 cells [209, 261]. Moreover, APOE4-induced LDs result in the impairment of microglial surveillance function within neuronal networks, thereby compromising their ability to monitor neuronal activity [209]. ApoE4 microglia demonstrate compromised mitochondrial oxidative capacity to metabolize FAs and exhibit downregulation of genes involved in lipid catabolism, thereby further contributing to the accumulation of LDs and the development of pro-inflammatory microglia in AD [209,262–264]. ApoE4 neurons are capable of accumulating LDs, and the cholesterol contained within these LDs can elevate p-tau levels, a process that may be mitigated by inhibiting the cholesterol synthesis pathway [265, 266]. Furthermore, ApoE4 neurons may impair astrocytic clearance of neuronal lipids [267].

Tau protein pathology represents a key feature of Alzheimer's disease [258], with abnormal accumulation of LDs observed in the brains affected by tau protein disorders. Unsaturated lipids originating from tauopathy iPSC neurons and transferred to microglia have the potential to cause LD accumulation, potentially by inhibition of neuronal AMPK signaling. AMPK possesses the capacity to inhibit lipid synthesis in neurons and promote lipid phagocytosis, thus reducing lipid flow to microglia. Deletion of AMPK from neurons in the early stages of Tau protein pathology can result in an increase in the expression of genes involved in LD synthesis, such as PLIN3 and lipid phosphate phosphohydrolase (lpin1), leading to elevated LD content and exacerbation of pro-inflammatory microglia proliferation, thereby promoting neuropathology [2].

Lower levels of lipoprotein lipase (LPL) have been observed in the central nervous system of AD patients [268]. Research has shown that a lack of LPL in microglia leads to an increase in LD accumulation [269]. Deficiency of LPL in microglia results in a polarization towards a pro-inflammatory state, characterized by compromised lipid uptake and reduced fatty acid oxidation (FAO), along with elevated cholesterol ester levels and diminished cholesterol efflux. Additionally, LPL-deficient microglia display pro-inflammatory lipidomic signatures [269, 270].

Neuroinflammation is recognized as a key biomarker of Alzheimer's disease, typically linked to dysregulations in cholesterol metabolism [271]. Neuroinflammation initiates the activation of microglia, which exhibit elevated levels of Cholesterol 25-Hydroxylase (Ch25h), an enzyme responsible for hydroxylating cholesterol to generate 25-hydroxycholesterol (25HC). 25HC is an oxidized steroid that plays a crucial role in the regulation of cholesterol metabolism in mangy cell types within CNS including astrocytes [272]. In astrocytes exposed to 25HC, this compound enhances the activity of Sterol O-acyltransferase 1 (SOAT1) also referred to ACAT1, resulting in a twofold increase in cholesterol esters and an accumulation of LDs, effects that can be inhibited by SOAT/ACAT inhibitors [273].

Glioma

Due to the rapid proliferation, active metabolism, and strong invasiveness of malignant glioma, there is

an increased nutritional demand for tumor cells that necessitates metabolic changes which are characterized by heightened lipid uptake, synthesis, and storage in response to elevated glucose consumption [274–276]. Previous studies have indicated that compared to normal brain tissues, malignant gliomas exhibit higher levels of various lipid classes, particularly CE [275, 277, 278]. These distinct lipids not only serve as crucial energy reservoirs during tumor progression but also play a significant role in oncogenic signal transduction [279, 280]. Consequently, they can potentially be utilized as markers for diagnosing and prognosticating high-grade glioma. Sterol regulatory element-binding proteins-1 (SREBP-1) acts as a vital metabolic regulator of these differential lipids and is specifically upregulated in high-grade gliomas [281–283]. In response to increased cholesterol demand, the inactive complexes of SREBPs and SREBP cleavage-activating protein (SCAP) initially bound to the ER membrane dissociate from insulin-inducible gene protein (Insig), which is also located on the ER membrane. Subsequently, they are transported to the Golgi apparatus for two proteolytic activations before transforming into nuclear transcription factors that promote ER cholesterol synthesis. The process is effectively summarized by Cheng et al. [280]. However, this process is sensitive to elevated cholesterol concentrations within the ER; excess cholesterol can be esterified into CE by SOAT and stored within LDs [282,284].

