Lipid droplets in astrocytes: Key organelles for CNS homeostasis and disease (Review)

YUCHEN WANG[1,2*], BOXUAN WANG[1,2*], JINCHAO HOU[1,2], XIAODONG HUO[1], CHENLIN LIU[1], RUILI GUAN[1], HONGGANG CHEN[1], YANG ZHOU[1], JIANBIN ZHANG[1], CONGCONG ZHUANG[1] and YUANKANG ZOU[1]

[1]Department of Occupational and Environmental Health and the Ministry of Education Key Lab of Hazard Assessment and Control in Special Operational Environment and the Shaanxi Provincial Key Laboratory of Environmental Health Hazard Assessment and Protection, School of Public Health, Fourth Military Medical University, Xi'an, Shaanxi 710032, P.R. China; [2]Cadet Regiment, School of Basic Medical Sciences, Air Force Medical University, Xi'an, Shaanxi 710032, P.R. China

Received July 31, 2025; Accepted October 24, 2025

DOI: 10.3892/ijmm.2025.5691

Abstract. Astrocytes, the predominant glial cells within the central nervous system, participate in a variety of processes, including metabolic homeostasis, regulation of blood-brain barrier function, and the integration of neuronal function and structure. Lipids, which are critical components of astrocyte architecture and functionality, play a pivotal role in energy production, membrane fluidity, and the integration of astrocyte-neuronal structure and function via lipid droplet storage and lipid metabolism. Research indicates that the proper storage of lipid droplets (LDs) in astrocytes is essential for maintaining normal physiological functions of the CNS. Fatty acids released from astrocyte LDs undergo β-oxidation within mitochondria and are intricately linked to neuronal inflammatory signaling, oxidative stress and mitochondrial energy production. Furthermore, dysregulated lipid metabolism in astrocytes is strongly linked to the onset and progression of neurological disorders. The alteration of lipid metabolic profiles in astrocytes across various microenvironments, along with the identification and screening of critical lipid metabolites, has emerged as a focal point in current research. Nonetheless, the precise mechanisms through which aberrant lipid metabolism in astrocytes influences the onset and progression of neurodegenerative diseases require further elucidation. This article seeks to synthesize recent advancements in the study of LDs-key organelles responsible for lipid homeostasis in astrocytes-to elucidate the response characteristics and underlying mechanisms of lipid metabolism in these cells. Furthermore, it aims to investigate the therapeutic potential of inhibiting abnormal lipid secretion and excessive lipid accumulation in astrocytes in the context of neurodegenerative disease progression.

Correspondence to: Dr Yuankang Zou or Dr Congcong Zhuang, Department of Occupational and Environmental Health and the Ministry of Education Key Lab of Hazard Assessment and Control in Special Operational Environment and the Shaanxi Provincial Key Laboratory of Environmental Health Hazard Assessment and Protection, School of Public Health, Fourth Military Medical University, 169 Changle West Road, Xincheng, Xi'an, Shaanxi 710032, P.R. China
E-mail: zouyksyd@fmmu.edu.cn
E-mail: 13644843984@163.com

*Contributed equally

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APOE, apolipoprotein E; ATGL, adipose triglyceride lipase; Aβ, amyloid-beta; BBB, blood-brain barrier; CNS, central nervous system; CPT-1, carnitine palmitoyltransferase-1; DHA, docosahexaenoic acid; ER, endoplasmic reticulum; FFAs, free fatty acids; IL-1β/3/6/10/15/17, interleukin 1β/3/6/10/15/17; LDs, lipid droplets; LXR, liver X receptor; NDDs, neurodegenerative diseases; NF-κB, nuclear factor κB; OXPHOS, oxidative phosphorylation; PD, Parkinson's disease; PLIN3, perilipin 3; PPARs, peroxisome proliferator-activated receptors; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding protein; TNF-α, tumor necrosis factor α

Key words: astrocytes, neurons, lipid droplets, neurodegeneration, lipid metabolism, β-oxidation

Contents

1. Introduction

Population aging represents a significant social challenge on a global scale. As human lifespans extend and fertility rates continue to decline in developed nations, projections indicate that by 2050, the global population of individuals aged 65 years and older will reach 2.1 billion (1). Among the most substantial social burdens associated with aging is the prevalence of neurodegenerative diseases (NDDs) (2). NDDs encompass a

group of neurological disorders characterized by the progressive degeneration of neurons within the central nervous system (CNS) (3), thereby adversely impacting the quality of life and well-being of millions worldwide. The incidence of NDDs increases exponentially with advancing age (2). Current research indicates that significant damage to the structure and function of neural networks, coupled with extensive neuronal loss leading to heterogeneity and disruption of neural circuit integrity, are key characteristics of NDDs (3-5). Nevertheless, due to the intricate biological mechanisms underlying NDDs and the challenges associated with developing targeted pharmacological interventions, effective treatment of these disorders remains a formidable challenge (6,7).

Studies have shown that pathological protein aggregation, synaptic and neuronal network dysfunction, protein homeostasis abnormalities, cytoskeletal abnormalities, energy metabolism changes, DNA and RNA defects, and inflammation are typical features of NDDs such as Alzheimer's disease (AD), Parkinson's disease (PD), primary tauopathies, frontotemporal dementia and amyotrophic lateral sclerosis (ALS) (3). Neuroinflammation is a significant pathological marker of NDDs, and the activation of neuroinflammatory signals plays a clear role in neurodegeneration (8).

The interaction between astrocytes and both resident and infiltrating cells within the CNS is pivotal in modulating tissue states under both physiological and pathological conditions. Research has demonstrated that astrocytes are responsive to inflammatory signals and can promote inflammation (9,10), thereby regulating various life processes within the nervous system under these conditions. Importantly, the pathological microenvironment of the nervous system can activate astrocytes (11-13), which are essential for preserving neuronal health and function. Recent studies have indicated that astrocytes provide critical support to neurons (14), and their phenotypic transformation is intricately linked to the onset and progression of NDDs (15). Further investigations have revealed that astrocytes are involved not only in the formation of synaptic networks but also in maintaining glutamate homeostasis between astrocytes and neurons (16,17), a balance crucial for normal neuronal function. Furthermore, reactive astrocytes are characteristically activated in NDDs, interacting with various types of neurons and thereby accelerating the progression of these disorders. Research has demonstrated that reactive astrocytes have a substantial impact on synaptic function, energy homeostasis, protein aggregation and neurodegeneration (18). The rapid advancements in single-cell sequencing, flow cytometry sorting and metabolomics have progressively illuminated the critical role of astrocytes in the risk association of NDDs. However, the precise biological mechanisms underlying these associations have yet to be fully elucidated.

Lipid metabolism constitutes a fundamental aspect of the brain's metabolic processes, with fatty acids serving as the primary substrates in this context (19-23). LDs function as essential organelles for the storage of fatty acids and play critical roles in inflammation, metabolic disorders and cellular communication (24,25). While the biological functions of LDs have been extensively investigated in peripheral organs such as the liver and heart, their roles within the brain, a central organ, have received comparatively less attention (26). Recently, there has been a growing recognition among researchers regarding the presence and significance of LDs as dynamic organelles within the CNS (25,26). LDs are found in various neural cell types, with a particularly high concentration in astrocytes (27,28). Nonetheless, the implications of abnormal astrocytic LDs in the onset and progression of NDDs, as well as the specific mechanisms involved, remain inadequately elucidated. This article aims to synthesize and discuss the functions of astrocytic LDs and the impact of LD abnormalities on the initiation and progression of NDDs, with the objective of exploring potential therapeutic strategies and innovative research directions focused on LDs.

2. Biogenesis and composition of astrocytic LDs

Core functions of astrocytes. The CNS exhibits considerable cellular heterogeneity. Its cellular composition encompasses not only neurons but also a diverse array of glial cells, including astrocytes, oligodendrocytes, ependymal cells and peripheral glial cells. Among these, astrocytes are the most prevalent glial cell type within the CNS, fulfilling essential functions such as supporting and nourishing neurons (29,30), regulating the integrity of the blood-brain barrier (BBB) (31), maintaining the homeostasis of the cellular microenvironment (32) and mediating immune responses (33). Recent investigations have elucidated the heterogeneity among astrocytes, with single-cell RNA sequencing technology identifying multitudinous transcriptionally distinct astrocyte states, including ATPase Na^+/K^+ transporting subunit β 2 astrocytes, S100 calcium binding protein A4 astrocytes, G protein-coupled receptor 84 astrocytes, complement C3/G0/G1 switch 2 astrocytes, glial fibrillary acidic protein/transmembrane 4L6 family member 1 astrocytes, glutathione synthetase/crystallin αB astrocytes (30,34). In individuals with temporal lobe epilepsy, as well as in murine models of epilepsy, there is a notable accumulation of lipids within astrocytes, resulting in the emergence of lipid-accumulating reactive astrocytes, termed LARAs. This newly identified subtype of reactive astrocytes is distinguished by an upregulation of apolipoprotein E (APOE) expression. Reactive astrocytes are prevalent in a range of human NDDs, providing valuable insights and potential research pathways for targeting lipid metabolism in specific astrocyte subtypes during the development and treatment of NDDs (35). Research suggests that the various astrocyte subtypes are not only integral to the maintenance of nervous system homeostasis but also help to find new astrocyte subtypes as a target for CNS repair (30,34).