As previously noted, LDs can mitigate ferroptosis by sequestering lipid substrates, while lipophagy plays a crucial role in the ferroptosis process [235, 236]. Furthermore, study has demonstrated that ionizing radiation—an essential modality for eradicating malignant tumors—induces the accumulation of LDs adjacent to damaged mitochondria and facilitates the transport of fatty acids to these organelles. During mitophagy, compromised mitochondria release FFAs into the cytoplasm, thereby supplying substrates for ferroptosis [115]. We propose that in malignant tumors utilizing LDs as supplementary energy sources, enhancing either lipophagy or mitophagy may serve as viable strategies for inducing ferroptosis in tumor cells, representing a promising avenue for therapeutic intervention.

Glioma-associated microglia/macrophages (GAMs) constitute a critical component of the glioma microenvironment [285, 286]. Glioma cells enriched with LDs facilitate the recruitment, infiltration, and functional alterations of GAMs via paracrine signaling [287]. By establishing a highly immunosuppressive microenvironment and secreting factors that facilitate neovascularization, GAMs contribute to the progression and drug resistance of GBM, often correlating with poor patient prognosis [287, 288]. Targeting the lipid metabolism of gliomas can modulate the function of GAMs and revert the immunosuppressive microenvironment [289]. Additionally, the immune cells that regulate these tumor microenvironments can serve as potential therapeutic targets for GBM [290].

Aging

The accumulation of LDs is not only associated with pathological processes, but also with physiological processes such as aging. LDs are primarily found in microglia (LDAM) during aging, rather than other cell types [172].

A key factor contributing to the formation of LDAM is the decline in phagocytosis, which mainly manifests as impaired lysosomal function associated with aging. This leads to a weakened ability for macrolipophagy and CMA-mediated lipophagy to effectively degrade LDs within LDAM [291–295]. Aging can induce M1 polarization of microglia and upregulate the expression of pro-inflammatory genes [296, 297]. The enhancement of microglial proinflammatory response, as previously discussed, would augment their phagocytic activity, paradoxically, this contrasts with the reduced phagocytosis observed in LDAM [172, 294].

We postulated that age-related inflammation may modify the metabolic profile of microglia and facilitate an elevation in lipid anabolism [178]. However, due to mitochondrial dysfunction associated with aging, the augmented synthesis of FAs cannot be timely metabolized and oxidized [291, 298, 300]. Consequently, these FAs are initially sequestered within LDs as a protective measure against lipid toxicity resulting from excessive accumulation. Additionally, LDAM lacks sufficient energy for driving morphological changes and performing phagocytic functions [217]. Furthermore, unlike pathological conditions where there is a significant amount of material available for phagocytosis, physiological aging does not involve such extensive uptake.

In addition, the aging of mitochondrial function leads to increased production of ROS, while the reduced level of autophagy hinders timely removal of aging mitochondria. On one hand, ROS accumulation can mediate the expression of inflammatory factors associated with oxidative stress; on the other hand, it can initiate LD accumulation to accommodate protective unsaturated lipid components in response to oxidative stress [163, 253, 291]. On the contrary, it has been demonstrated that LD accumulation in LDAM can elevate cellular ROS burde [178]. Conflicting reports exist regarding whether ROS is a cause or consequence of LD formation [301,302].

The mechanisms underlying the monitoring and phagocytic clearance of microglial cells, which fulfill phagocytic functions within the central nervous system,

remain poorly elucidated [294, 303]. Targeting LDAM may represent an appealing therapeutic approach for delaying aging and age-related neurodegeneration.

Discussion

This review summarizes the composition, biogenesis, and turnover of LDs in CNS. It also examines the distinct formation mechanisms of LDs across various cell types under diverse pathological conditions, their biological functions, and their interactions with neuroinflammation. LDs serve not only as passive lipid storage compartments, but also play a pivotal role in the initiation and progression of diverse pathophysiological processes, such as stress, neuroinflammation, and energy metabolism, depending on the state of the central nervous system (e.g., ischemia, neurodegeneration, and aging) [21, 55, 110, 304]. As the two most prevalent types of glial cells in CNS, microglia and astrocytes containing LD exhibit distinct functional phenotypes, which can either confer protection against disease effects on the CNS or exacerbate disease progression [172,173]. LDs in microglia are primarily linked to inflammation, along with alterations in microglial phenotype and their phagocytic function. Conversely, astrocytes typically exhibit LD formation in response to stressors such as lipid toxicity. Revealing the functional phenotypes of various LD-containing glial cells could serve as the fundamental focus in endeavors to postpone the onset and progression of the disease [305].

In recent years, extracellular vesicles (EVs) have emerged as a focal point in the investigation of physiological and pathological processes within the nervous system [306–308]. LDs exhibit a comparable morphology and structural composition to EVs. Nevertheless, there is a paucity of research dedicated to their comparative analysis. Here, we delineate the similarities and distinctions between these two entities concerning their composition, dimensions, biosynthetic and degradative pathways, sites of biological impact, classification, and methodologies for isolation and detection (Table 1). Owing to technological constraints, prior research has predominantly focused on the physicochemical attributes and biological behaviors of LDs within cellular environments, precluding their isolation ex vivo to achieve high-purity samples. Furthermore, the absence of a comprehensive classification and nomenclature framework for LDs has led to a less nuanced understanding of their heterogeneity compared to that of EVs [309, 310]. The burgeoning advancements in EVs separation and detection technologies suggest that novel techniques will likely facilitate the isolation and purification of LDs, thereby enabling a more precise characterization and enhancing our comprehension of the distinct roles LDs play in various neurological disorders [309]. Additionally, the influence of the interplay between LDs and EVs on both intra- and extracellular communication remains an intriguing area of inquiry.

Neuroinflammation facilitates lipid exchange between brain cells and between brain cells and the peripheral circulation. This process encompasses the cellular uptake of exogenous lipids and the efflux of intracellular lipids. Exogenous lipid sources encompass dead cells and myelin debris, amyloid β peptides (Aβ), and lipoprotein particles that are transferred between cells and from the peripheral bloodstream. Lipids in peripheral blood form complexes with apolipoproteins to create lipoprotein particles, which can traverse the blood–brain barrier, particularly when it becomes more permeable due to inflammatory conditions, thereby entering brain tissue [264]. Microglia facilitate the enhanced uptake of these lipoprotein particles through the up-regulation of Low-Density Lipoprotein Receptor (LDLR), TREM2, and LPL [311–313]. Astrocytes may also acquire lipids from alternative cellular sources, including APOE secreted by active neurons, to alleviate the lipid burden within neurons [141]. The internalized lipoprotein particles serve as a source of lipids, such as fatty acids and cholesterol, for these glial cells.

However, neuroinflammation induces lipid efflux in various cell types within the CNS, such as neurons, astrocytes, and microglia, as well as pericytes and endothelial cells, which are critical components of the blood–brain barrier [314–316]. These cells frequently efflux cholesterol via two primary mechanisms: firstly, by upregulating cholesterol 24S-hydroxylase (CYP46A1), which facilitates the conversion of cholesterol into 24(S)-hydroxycholesterol (24-OHC), a compound capable of freely crossing the blood–brain barrier [317]. Secondly, the activation of liver X receptor (LXR) by intracellular fatty acids, cholesterol, and their metabolites enhances the expression of ATP-binding cassette (ABC) transporters, which facilitate the transport of cholesterol to extracellular apolipoprotein-containing lipoprotein particles [318, 319]. Furthermore, Shiraz Dib et al. introduced an alternative mechanism of cholesterol efflux that involves passive diffusion [314].