Astrocytes play a crucial role in the construction of neural circuits by engaging in calcium signaling responses (36), neurotransmitter reuptake (37,38), maintenance of ion (39) and inorganic phosphate homeostasis (40), and involvement in synaptic formation and elimination (41). The membranes of astrocytes are enriched with glutamate transporters, such as glutamate transporter 1 (42) and glutamate-aspartate transporter (43), which facilitate the rapid clearance of glutamate from the synaptic cleft following neurotransmission, effectively preventing glutamate-induced excitotoxicity and providing metabolic and nutritional support to neurons. Research indicates that this adaptive inflammatory response of astrocytes encompasses both anti-inflammatory and pro-inflammatory effects (44). In the initial phase of infection, characterized by

acute inflammatory injury, anti-inflammatory cytokines such as transforming growth factor-β and interleukin 10 (IL-10) play a protective role by mitigating inflammation and safeguarding neuronal integrity. Conversely, during the chronic phase of infection, the extensive release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and IL-1β, significantly contributes to neuronal dysfunction and the advancement of NDDs. Studies have demonstrated that IL-1β stimulates over-activated astrocytes to secrete vascular endothelial growth factor, which increases the permeability of the BBB and exacerbates inflammation (45).

The intricate coordination between astrocytes and neurons is essential for the functionality of the CNS. Empirical evidence indicates that astrocyte-neuron coupling not only furnishes metabolic support to neurons (46), but also modulates the ionic milieu of the neuronal microenvironment (47) and facilitates the release and transmission of synaptic vesicles. Concurrently, under physiological conditions, astrocytes synthesize and release various lipids while facilitating their transport to neurons, thereby supporting synaptic formation and function (48,49). In the context of brain injury and NDDs, the activation of astrocytes and the presence of aberrant inflammatory responses can profoundly impact neuronal function and survival, leading to disruptions in neural network connectivity.

Molecular structure, biogenesis and function of LDs. LDs serve as the primary organelles for lipid metabolism and storage within cells, encapsulated by a monolayer of phospholipid membrane. These organelles predominantly consist of neutral lipids and phospholipids. LDs function as energy storage entities, playing a crucial role in lipid metabolism and energy homeostasis. They are ubiquitously present across various cell types, with a pronounced presence in adipocytes, where they occupy a significant portion of the cytoplasmic volume and exhibit a unique organelle architecture. Notably, LDs are the sole organelles characterized by a core of hydrophobic neutral lipids enveloped by a phospholipid monolayer. The core is primarily composed of triglycerides and a minor fraction of cholesterol esters. Research indicates that the expansion of LDs involves the lipid transport facilitated by APOE and the accumulation and budding of newly synthesized neutral lipids at the endoplasmic reticulum (ER) (27). The budding process of LDs is regulated by alterations in the contact angle between the ER and LDs, as well as the asymmetry in monolayer tension. LDs originate in the ER, where acetyl-CoA and glycerol 3-phosphate facilitate the synthesis of triglycerides (50). Initially, triglycerides are incorporated between the phospholipid bilayers, subsequently promoting the localized aggregation of lipid crystals and the recruitment of additional lipid components, thereby facilitating the expansion of LDs formation. Upon budding from the ER, LDs migrate into the cytoplasm, where they can further expand and interact with various organelles, assimilating triglycerides and fatty acids, which contributes to their volumetric increase (51). The elevation of neutral lipid levels within the ER enhances LD formation, serving to sequester potentially harmful free fatty acids (FFAs) and mitigate lipotoxicity (52). Cellular stress can trigger LD biogenesis, stimulating lipid synthesis, autophagy, lysosomal phospholipid conversion or an increase in phospholipase activity, thereby modulating LD formation and maintaining intracellular lipid homeostasis (Fig. 1).

Recruitment and functional regulation of lipid-associated proteins. Proteins associated with LDs are essential for their functional roles. These proteins are transported to LDs via distinct mechanisms, influencing the development, maturation and degradation of LDs. Class I proteins are directly targeted to LDs from the ER. Examples of Class I LD proteins include the lipid biosynthesis enzymes glycerol-3-phosphate acyltransferase 4 and diacylglycerol O-acyltransferase 2 (DGAT2), caveolin-1 and caveolin-2 (53). An example is ceramide - the production of acylated ceramides is catalyzed by the key lipid-synthesizing enzyme DGAT2 on lipid droplets. It relies on its N-terminal hydrophobic domain to embed itself in the ER membrane, ensuring stable localization to LDs and efficient catalysis of triglyceride synthesis, thereby targeting biogenesis to LDs. By contrast, Class II proteins are directed to the surface of LDs from the cytoplasm through amphipathic helices or extended hydrophobic residues. The recruitment of these proteins by LDs is modulated by developmental requirements or the metabolic state of the cell. Specific proteins, including recombinant perilipin 3 (PLIN3), reticulon 4 (RTN4), cytoskeletal linker protein 7, receptor expression-enhancing protein 5, Seipin and peroxisome biogenesis factor 30 (PEX30), are integral to LD formation. DGAT1/2 catalyzes the final step of triglyceride synthesis and marks the initiation point of LD biogenesis (54); Seipin promotes the initial aggregation of neutral lipids through tissue-specific ER domains and ensures the proper morphology and size of nascent LDs (55); Fat storage-inducing transmembrane protein 2 facilitates the transfer of neutral lipids into developing LDs, promoting LD expansion (56). Notably, Seipin influences the budding and formation of LDs through its impact on the levels of phosphatidylcholine, phosphatidylinositol and diacylglycerol (DAG). Newly formed LDs bud from the ER and require the core regulatory actions of PLIN family proteins to develop into fully functional LDs. The cell death-inducing DFF45-like effector family proteins serve as key regulators of LD growth and fusion. They mediate the directed transfer of neutral lipids from small to large LDs by forming bridging structures between adjacent LDs, thereby promoting LD growth and fusion (57). The PLIN family members (PLIN1 to PLIN5) are representative proteins found on the surface of LDs, classified as type II proteins that regulate interactions between LDs and the cytoplasmic environment. Each PLIN family member exhibits unique expression patterns and possesses distinct fundamental functions (58). PLIN4 possesses the ability to interact with the LD membrane and establish a protective barrier, thereby shielding LDs from degradation by lipases. PLIN3 contributes to the stability and metabolic processes of LDs (59), while RTN4 is implicated in their formation and localization. Cytoskeletal linker protein 7 potentially regulates LD formation by modulating the cytoskeletal architecture. Additionally, PEX30 facilitates LDs formation by modulating the ER domain (60).

Neurotrophic functions of lipid

Cholesterol. The brain is the organ with the highest cholesterol content in the body, and maintaining cholesterol