Cholesterol efflux and the esterification of cholesterol into LDs may function as complementary passive mechanisms to restore cellular homeostasis by alleviating the intracellular lipid burden [203]. In the study conducted by Anil G. Cashikar et al., the simultaneous occurrence of cholesterol esterification and cholesterol efflux via the LXR/ABCA1 pathway was observed in astrocytes exposed to inflammation-induced microglial secretion of 25HC [273].

As previously discussed, LDs have exhibited paradoxical proinflammatory or anti-inflammatory effects

Table 1 The contrast between lipid droplets and extracellular vesicles

	Lipid Droplets (LDs)	Extracellular Vesicles (EVs)
The Structure and Composition	As previously mentioned, the outer layer of LDs consists of a monolayer composed of phospholipid membrane, while the contents primarily consist of neutral lipid TAG and CE, along with a small quantity of lipophilic compounds. Currently, there is no available information regarding the presence of proteins or nucleic acids within the contents [309]. LD proteins are exclusively localized on the phospholipid monolayer and play crucial roles in various processes such as LD formation, development, maturation, degradation, and interaction with intracellular organelles	The outer layer of EVs is composed of a bilayer of phospholipids, while their contents encompass nucleic acids, proteins, lipids, cytokines, metabolites and other biomolecules that can reflect the status of parental cells [306, 322, 323]. The composition and abundance of these vesicular contents will undergo dynamic changes in accordance with different cell types and conditions [324–326]. Furthermore, these contents serve as crucial mediators for intercellular communication by being exchanged with different target cells to exert specific biological effects based on varying requirements [327, 328]
Size	40–100 nm The size of LDs can dynamically alter in response to various stimuli	Small (20–200 nm): exomeres (> 50 nm), supermeres (> 25 nm), exosomes (40–200 nm) and defensosomes Large (200 nm-10 μm): Microvesicles (100 nm-1 μm), migrasomes (500–3000 nm), apoptotic bodies(50 nm-5 μm) and large oncosomes (1–10 μm) [309]
Biogenesis	Neutral lipids are synthesized and accumulated within the lumen of the endoplasmic reticulum (ER), undergoing a series of sequential stages including nucleation, expansion, budding, and detachment to ultimately form mature LDs	Endocytic pathway: The cytosol undergoes invagination to generate early sorting endosomes (ESEs) and matures into late sorting endosomes (LSEs), which are facilitated by ESCRT (endosomal sorting complex required for transport) proteins and cargo sorting, resulting in the formation of intraluminal vesicles (ILVs). Eventually, LSEs transition into multivesicular bodies (MVBs), which subsequently merge with the plasma membrane, leading to the extracellular release of ILVs [329–331] Plasma membrane pathway: The extracellular microvesicles generated through this pathway are typically large in size and result from the outward budding of the plasma membrane. Subsequently, they are released into the extracellular space after selectively incorporating proteins, nucleic acids, and lipids [332, 333]
Categorization	The current classification standard is not yet clearly defined	The classification of EVs is based on their biogenesis pathway, size, density, and biophysical characteristics [306, 309]
Degradation	Lipolysis, chaperone-mediated autophagy and macrolipophagy	The recipient cells have the ability to internalize EVs, which can subsequently undergo degradation through the autophagolysosomal pathway [334]
Cell origin	LDs can be observed in various types of brain cells during pathological conditions, with astrocytes and microglia being the most frequently affected. However, ependymal cells are the sole cell type within the brain that is capable of physiologically generating LDs	The release of EVs is a capability possessed by nearly all types of cells [307]
Site of action	The LDs typically engage in intracellular interactions with organelles such as mitochondria and endoplasmic reticulum, or actively participate in cell signaling pathways through their own protein or lipid constituents. In essence, their primary localization is within the cytoplasm	The EVs in the central nervous system (CNS) have the ability to traverse the blood–brain barrier and be released into both the bloodstream and cerebrospinal fluid (CSF), or they can be internalized by neighboring cells to facilitate intercellular communication [308, 335, 336]
Isolation	The isolation of LDs is typically performed from cell or tissue lysates rather than from cell culture media or biological fluids. Currently, there are no established guidelines for the isolation process	EVs are typically isolated from cell culture media or biological fluids based on their size, density, subcellular origin, and molecular composition. The focus is primarily on eliminating extracellular contaminants such as proteins, cell debris, and other overlapping subsets of EVs [309, 337]. However, achieving complete isolation and purification of EVs remains challenging; therefore, it is recommended to employ a combined complementation method. The method of density gradient ultracentrifugation is extensively employed for the isolation of EVs [338–340]

Table 1 (continued)

	Lipid Droplets (LDs)	Extracellular Vesicles (EVs)
Detection	The intracellular LD was primarily subjected to analysis. Fluorescence-based microscopy: Bodipy, a fluorescently labeled antibody targeting LD protein markers [341]. Non-fluorescence based microscopy: stimulated Raman light scattering microscopy, atomic force microscopy (AFM) [342, 343]	The isolated EVs were detected. The commonly used testing methods include Nanoparticle tracking analysis (NTA), tunable resistive pulse sensing (TRPS), high-resolution flow cytometry etc. [344–346]

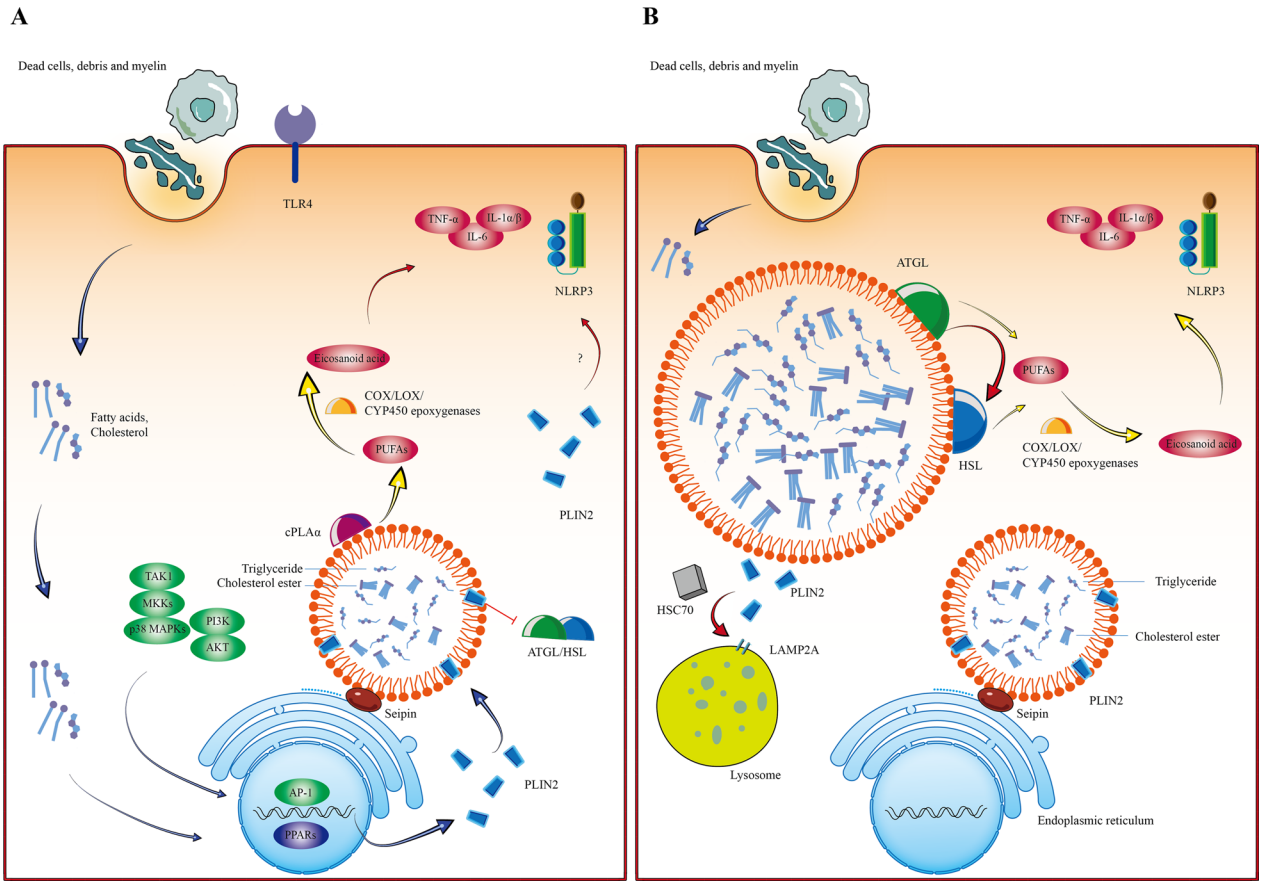

Fig. 3 Distinct Mechanisms Underlying the Proinflammatory Effects of Lipid Droplets in the Two Stages Following Cerebral Ischemia–Reperfusion Injury. **A**: PLIN2 assumes a pivotal role in the process by which lipid droplets contribute to neuroinflammation during the early stages following cerebral ischemia–reperfusion injury. **B**: In the later stages following cerebral ischemia–reperfusion injury, the ATGL/HSL pathway serves as the primary mechanism for the degradation of triglycerides within lipid droplets, thereby supplying precursors essential for the synthesis of inflammatory lipid mediators. This pathway is a critical factor in the promotion of neuroinflammation by lipid droplets. *TLR4* Toll Like Receptor 4, *TNF-α* tumor necrosis factor α, *IL* Interleukin, *NLRP3* nucleotide-binding oligomerization domain like receptor pyrin domain containing 3. *COX* cyclooxygenase, *LOX* Lipoxygenases, *CYP* Cytochrome P45, *cPLA2α* calcium-dependent cytosolic phospholipase A2 alpha, *PUFAs* polyunsaturated fatty acids, *TAK1* TGF-β-activated kinase 1, *MKKs* mitogen-activated protein kinase kinases, *p38 MAPKs* phosphorylated p38 mitogen-activated protein kinases, *AP-1* activator protein-1, *PI3K* phosphatidylinositol 3-kinase, *AKT* protein kinase B, *ATGL* adipose triglyceride lipase, *HSL* hormone-sensitive lipase, *PLIN* perilipin, *LAMP2A* lysosome-associated membrane protein 2A