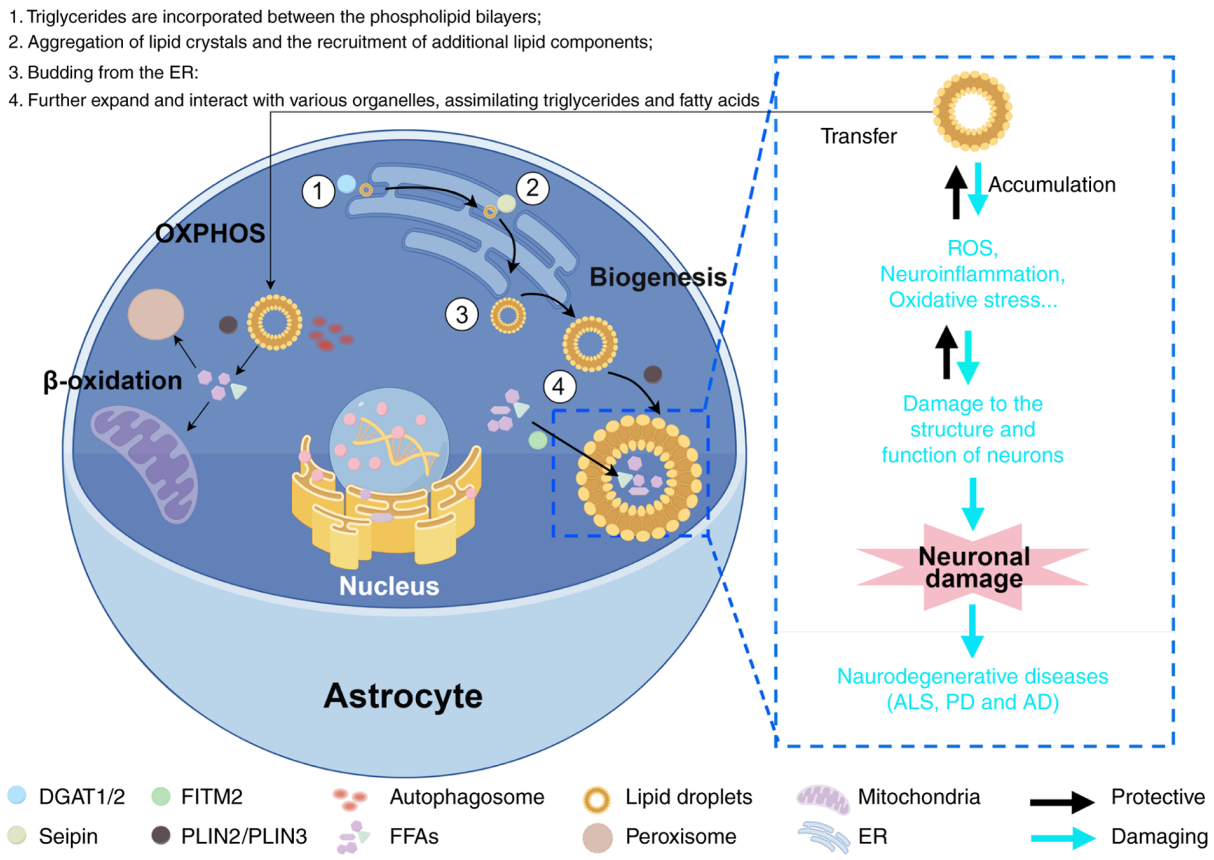

Figure 1. The biogenesis of lipid droplet formation and the role of astrocyte lipid metabolism in neurodegenerative diseases. ER, endoplasmic reticulum; ROS, reactive oxygen species; DGAT1/2, diacylglycerol O-acyltransferase 1/2; FITM2, fat storage inducing transmembrane protein 2; PLIN2/3, perilipin 2/3; FFAs, free fatty acids; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease.

homeostasis is essential for proper brain function. A deficiency in cholesterol can impair memory formation, while excessive cholesterol accumulation can damage neuronal synaptic plasticity and induce neuronal apoptosis (61). Although cholesterol in the brain is synthesized locally, the capacity for cholesterol synthesis varies among different cell types. Astrocytes, for instance, possess a greater ability to synthesize cholesterol from acetyl-CoA compared to neurons, which have lower levels of cholesterol synthesis enzymes (62). Astrocytes can supply cholesterol to surrounding neurons. Research has identified key cholesterol transporters, including APOE (63) and members of the ATP-binding cassette transporter family, such as ATP-binding cassette subfamily A member 1 (ABCA1) (64) and ABCG4 (65). Astrocytes facilitate cholesterol transport by synthesizing lipoproteins and apolipoproteins. Research indicates that astrocytes secrete cholesterol-rich lipoproteins containing APOE, primarily mediating neuronal lipid uptake through endocytosis facilitated by low-density lipoprotein receptor (LDLR) and LDLR-related protein 1 (LRP1) co-receptors. Different APOE homozygous expression states also determine the efficiency and specificity of lipid shuttles. Phospholipid-rich, small high-density lipoprotein particles are readily recognized by APOE2 and APOE3, whereas APOE4 more frequently binds to triglyceride-rich large very-LDL particles (66). The presence of the BBB renders cholesterol metabolism in the brain relatively independent from systemic cholesterol metabolism. Lipoproteins are exclusively synthesized within the CNS, where cholesterol sourced from astrocytes is crucial for the formation of neuronal membranes and synapses. This astrocytic cholesterol is instrumental in modulating various biochemical processes within the synaptic membrane, such as membrane fluidity and ion channel function (67). Furthermore, evidence from macrophage-specific ABCA1-knockout mice demonstrates that cholesterol significantly influences multiple regulatory mechanisms, including membrane protein activity and localization, lipid raft formation, glucose transport and inflammatory signaling (61,68). Lipid rafts, which are membrane microdomains enriched with cholesterol and sphingolipids, are recognized as pivotal regulators of numerous membrane protein activities (69). The activation of pro-inflammatory receptors, such as Toll-like receptor 4 (TLR4), predominantly occurs within these cholesterol-rich membrane regions. Cholesterol also impacts the membrane transport and functionality of the glucose transporter glucose transporter 1 (70). In comparison to the APOE3 isoform, APOE4 demonstrates reduced efficacy in inhibiting neuronal cholesterol synthesis and facilitating acetylation-mediated memory formation (63).

Astrocyte-secreted lipid factors function as signaling molecules that significantly impact neuronal proliferation, migration and synapse formation (71). The sterol regulatory element-binding protein (SREBP) family, particularly SREBP2, is integral to lipid metabolism, as it regulates the transcription of numerous genes involved in sterol synthesis (72).

Presently, it is yet to be determined and confirmed whether astrocyte-derived effectors can be transported to neurons and subsequently influence memory formation. Furthermore, the degree to which astrocytes adapt to neuronal demands and sustain brain cholesterol homeostasis warrants further investigation.

Sphingolipids. Sphingolipids, a class of lipids containing sphingosine, encompass ceramides and sphingomyelins and serve as essential components of cellular membranes, including lipid rafts. Metabolites derived from sphingolipids have been recognized as significant regulators of inflammation, autophagy, cellular growth and survival (73). Notably, ceramides, which can be further modified to form gangliosides, are implicated in the pathogenesis of NDDs (74). Given that *de novo* synthesis of sphingolipids also occurs in the ER, recent research has demonstrated that ceramides can be converted into acylglyceramide through the action of DAG O-acyltransferase and subsequently stored in LDs (75). Sphingolipids fulfill multiple roles in astrocyte function, particularly in the context of NDDs, where alterations in their structure and metabolism are observed. Astrocytes modulate synaptic architecture and neuronal functionality through the regulation of sphingolipids, including the production of gangliosides. In the context of AD, membrane gangliosides engage in interactions with amyloid proteins, thereby facilitating plaque formation and influencing the fibrillation process of α-synuclein (76). This conclusion has been validated *in vitro* using human SH-SY5Y cells and membrane liposome models (77). The aggregation of gangliosides, mediated by antibodies, has the potential to activate signaling pathways that suppress neuronal growth. Gangliosides synthesized by astrocytes contribute to the enhancement of neurite outgrowth, the regulation of neuronal inflammation and the stabilization of neuron-astrocyte interactions (78).

Phospholipids. Phospholipids constitute essential components of cellular membranes, forming phospholipid bilayers that are vital for maintaining neuronal membrane fluidity, facilitating signal transduction and supporting synaptic function. The brain synthesizes substantial quantities of phospholipids, including phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine and phosphatidylinositol. These phospholipids are conveyed to neurons via vesicle and protein-mediated transport systems, thereby influencing neuronal fate (71). Empirical studies have demonstrated that phosphatidylethanolamine promotes the differentiation of nerve cells into astrocytes by interacting with phosphatidylethanolamine binding protein 1 through the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase signaling pathway, whereas phosphatidylcholine exerts an antagonistic effect (79,80).

3. Lipid metabolism in astrocytes

Neurons possess a restricted capacity for fatty acid oxidation. Together, neurons and astrocytes constitute a critical coupled unit for cerebral energy metabolism. Astrocytes supply metabolic substrates and antioxidant factors to neurons, thereby enhancing the efficiency of neuronal information transmission (81). By storing and releasing lipids via LDs, astrocytes fulfill the metabolic demands of neurons, which is essential for neuronal function and the maintenance of brain homeostasis. Lipid metabolism represents a significant aspect of the interaction between neurons and astrocytes. Research indicates that lipids recycled from neurons are transferred to astrocytes, where they are stored in LDs prior to mitochondrial metabolism (82).

The accumulation of neutral lipids in astrocytes primarily occurs through two pathways. Firstly, activated neurons produce FFAs, which are subsequently secreted as APOE4 lipid particles. These particles are internalized by neighboring astrocytes via endocytosis and are stored in LDs. Docosahexaenoic acid (DHA) is an unsaturated fatty acid with neuroprotective effects on cognitive function and memory, and its reduced levels are associated with the progression of NDDs (83). In the brain, DHA exists in two forms: Phospholipid-bound and free. The major facilitator superfamily domain containing 2A (MFSD2A) is exclusively present in the endothelial cells forming the BBB and transports phospholipid-bound DHA in the form of lysophosphatidylcholine (LPC) in a sodium-dependent manner, enabling its passage across the BBB into the brain. This process is critical for maintaining brain lipid composition (84). FFAs bind to cell membrane proteins, such as the MFSD2A protein that transports omega-3 DHA into the brain as LPC-DHA (84), and plasma membrane fatty acid-binding proteins (FABPs) located on the BBB endothelial cell membrane, which promotes the uptake and activation of long-chain fatty acids and CD36 (85,86), which mediates cellular uptake of various lipids including long-chain fatty acids, enabling their passage through the BBB into cells. Once inside the body, fatty acids form complexes with FABP7, facilitating their transport from the cell membrane to various metabolic sites within the cell. Although FABP3 and FABP5 are present, FABP7 is the predominant isoenzyme in the brain and is crucial for the regulation of dendritic morphology and synaptic transmission in neurons (87). Furthermore, in the astrocyte-specific carnitine palmitoyltransferase-1 (CPT-1) A knockout mouse model, astrocytes exhibit preferential expression of CPT-1, an essential enzyme in the β-oxidation of long-chain fatty acids, thereby providing energy for cellular functions (88). LPC-DHA differs from non-esterified DHA transport mediated by fatty acid transport protein 1 and cellular metabolic pathways mediated by CD36 as a long-chain free fatty acid transporter (89). Lipids acquired through these distinct pathways can be utilized in astrocytes for energy production, membrane synthesis or storage within LDs, thereby participating in the brain-wide lipid distribution network.

The formation of LDs is integral to the regulation of fatty acid storage and hydrolysis, as well as providing substrates for β-oxidation, thereby playing a pivotal role in lipid metabolism. Under conditions of stress, such as starvation, β-oxidation of LDs serves as an alternative energy generation pathway for various cell types, including astrocytes. Research has highlighted the significance of oxidative phosphorylation (OXPHOS) activity in astrocytes for fatty acid degradation and the maintenance of lipid homeostasis in the brain. A deficiency in OXPHOS activity within astrocytes not only leads to the accumulation of LDs but also precipitates AD-like pathologies, including synaptic loss, neuroinflammation, demyelination and cognitive dysfunction (82). When the

fatty acid load surpasses the OXPHOS capacity of astrocytes, there is an increase in acetyl-CoA levels, which subsequently promotes the acetylation and activation of signal transducer and activator of transcription 3 (82). Following lipid overload, these abnormally activated astrocytes will stimulate neuronal fatty acid oxidation and oxidative stress responses, which in turn activate microglia through IL-3 signaling and start inflammatory signaling cascades (82). Research has established that the formation of LDs can subsequently impact mitochondrial function. For instance, astrocytes exposed to lipid mixtures can initiate the formation of intracellular LDs, which results in a reduction of mitochondrial membrane potential and an increase in mature apoptotic inducible factor levels, culminating in mitochondrial dysfunction (90). The defects in OXPHOS and the accumulation of LDs exhibit a mutually reinforcing and synergistic relationship. Further investigations have demonstrated that OXPHOS defects contribute to abnormal LD accumulation and trigger NDDs (91). A targeted knockout of the key OXPHOS gene, mitochondrial transcription factor A, in astrocytes has shown significantly elevated levels of FFAs, triacylglycerols, monoglycerides and cholesterol esters in the brains of mice, accompanied by progressive neurodegeneration (82). This study confirmed that mitochondrial dysfunction impairs astrocytic energy metabolism, with a pronounced enrichment in lipid metabolism pathways. Consequently, this leads to abnormal LD accumulation and drives astrocyte-mediated neurotoxicity.

LDs mediate fatty acid channeling through contact sites with organelles. LDs form tight physical connections with mitochondria and peroxisomes via membrane contact sites, actively participating in and regulating the network hub of lipid trafficking. In normal astrocytes, LDs typically cluster near the nucleus and reside adjacent to mitochondria and the ER. Through direct connections, these droplets create microenvironments that direct fatty acid transport to mitochondria. The key mechanism involves efficient flow from the LD core to mitochondria for β-oxidation, rapidly generating ATP to fuel astrocyte energy-consuming processes (28). Very long-chain fatty acids (VLCFAs), which mitochondria cannot directly β-oxidize, are primarily degraded by peroxisomes. Research indicates peroxisomes play a vital role in the oxidation and degradation of long-chain and VLCFAs, contributing significantly to reactive oxygen species (ROS) production and clearance, thereby helping maintain cellular redox balance. VLCFAs require preliminary oxidation within peroxisomes before entering mitochondria for β-oxidation, a process facilitated by the LD-peroxisome contact site (92).

Precise regulation of LD degradation by lipophagy. In the CNS, neurons rely on autophagy to maintain synaptic neurotransmission and prevent neurodegeneration (93). Autophagosomes selectively engulf LDs to promote lysosomal degradation-a process termed lipophagy. During energy deficiency, phagocytes ensure LD degradation through this pathway, which is crucial for lipid and energy homeostasis (94). During lipophagy, a double-membrane autophagosome engulfs LDs or partial LDs and fuses with lysosomes containing acid hydrolases, degrading LDs into FFAs (95). Studies in PD models reveal that pathological progression correlates with the PLIN4/LD/mitochondrial autophagy axis, where PLIN4 upregulation leads to abnormal LD accumulation (96).

ATGL/HSL/MGL regulation of fatty acid mobilization and OXPHOS homeostasis in astrocytes. Enzymatic lipolysis is the primary mechanism for fatty acid mobilization. Research indicates that adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) are two key enzymes in lipid mobilization. ATGL hydrolyzes the first ester bond to produce DAG and fatty acids, followed by HSL converting DAG into monoglyceride and fatty acids (97). Modulating ATGL expression alters LD mobilization in cells and tissues (98). Studies reveal that ATGL promotes LD accumulation in mouse microglia and suppresses lipopolysaccharides (LPS)-induced neuroinflammation (99). Enzyme-controlled lipolysis is tightly coupled with the OXPHOS capacity of astrocytes. Research indicates that knocking out carnitine palmitoyltransferase-1A (a key enzyme in mitochondrial fatty acid oxidation) in adult mouse astrocytes inhibits fatty acid oxidation and alters the brain's metabolomic profile, leading to cognitive impairment (100). Against a backdrop of heightened synaptic activity, efficient lipolysis provides substrates for OXPHOS, ensuring astrocytes effectively support neuronal function.

4. LDs in astrocytes are closely related to lipid metabolism

Astrocyte LDs influence numerous neurobiological processes through lipid metabolism, such as neurogenesis, neuronal structure and function, microglial activation, oligodendrocyte function, neuroimmunity and nerve cell senescence (Fig. 2).

Lipid metabolism in astrocytes and neurogenesis. Astrocytes play a critical role in regulating neuronal metabolism and maintaining brain homeostasis through the storage and release of lipids via LDs. Their lipid metabolism is essential for supporting energy production, cell membrane synthesis and neuronal repair, as well as modulating neuronal activity, which in turn influences neurogenesis (101). Studies using a mouse model of middle cerebral artery occlusion indicate that the overexpression of endothelin-1 (ET-1) in astrocytes within the murine brain can adversely affect hippocampal neurogenesis following cerebral ischemic injury, with peroxiredoxin 6 implicated in this process (102). Nonetheless, the impact of ET-1 overexpression in astrocytes on lipid metabolism and the underlying pathways requires further elucidation. Given that neurons possess a limited capacity for lipid synthesis during development, the provision of lipids by astrocytes is vital for neuronal growth and differentiation. Lipids, including cholesterol and fatty acids, are indispensable for the formation of neuronal membranes and synapses, and lipid factors secreted by astrocytes also influence neuronal proliferation and migration.

Lipid metabolism is intricately regulated by the PLINs and SREBPs, which subsequently influence the formation and functionality of LDs (103,104). Regulatory factors of lipolysis, such as PLINs, modulate the lipolytic process by governing the recruitment of lipases and their cofactors to the surface of LDs. For instance, PLIN1 acts as an inhibitor of lipolysis, and in a chronic PD mouse model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine combined with