following I/R in various studies. We hypothesize that cPLA2α and ATGL/HSL may facilitate the production of inflammatory lipid mediators at distinct time points post-I/R, thus contributing to the neuroinflammatory signaling pathway (Fig. 3).

Acute inflammation may play a role in the up-regulation of PLIN2 within one day following I/R [39, 173]. Additionally, the substantial quantity of FFAs generated through the process of microglia engulfing and degrading cell death debris and myelin can induce PLIN2 expression via the stimulation of PPAR [204, 320]. It has been demonstrated that the upregulation of PLIN2 precedes the increase in the number of LDs [173]. Furthermore, PLIN2 may play a role in the upregulation of inflammatory levels following I/R, as previously mentioned, and it may also protect nascent LDs from lipolysis by ATGL/HSL [31]. On the other hand, inflammation can activate cPLAα to generate inflammatory lipid mediators through the decomposition of glycerol phospholipids, thereby participating in the acute inflammatory response following I/R [321]. Concurrently, PLIN2 may play a role in sustaining the abundance of phospholipids, which serves as a precursor for the cPLAα pathway to produce these inflammatory lipid mediators [204]. At this juncture, it is primarily PLIN2 that exerts a significant influence on the promotion of inflammation. PLIN2 functions as a marker for LDs, thereby creating the impression that

an increase in the number of LDs is correlated with an upregulation of inflammation levels.