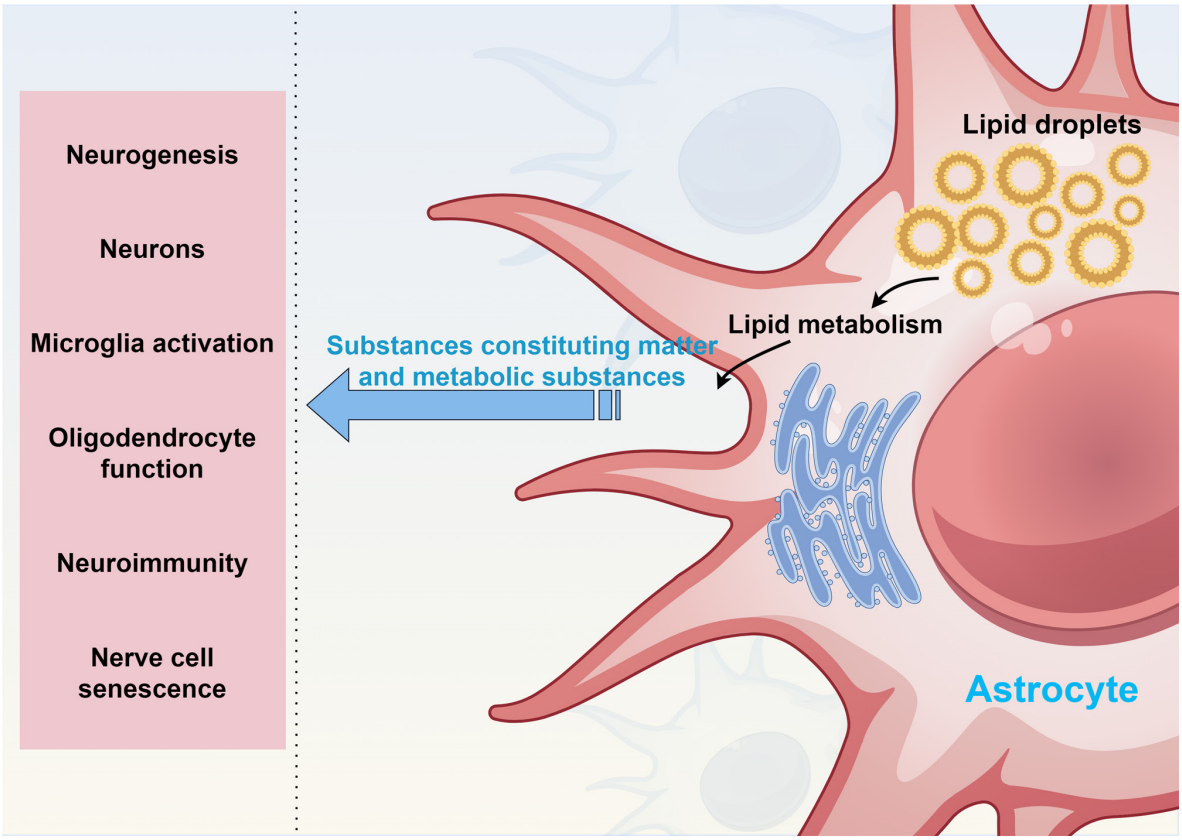

Figure 2. Numerous neurobiological processes are influenced by astrocyte lipid droplets through lipid metabolism.

probenecid, PLIN4 was confirmed to promote the formation of LDs (105,106). Transcription factors, including the SREBP family, play a crucial role in regulating the expression of genes involved in lipid synthesis. The depletion of astrocyte-specific SREBP2 has significant implications for brain development and function, manifesting in reduced synaptic growth of neurons and a decrease in overall brain size and weight (107).

The coupling between astrocytes and neurons involves lipid metabolism. The coordination of lipid metabolism between neurons and glial cells is essential for the proper functioning of the nervous system. Astrocytes play a pivotal role in this process by storing and releasing lipids through LDs, thereby supplying lipids necessary for energy production, cell membrane synthesis and repair in neurons. Additionally, these lipids serve as signaling molecules that modulate neuronal activity. Research has demonstrated that regulating neuronal glycerolipid metabolism by enhancing the synthesis of phospholipids, which are integral to cell membrane composition, while concurrently reducing the synthesis of storage lipids such as triglycerides, can facilitate the regeneration of nerve axons following injury (108).

Recent research has increasingly elucidated the critical role of cholesterol and phospholipids supplied by astrocytes in neuronal synapse formation and axon growth (109). Initial investigations established that cholesterol derived from glial cells, secreted by astrocytes and transported via the lipoprotein APOE, serves as a potent cofactor in the induction of retinal ganglion cell synapse formation (110). Subsequent studies identified additional astrocyte-secreted proteins, including thrombospondin ½ (111), hevin (112) and glypicans (113), which facilitate the formation of excitatory synapses and enhance glutamatergic activity. However, the mechanisms by which developing astrocytes regulate axon growth remain less understood. Recent investigations have revealed that astrocyte-derived exosomes, particularly the hepatic and glial cell adhesion molecule signal present on their surface, play a developmental role in modulating the axon growth of cortical pyramidal neurons (114). APOE, the primary cholesterol transporter secreted by astrocytes, plays a crucial role in promoting synaptogenesis while markedly inhibiting the stimulatory impact of astrocyte-derived exosomes on axonal growth (114). Notably, a deficiency in APOE during developmental stages has been indicated to lead to a significant reduction in the spine density of cortical pyramidal neurons (114). This study suggests that astrocyte exosomes, through their surface contact mechanisms, work in opposition to APOE to collectively regulate axonal growth and dendritic spine formation in pyramidal neurons during the early postnatal period (114). Consequently, astrocytes are capable of transferring lipids to neurons via both direct and indirect pathways, including the active transport of APOE and lipoprotein particles.

Fatty acids constitute the fundamental building blocks of all lipid types, rendering the precise regulation of their metabolic balance in the brain essential for optimal lipid functionality. Excessive FFA intake can lead to cellular accumulation and subsequent damage (115); thus, mitigating excessive FFA intake is an effective strategy to avert lipid toxicity. Neurons facilitate the release of FFAs via APOE particles, which are subsequently internalized by astrocytes

through endocytosis and sequestered in LDs as triglycerides, thereby mitigating their cytotoxic effects (116). Upon entry into astrocytes, the FFAs released are assimilated by LDs and utilized as substrates for mitochondrial β-oxidation. This process enables mitochondria to catabolize stored fatty acids, thereby generating energy and sustaining normal neurological function. The formation of astrocytic LDs and the intercellular lipid transport from neurons to glial cells are modulated by APOE levels. Astrocytic APOE may play a regulatory role in lipid transfer, while neuron-derived APOE is implicated in lipid transport during oxidative stress, collectively contributing to the maintenance of lipid metabolic equilibrium and neurological function in the brain (117).

Lipid metabolism of astrocytes and microglial activation. Microglia serve as the principal immune cells within the CNS, playing a crucial role in the clearance of cellular debris and the modulation of neuroinflammation. A substantial body of research suggests that the activation of microglia and their interactions with astrocytes significantly influence the inflammatory processes associated with NDDs and brain injury (9,118,119). Under stress conditions, including oxidative stress, inflammation and aging, the phagocytic activity and inflammatory responses of microglia may contribute to LD accumulation in the brain. This process is predominantly regulated by the TLR4 and nuclear factor κ-light-chain-enhancer of nuclear factor κB (NF-κB) signaling pathways. LPS, functioning as TLR4 ligands, initiate the TLR4 signaling cascade, subsequently activating downstream signaling molecules such as myeloid differentiation factor 88 and Toll/IL-1 receptor-domain-containing adapter-inducing interferon (IFN)-β, and facilitating the formation of LDs within microglia (120). The substantial accumulation of LDs in microglia may result from enhanced lipid synthesis coupled with diminished lipid catabolism. Fatty acids stored in microglial LDs can be mobilized through the enzymatic activity of two lipases, ATGL and HSL, when required for stress responses, thereby contributing to metabolic processes or inflammatory reactions (121).

Peroxisome proliferator-activated receptors (PPARs) and NF-κB transcription factors are integral to lipid metabolism and inflammatory responses. The activation of TLR4 can further stimulate the NF-κB signaling pathway, resulting in substantial production of inflammatory cytokines and the onset of neuroinflammation. Research has identified a strong association between the accumulation of LDs in microglia and the dysfunction of the aging brain, as well as the establishment of a pro-inflammatory state. Astrocytes promote phagocytic activity in microglia by secreting cytokines. When microglia undergo metabolic changes characterized by LD accumulation, phagocytosis becomes impaired. This process is often regarded as an inflammatory marker involved in NDDs, thereby accelerating neuronal degeneration (122). This accumulation is significantly implicated in the pathogenesis of various neuroinflammatory and NDDs. Evidence suggests that LD accumulation in microglia within the aging mouse brain can induce the production of ROS and the secretion of pro-inflammatory cytokines, thereby contributing to neurodegeneration (122). In AD, both postmortem brain tissue from patients with AD and AD mouse models demonstrate that amyloid β (Aβ) deposition and hyperphosphorylated tau protein can activate microglia, leading to chronic inflammation and neurodegeneration (123). In PD, studies using human induced pluripotent stem cell (iPSC)-derived astrocyte models (carrying the APOE4 genotype) and APOE-targeted replacement mouse brain tissue models reveal that the degeneration of dopaminergic neurons activates microglia, which release inflammatory mediators that further damage the remaining neurons (124). Thus, microglial activation is a critical factor in the development of neuroinflammation and NDDs.

Lipid metabolism plays a crucial role in modulating inflammation and neuroprotection by regulating LD formation and fatty acid release. As research progresses, genome-wide transcriptome analyses have elucidated that the human-specific variant APOE4 disrupts lipid metabolism in astrocytes and microglia (125). This disruption elucidates how APOE4-induced dysregulation, both cell-autonomous and non-cell-autonomous, may elevate the risk of AD. Studies have demonstrated that the activation of microglia in a male rat spinal cord injury model can stimulate astrocytes to secrete and release increased levels of lipocalin 2 (LCN2), resulting in neuronal damage and extensive neuronal loss within the CNS (126,127). Glial cells exhibit distinct interactions in lipid metabolism. Aβ-exposed astrocytes secrete LCN2, which activates the pro-inflammatory function of microglia and further stimulates astrocytes to secrete and release higher levels of LCN2 in a bidirectional manner (128). Research indicates that reducing LCN2 levels can diminish the activation of neurotoxic α1-subtype astrocytes, offering a more effective pathway for preventing neuronal cell death (129). Microglia bridge the gap between lipid dysregulation and neurodegeneration in PD by sensing metabolic disturbances. Oxidized lipids and glycosphingolipids activate microglia, which in turn promote A1-type astrocyte activation through inflammatory cytokine release, further accelerating PD progression (130). Therefore, modulating the lipid metabolism interaction pathway between these cells holds promise for achieving precise interventions against various NDDs. Furthermore, another research group has highlighted the significant role of BTB and CNC homolog 1 (BACH1) in maintaining metabolic homeostasis in microglia during mouse brain development (131). BACH1 influences microglial metabolism by inhibiting key glycolytic enzymes, hexokinase 2 and glyceraldehyde 3-phosphate dehydrogenase, thereby reducing lactate production. This metabolic alteration leads to a decrease in lactate-dependent histone modifications at the leucine rich repeat containing 15 (LRRC15) promoter region, consequently affecting the expression of the LRRC15 gene. LRRC15 is a factor secreted by microglia, which participates in the JAK/STAT signaling pathway by binding to the CD248 receptor and regulates astrocyte generation (131).

Lipid metabolism of astrocytes and maintenance of oligodendrocyte function. The brain primarily relies on glucose for its energy requirements and lacks alternative forms of energy storage, except for glycogen present in astrocytes. During conditions such as starvation, the brain can utilize ketone bodies (KB), which are derived from the breakdown of fatty acids in the liver, to meet the energy demands of central neurons. Recent research has identified that cortical glial cells in the fruit fly brain can synthesize KB from their

own stored LDs and subsequently transport these to neurons via monocarboxylate transporters for energy provision (132). Oligodendrocytes, in addition to their role in myelin formation, contribute to the energy metabolism of axons by supplying pyruvate and lactate. A recent study highlighted that the interaction between astrocytes and oligodendrocytes is crucial for myelin regeneration (133). Persistent activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway in astrocytes has been shown to inhibit the cholesterol biosynthesis pathway, consequently impairing myelin regeneration. The experiment demonstrated in a mouse model of focal demyelination that activation of Nrf2 in astrocytes results in the suppression of the cholesterol biosynthesis pathway, consequently impairing myelin regeneration (133). In the CNS, astrocytes and oligodendrocytes collaborate, particularly in lipid metabolism and the maintenance of myelin, to ensure efficient nerve conduction. Astrocytes supply oligodendrocytes with essential lipids, including cholesterol and phospholipids, which are crucial for myelination. Astrocytes supply lipids to oligodendrocytes via an SREBP2-dependent pathway to regulate myelin maintenance/regeneration. Under the regulation of the key transcription factor SREBP2, astrocytes synthesize large amounts of cholesterol through their own mevalonate pathway and transport it to oligodendrocytes via lipoproteins such as APOE. Research confirms that SREBP controls gene transcription in the cholesterol biosynthesis pathway, enhancing cholesterol synthesis when SREBP2 is overexpressed (134). By contrast, phospholipids and fatty acids are conveyed through vesicular and protein-mediated mechanisms, as well as via lipoproteins and FABPs. Dysregulation of lipid metabolism can lead to myelin damage and neurodegeneration (135).

Lipid metabolism of astrocytes and neuroimmunity. The heterogeneity of astrocyte responses in CNS pathology involves the roles of astrocytes and recruited peripheral cells in facilitating disease progression. Research indicates that in postmortem brain tissue from patients with ischemic stroke and in mouse models of transient focal cerebral ischemia, astrocytes express IL-15 upon stimulation. This factor recruits CD8+ T cells during brain injury and enhances their effector functions (136). Notably, the interaction between astrocytes and T cells is reciprocal; T cells can also influence astrocyte responses. Astrocytes express receptors for IL-17 and granulocyte-macrophage colony-stimulating factor (GM-CSF), cytokines produced by pro-inflammatory T helper 17 (Th17) cells, which are implicated in the pathologies of multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE), and other diseases. Initial findings from *in vivo* mouse experimental autoimmune EAE models and *in vitro* primary mouse astrocyte models suggested that IL-17 derived from Th17 cells upregulates the production of pro-inflammatory cytokines GM-CSF and C-X-C motif chemokine ligand 1, C-X-C motif chemokine ligand 2 and C-C motif chemokine ligand 20 in an NF-κB activator 1-dependent manner, thereby promoting leukocyte recruitment to the CNS during EAE (137,138). Recently, it has been reported that IFN-γ produced by natural killer (NK) cells can induce TNF-related apoptosis-inducing ligand expression in syngeneic astrocytes, enabling pro-inflammatory T cells expressing death receptor 5 to undergo apoptosis (137,139). Notably, NK cells acquire the ability to produce IFN-γ in intestinal tissues through the meningeal circulation in response to signals provided by the commensal microbiota (140). These findings identify mechanisms of the gut-CNS axis for controlling inflammation, which not only reveal the potential role of the microbiota in the pathologies of neurological diseases but also provide promising targets for therapeutic intervention.

Astrocyte-derived lipid metabolites play a crucial role in modulating the activation and differentiation of immune cells, including T cells and B cells, and in safeguarding neurons against oxidative stress by activating antioxidant pathways, such as the Nrf2 signaling pathway. Empirical evidence indicates that disruptions in astrocytic lipid metabolism can initiate neuroimmune responses and contribute to the pathogenesis of NDDs (82). Notably, through specific knockout of genes encoding key components of OXPHOS mitochondrial dysfunction in mouse astrocytes results in the abnormal accumulation of LDs within the hippocampus, which subsequently activates both astrocytes and microglia, thereby eliciting a neuroimmune response (82). This aberration in lipid metabolism has also been observed in AD model mice, implying a potential link between lipid metabolic disturbances in AD and dysfunctional mitochondrial activity in astrocytes.

Astrocyte lipid metabolism and nerve cell senescence. Cell senescence refers to the state where cells enter an irreversible non-dividing state after undergoing a certain number of divisions, preventing the excessive proliferation of damaged cells and inhibiting the occurrence of pathological reactions (141) such as cancer. Certain studies have found that glial cells with high activating protein 1 (AP-1) activity have abnormal morphology, produce matrix metalloproteinases and promote tau-related aging pathological reactions (20,142). However, the mechanism of senescent glial cell generation and how they affect neuronal senescence remain elusive.

Recent studies have elucidated the origin of senescent glial cells characterized by abnormally elevated AP-1 activity and their influence on neuronal aging (20,143). It has been discovered that mitochondrial dysfunction in neurons initiates the formation of senescent glial cells, which subsequently induce the excessive accumulation of LDs in non-senescent glial cells. Under chronic oxidative stress conditions (such as persistent mitochondrial damage), the excessive accumulation of LDs observed in AD mouse models becomes maladaptive, impairing phagocytic function and promoting tau protein aggregation. Chronic inflammation and lipid metabolism disorders activate inflammatory signaling pathways, such as NF-κB and MAPK, thereby enhancing the production of inflammatory mediators and exacerbating neuronal aging. In addition, lipid metabolites adversely affect mitochondrial function, resulting in dysfunction and further accelerating neuronal aging.

5. NDDs are linked to irregular LDs in astrocytes

Abnormal LDs in astrocytes are critical initiators of NDDs, including AD, PD and ALS. In AD, dysregulated lipid metabolism impairs Aβ clearance and inflammatory responses, leading to Aβ accumulation, neuroinflammation and increased neuronal injury (115). In PD, impaired lipid

metabolism disrupts dopaminergic neurons, accelerating disease progression. Similarly, in ALS, studies of postmortem spinal cord tissue from patients and ALS mouse models reveal that astrocyte dysmetabolism contributes to inflammation and neuronal death, with aberrant LDs accumulation enhancing ROS production and exacerbating neuronal damage (144). The accumulation of glial cell LDs is a prominent feature in motor neuron diseases such as ALS and may be prevalent across various NDDs (145). Astrocytic lipid metabolism is intricately linked to neuronal function, and oxidative stress can induce LD formation, thereby accelerating neurodegenerative processes. Dysregulation of lipid metabolism in astrocytes has been implicated in neuropsychiatric disorders, affecting neuronal activity regulation, neurotransmitter release and synaptic pruning processes. Astrocytes facilitate synaptic pruning through interactions with microglia during developmental stages. For instance, astrocytes promote synaptic pruning during development through an IL-33-mediated mechanism related to microglia-dependent synaptic pruning (146,147). In addition, the complement produced by astrocytes in an acute epilepsy mouse model has been shown to trigger microglia-dependent pruning to reshape neural circuits (148) (Fig. 1).