Three days post I/R, a significant increase in LD formation is observed [174], indicating that intracellular free lipid levels decline to a point where they no longer effectively stimulate PPARs to promote PLIN2 expression. Consequently, the PLIN2 level diminishes, as lipases such as ATGL/HSL typically require the removal of PLIN2 via the CMA pathway to exert their functions [37, 87]. Furthermore, at this time point, the lipid composition of LDs is predominantly comprised of TAG [174], which serves as a substantial source of lipid precursors for the generation of inflammatory lipid mediators via the ATGL/HSL pathway. Therefore, the inhibition of ATGL enzyme activity at this time point led to a reduction in the levels of inflammatory factors, indicating that the suppression of LD breakdown is correlated with the attenuation of inflammation.

This elucidates the paradoxical phenomenon wherein LDs exhibit either pro- or anti-inflammatory properties following I/R in various studies. Furthermore, cPLA2α and ATGL/HSL may operate independently to generate inflammatory lipid mediators at distinct time points post I/R. This insight could facilitate the development of more precise strategies for mitigating inflammation after I/R, such as inhibiting neuroinflammation by antagonizing PLIN2 during the acute phase and reducing inflammatory mediators by suppressing ATGL enzyme activity in the subacute or chronic phases following I/R. Additional research is necessary to validate this hypothesis.

Conclusion

Under various inducing factors, the composition, distribution, and function of LDs in CNS exhibit heterogeneity. The question of whether these LDs serve as a protective mechanism or act as a driving force for pathology remains to be elucidated. Future research should further employ lipidomics and proteomics technologies to explore the subtle compositional changes and corresponding functional disparities of LDs in diverse pathological stages and distinct spatial locations.