The formation of LDs in the brains of AD mouse models is intricately linked to processes such as inflammation, oxidative stress and aging. A reduction in the OXPHOS capacity of astrocytes adversely affects the lipid distribution, leading to issues such as synaptic loss, altered astrocyte reactivity and heightened oxidative stress (82). These factors are critical contributors to neuroinflammation and cognitive dysfunction. Various alleles of APOE, including E2 and E3, exhibit neuroprotective effects, in contrast to the APOE4 allele, which is a significant genetic risk factor for AD. Previous studies have demonstrated that PLIN3, possessing apolipoprotein-like characteristics, promotes the conversion of liposomes into lipid rafts. This membrane remodeling function is attributed to the C-terminal (quadruple helix bundle) domain of PLIN3. The C-terminal region of PLIN3 shares homology with the N-terminal domain of APOE, which is known to promote small LD formation. This domain binds to PLIN3 via a hydrophobic cleft, jointly regulating LD transport and facilitating droplet-lysosome contact (59,149). This interaction provides a potential therapeutic target for developing strategies to address NDDs by specifically modulating the interaction between APOE4 and LD regulatory proteins. APOE4 affects lipid transfer ability and reduces the production of LDs. In glial cells expressing APOE4, there is an increase in LDs, and functional deletion of APOE4 results in fewer lipoprotein particles and lipid accumulation in astrocytes (150). APOE4 is characterized by low lipid-binding capacity, reduced protein stability and diminished affinity for brain lipoprotein particles. Neuronal lipid transport proteins such as ABCA1 (151) and ABCA7 (152), LRP1 (153), and genes related to endocytosis are associated with an elevated risk of AD. Astrocytes produce cytokines that are associated with depression and anxiety-like behaviors. For instance, adenosine signaling in amygdala astrocytes promotes anxiety-related phenotypes in regionally and synaptically specific ways (154). Targeting astrocyte cytokine production may provide new treatment options for depression and related disorders. The accumulation of LDs in astrocytes has the potential to activate inflammatory signaling pathways, thereby exacerbating neuroinflammation. This process can disrupt normal metabolic functions, resulting in energy deficiencies and abnormalities in metabolite production, which may exert neurotoxic effects. Furthermore, the accumulation of LDs in astrocytes is associated with mitochondrial dysfunction and can compromise protein quality control mechanisms, leading to the accumulation of misfolded proteins and the induction of apoptosis or necrosis (90). In the early stages of AD, lipid imbalances and LD accumulation are particularly pronounced in astrocytes of individuals carrying the APOE4 allele, who exhibit increased LD accumulation and diminished fatty acid uptake and oxidation (155). These phenomena have been confirmed in postmortem brain tissue from APOE4 carriers and in APOE4 mouse models. Additionally, neuronal mitochondrial abnormalities that contribute to astrocytic LD accumulation, as observed in a mouse model of Leigh syndrome with mitochondrial dysfunction, may represent an early indicator of neurodegeneration (156).

While the brain primarily utilizes glucose as its main energy source, lipids play a crucial structural and functional role in brain activity. Given that excessive FFAs are linked to lipid toxicity, their concentrations must be meticulously regulated. Research indicates that OXPHOS in astrocytes is essential for the catabolism of fatty acids, thereby maintaining lipid homeostasis (82). A deficiency in astrocytic OXPHOS can lead to significant damage to brain lipid structures and activate several critical pathological mechanisms. These mechanisms include synaptic loss and dysfunction, reactive astrocyte dysfunction, reactive astrogliosis, microglial activation, oxidative stress and demyelination. Collectively, these pathological processes contribute to neuroinflammation, neurodegeneration and cognitive impairment (157). Consequently, strategies aimed at preserving or restoring the equilibrium between fatty acid load and mitochondrial catabolism hold promise for mitigating reactive astrocyte hyperplasia. Furthermore, such strategies may enhance the adverse cerebral environment and ameliorate cognitive deficits. This represents a potentially promising avenue for future research (Table I).

6. Discussion

Astrocytes play a crucial role in maintaining the normal functioning of the nervous system and safeguarding it against diseases. The pathophysiology of astrocytes is intricate, highly heterogeneous and variable, with responses that can differ based on the specific contexts and environments associated with disease. Any form of brain injury elicits an astrocytic response aimed at preserving or restoring homeostasis. In cases of severe injury, reactive astrogliosis is initiated, which serves to protect the surrounding neural tissue. A significant mechanism underlying neurological dysfunction in most neurological disorders is the loss of astrocytic function. Although the role of lipids in the distribution of brain regions and NDDs has not been fully elucidated, advancements in single-cell sequencing technology and matrix-assisted laser desorption/ionization mass spectrometry imaging mass spectrometry have enabled the direct detection of intramembranous LDs and lipid metabolism (158).

The impairment of astrocyte function can result in the accumulation of detrimental lipid metabolism byproducts

Table I. Changes in astrocytic LDs and related metabolism in NDDs.

Condition	Astrocyte related indicators	Direction of change	Model system	Key references
AD	Number of LDs	↑	Brain tissue from deceased patients with AD (*post mortem*)	Smolic *et al* (28); Mi *et al* (82)
			AD mouse model (*in vivo*)	Smolic *et al* (28)
			Human-derived iPSC-differentiated astrocyte model (*in vitro*)	Zhang *et al* (115); Tcw *et al* (125)
	Size of LDs	↑	APOE4 transgenic mice (*in vivo*)	Windham *et al* (27)
			Aging mouse brain tissue model (*in vivo*)	Byrns *et al* (20)
	PLIN2 protein levels	↑	Human-derived iPSC-differentiated astrocyte model (*in vitro*)	Zhang *et al* (115)
	β-oxidation capacity of lipids	↓	APP/PS1 mice (*in vivo*)	Konttinen *et al* (163)
			Human-derived iPSC-differentiated astrocyte model (*in vitro*)	Zhang *et al* (115)
	Cholesterol	↑	ABCA1$^{-M/-M}$ (macrophage-specific ABCA1 knock-out) mice model (*in vivo*)	Owen *et al* (68)
PD	Number of fat droplets	↑	MPTP/p induced mouse model of PD (*in vivo*)	Han *et al* (105)
			α-synuclein overexpression cell model (*in vitro*)	Wang *et al* (124)
			Human-derived iPSC-differentiated astrocyte model (*in vitro*)	Tcw *et al* (125)
	CPT1A expression	↓	Human-derived iPSC-differentiated astrocyte model (*in vitro*)	Su *et al* (88); Han *et al* (105)
	PLIN4 protein levels	↑	MPTP/p induced mouse model of PD (*in vivo*)	Han *et al* (105); Wang *et al* (124)
	PLIN2 protein levels	↑	Human-derived iPSC-differentiated astrocyte model (*in vitro*)	Tcw *et al* (125)
	β-oxidation capacity of lipids	↓	Human-derived iPSC-differentiated astrocyte model (*in vitro*)	Tcw *et al* (125)
ALS	Number of fat droplets	↑	Brain tissue from deceased patients with ALS (*post mortem*)	Mallick *et al* (26)
			Rat spinal cord astrocyte-SOD1^{G93A} mutant motor neuron co-culture model (*in vitro*)	Madji *et al* (144); Zelic *et al* (145)
	PLIN2/3 protein levels	↑	mutant motor neuron co-culture model (*in vitro*)	Madji *et al* (144); Zelic *et al* (145)
			Rat spinal cord astrocyte-SOD1^{G93A}	
	Lactate transporter	↓	Astrocyte model cultured under ALS conditions	Madji *et al* (144)
	β-oxidation capacity of lipids	↓	Rat spinal cord astrocyte-SOD1^{G93A} mutant motor neuron co-culture model (*in vitro*)	Madji *et al* (144); Zelic *et al* (145)
Multiple sclerosis	CPT1A expression	↓	Mouse experimental autoimmune encephalomyelitis model (*in vivo*)	Morkholt *et al* (138)
	β-oxidation capacity of lipids	↓	Mouse experimental autoimmune encephalomyelitis model (*in vivo*)	Morkholt *et al* (138)
Aging	Number of fat droplets	↑	Aging human brain tissue (*post mortem*)	Marschallinger *et al* (122)
			Brain tissue from aged mice (*in vivo*)	Byrns *et al* (20); Marschallinger *et al* (122)
	Size of LDs	↑	Brain tissue from aged mice (*in vivo*)	Byrns *et al* (20); Marschallinger) *et al* (122)
	PLIN2 protein levels	↑	Brain tissue from aged mice (*in vivo*)	Marschallinger *et al* (122)

Table I. Continued.