Abbreviations

LD	Lipid droplet
CNS	Central nervous system
TAG	Triacylglycerol
DAG	Diacylglycerol
CE	Cholesterol ester
PC	Phosphatidylcholine
PE	Phosphatidyl ethanolamine
PI	Phosphatidyl inositol
PS	Phosphatidylserine
PA	Phosphatidic acid
ER	Endoplasmic reticulum
FIT2	Fat storage-inducing transmembrane protein 2
PLIN	Perilipin
ATGL	Adipose triglyceride lipase
ABCA	ATP-binding cassette transporter A Member
ABCG1	ATP Binding Cassette Subfamily G Member 1
AD	Alzheimer's disease
NLRP3	Nucleotide-binding oligomerization domain like receptor pyrin domain containing 3
OGD/R	Oxygen–glucose deprivation/Reperfusion
HSC70	Heat shock cognate protein
MPTP	Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
HSL	Hormone-sensitive lipase
FA	Fat acid
ROS	Reactive oxygen species
MDA	Malondialdehyde
NF-κB	Nuclear factor kappa-B
FFAs	Free fat acids
DGAT	Diacylglycerol O-Acyltransferase
ACAT	Acyl-CoA cholesterol acyltransferase
CGI-58	Comparative gene identification-58
Pnpla2	Patatin-like phospholipase domain containing 2
PPAR	Proliferator-activated receptor
mTORC	Mammalian target of rapamycin complex
FOXO	Forkhead box O
PKA	Protein kinase A
MGL	Monoglyceride lipase
CMA	Chaperone-mediated autophagy
LAMP2A	Lysosome-associated membrane protein 2A
ATG	Autophagy related protein
MAP1LC3/LC3	Microtubule-associated protein 1 light chain 3
LIR	LC3-interacting region
GTPase	Guanosine triphosphatase
PDM	Peridroplet mitochondria
Sirt	Sirtuins
AMPK	5′-Prime-AMP-activated protein kinase
PGC-1α	Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha
OxPhos	Oxidative phosphorylation
NRF1/2	Nuclear respiratory factor-1/2
TFAM	Transcription factor A, mitochondrial
HK	Hexokinase
VDAC	Voltage-dependent anion channel
OMM	Outer mitochondrial membrane
OL	Oligodendrocytes
FATP	Fatty acid transporters
SLC	Solute carrier protein
FABP	Fatty acid binding proteins
LDAM	Lipid droplet-accumulating microglia
Sig-1R	Sigma-1 receptor
GalCer	Galactosyl ceramide
LRP	Low density lipoprotein receptor-related protein
TREM2	Triggering receptor expressed on myeloid cells 2
MCAO	Middle cerebral artery occlusion
TGF-β1	Transforming growth factor beta 1
TLR	Toll like receptor
PUFAs	Polyunsaturated fatty acids
GPCR	G protein-coupled receptor
PGE2	Prostaglandin E2
IL-6	Interleukin 6
COX	Cyclooxygenase
MCP-1	Monocyte chemoattractant protein-1
α2-AR	Alpha-2-adrenergic receptors
β-AR	Beta-adrenergic receptor
MCT	Monocarboxylic acid transporter
HIF	Hypoxia-inducible factor
I/R	Ischemia and reperfusion
ApoE	Apolipoprotein E
iPSCs	Induced pluripotent stem cells
FAO	Fatty acid oxidation
25HC	25-Hydroxycholesterol
CH25H	Cholesterol 25-Hydroxylase
SOAT1	Sterol O-acyltransferase 1
SREBP	Sterol regulatory element-binding protein
SCAP	SREBP cleavage-activating protein

Insig	Insulin-inducible gene protein
TNF-α	Tumor necrosis factor α
GSK-3β	Glycogen synthase kinase 3 β
Nrf2	Nuclear factor erythroid 2-related factor 2
LPS	Lipopolysaccharide
TAK1	TGF-β-activated kinase 1
MKKs	Mitogen-activated protein kinase kinases
p38 MAPKs	Phosphorylated p38 mitogen-activated protein kinases
AP-1	Activator protein-1
PI3K	Phosphatidylinositol 3-kinase
AKT	Protein kinase B
SFAs	Saturated fatty acids
MUFAs	Monounsaturated fatty acids
SPMs	Specialized pro-resolving mediators
cPLA2α	Calcium-dependent cytosolic phospholipase A2 alpha
EPA	Icosapentaenoic acid
DHA	Docosahexaenoic acid
LOX	Lipoxygenases
CYP	Cytochrome P450
GPCRs	G protein-coupled receptors
STAT3	Signal transducer and activator of transcription 3
LAL	Lysosomal acid lipase
qPCR	Quantitative polymerase chain reaction
LPIN	Lipid phosphate phosphohydrolase
LPL	Lipoprotein lipase
GAMs	Glioma-associated microglia/macrophages
EVs	Extracellular vesicles
Aβ	Amyloid β peptides
LDLR	Low-density lipoprotein receptor
CYP46A1	Cholesterol 24S-hydroxylase
24-OHC	24(S)-hydroxycholesterol
LXR	Liver X receptor
ABC	ATP-binding cassette

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Jinning Song and jiaxi Li defined the topic of review. Longxiao Zhang wrote the manuscript and created the figures. Yunfei Zhou, Zhongbo Yang, Liangchao Jiang, Xinyang Yan, Wenkai Zhu, Yi Shen and Bolong Wang made contributions to the revision of the initial draft. All authors read and approved the final manuscript.

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