Condition	Astrocyte related indicators	Direction of Change	Model system	Key references
	β-oxidation capacity of lipids	↓	Brain tissue from aged mice (*in vivo*)	Jernberg *et al* (157)

NDDs, neurodegenerative diseases; LDs, lipid droplets; ALS, amyotrophic lateral sclerosis; AD, Alzheimer's disease; PD, Parkinson's disease; iPSC, induced pluripotent stem cell; APOE, apolipoprotein E; PLIN2/3/4, perilipin 2/3/4; APP/PS1, amyloid β precursor protein/presenilin 1; ABCA1, ATP-binding cassette subfamily a member 1; MPTP/p, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine/probenecid; CPT1A, carnitine palmitoyltransferase 1A; SOD1, superoxide dismutase-1.

and the progressive loss of neuronal support functions. While there are currently no specific therapies or drugs that directly target astrocyte LD storage and lipid metabolism, numerous pharmacological agents are known to influence astrocyte reactivity and astroglia-neuron interactions. Observations in adult mouse fasting models revealed elevated lysophosphatidic acid (LPA) levels in blood/cerebrospinal fluid following fasting. Upon crossing the BBB into the cortex, LPA increased cortical neuronal excitability (159). In a mouse model of ischemic stroke induced by middle cerebral artery occlusion, autotaxin (ATX) and LPA levels significantly increased in the cortex, leading to sustained glutamate-mediated hyperexcitability. However, when mice were genetically engineered to specifically knockout ATX or when ATX was pharmacologically inhibited, LPA levels decreased, the cortical excitatory/inhibitory balance was restored and neurological function improved (153). Research has demonstrated that ATX, an enzyme responsible for LPA synthesis and expressed by astrocytes in excitatory synaptic regions, can modulate glutamate transmission and is itself regulated by neuronal activity (160). This model proposes that pharmacologically inhibiting ATX through indirect mechanisms of neurotransmission may offer a novel therapeutic approach for neurological disorders such as schizophrenia. Enhancing the catabolic pathways and mobilizing internal energy reserves can improve the bioenergetic efficiency of astrocytes and their capacity to support neurons under stress, representing a promising metabolic therapeutic strategy. Supplementation with omega-3 polyunsaturated fatty acids, such as DHA, has been demonstrated to mitigate astrocyte activation and inflammatory responses by inhibiting inflammatory signaling pathways like NF-κB and AP-1, enhancing cell membrane fluidity and thereby indirectly improving astrocyte function (161,162). However, large-scale human clinical trials have yielded inconsistent results regarding cognitive enhancement, suggesting that efficacy may depend on disease stage and APOE genotype. The PPAR-δ agonist GW0742 has demonstrated potential therapeutic efficacy in preclinical models of AD by promoting fatty acid β-oxidation capacity in astrocytes and directly reducing LD accumulation (163). It has been observed to enhance CPT1A expression and fatty acid oxidation capacity in iPSC-derived astrocytes from fatty acid oxidation-deficient patients with AD, as well as to improve memory, increase neurogenesis and reduce inflammation-related gene expression in Aβ precursor protein/presenilin 1 AD mouse models. GW0742 can also significantly reduce BBB leakage and metalloproteinase-9 expression, while upregulating tight junction protein expression, reducing neutrophil recruitment to the brain and protecting BBB integrity (164). Nonetheless, GW0742 does not prevent the pro-inflammatory activation of iPSCs or astrocyte proliferation and may be insufficient to fully reverse metabolic damage, particularly in the context of glucose metabolism deficiencies, which could lead to uncoupled mitochondrial respiration and elevated oxidative stress (163). However, due to variations in APOE genotypes, the effects may differ, and this potential risk has not yet been fully evaluated. Glucose metabolism modulators can correct the metabolic reprogramming of astrocytes, thereby significantly reducing the expression of proinflammatory factors such as TNF-α and IL-6 in IL-1β-stimulated astrocytes (165). In the future, the combination of 'GW0742 combined with glucose metabolism modulator' holds promise for reshaping astrocytes into a neuroprotective phenotype. This approach may positively and indirectly enhance their glutamate transport function and BBB maintenance capacity, thereby improving therapeutic outcomes for NDDs. Similarly, liver X receptor (LXR) agonists can significantly attenuate tau pathology and neurodegeneration in APOE4 mice by promoting lipid efflux in astrocytes. These data suggest that enhancing glial lipid efflux may serve as a therapeutic approach to improve tau and APOE4-associated neurodegeneration. However, most non-selective LXR agonists strongly induce lipogenic genes such as SREBP-1c and fatty acid synthase in the liver, leading to hypertriglyceridemia and hepatic steatosis (166). Therefore, the beneficial effects of LXR agonists in AD models must be weighed against their known systemic side effects. Long-term regulation of cellular LDs is not without risk. Multiple studies indicate that inhibiting LD formation weakens the detoxification capacity of glial cells under acute oxidative stress. Research reveals that endogenous tau deficiency impairs LD formation in astrocytes, leading to elevated lipid peroxides, enhanced ROS production and increased cellular sensitivity to neurotoxicity (167). Similarly, studies on glioblastoma indicate that targeted inhibition of DGAT1 disrupts lipid homeostasis, exacerbating oxidative stress and increasing cell mortality, suggesting the critical role of LDs in buffering lipotoxicity (168). Therefore, future interventions should not simply aim to 'reduce LDs' but rather focus on restoring lipid homeostasis.

A significant challenge in developing therapies targeting astrocytes lies in the heterogeneity of these cells in both healthy and diseased states. Astrocyte subpopulations exhibit considerable variability in their distribution across different regions of the CNS, as well as in their roles in various diseases or disease states. Notably, certain pathogenetic mechanisms associated with astrocytes are prevalent across numerous neurological disorders. These mechanisms include neurotoxicity, dysregulation of extracellular glutamate levels, defects in potassium ion cycling and impaired lactate shuttling (169). Modulating these commonly dysregulated pathways in astrocyte activity may offer therapeutic targets for a range of neurological diseases that are influenced by astrocytic dysfunction.

Astrocytes are integral to the CNS, where they contribute to the maintenance of the BBB, facilitate intercellular communication and uphold metabolic homeostasis. The lipid metabolism of astrocytes is essential for preserving membrane fluidity, mitigating inflammation, and influencing the structure and signaling of organelles. The interplay of these metabolic pathways is crucial for the metabolic equilibrium of the nervous system; disruptions in these pathways can result in disorders of energy production, inflammation, excitotoxicity and the accumulation of toxic substances, all of which are common causative factors in various NDDs (170,171). A comprehensive understanding of these pathways in both health and disease contexts can elucidate the underlying causes of such diseases and provide a foundation for the development of novel therapeutic and nutritional strategies aimed at enhancing patient outcomes. In various disease contexts, a range of emerging astrocyte-related molecules may serve as potential therapeutic targets. Consequently, treatment strategies should focus on modulating specific molecules involved in astrocyte responses to bolster astrocyte defense mechanisms and improve astrocyte homeostasis, ultimately addressing CNS diseases through pathophysiological interventions.

Acknowledgements

Not applicable.

Funding

This work was supported by National Natural Science Foundation of China (grant nos. 82302116, 82020108026 and 82404215), Shaanxi Outstanding Youth Fund Project (grant no. 2023-JC-JQ-65) and the Fourth Military Medical University pilotage operation new flight program project (grant no. 2023-rcjfzyk).

Availability of data and materials

Not applicable.

Authors' contributions

YKZ and CCZ contributed to the overall conceptualization of the review. YCW, BXW and JCH drafted and revised the manuscript. XDH, CLL and RLG generated the figures. HGC, YZ and JBZ edited the manuscript and figures. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Rudnicka E, Napierala P, Podfigurna A, Meczekalski B, Smolarczyk R and Grymowicz M: The world health organization (WHO) approach to healthy ageing. Maturitas 139: 6-11, 2020.
2. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL and Bohr VA: Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol 15: 565-581, 2019.
3. Wilson DM III, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM and Dewachter I: Hallmarks of neurodegenerative diseases. Cell 186: 693-714, 2023.
4. Dugger BN and Dickson DW: Pathology of neurodegenerative diseases. Cold Spring Harb Perspect Biol 9: a028035, 2017.
5. Bhat MA and Dhaneshwar S: Neurodegenerative diseases: New hopes and perspectives. Curr Mol Med 24: 1004-1032, 2024.
6. Temple S: Advancing cell therapy for neurodegenerative diseases. Cell Stem Cell 30: 512-529, 2023.
7. Singh K, Sethi P, Datta S, Chaudhary JS, Kumar S, Jain D, Gupta JK, Kumar S, Guru A and Panda SP: Advances in gene therapy approaches targeting neuro-inflammation in neurodegenerative diseases. Ageing Res Rev 98: 102321, 2024.
8. Shi FD and Yong VW: Neuroinflammation across neurological diseases. Science 388: eadx0043, 2025.
9. Kwon HS and Koh SH: Neuroinflammation in neurodegenerative disorders: The roles of microglia and astrocytes. Transl Neurodegener 9: 42, 2020.
10. Guttenplan KA, Weigel MK, Prakash P, Wijewardhane PR, Hasel P, Rufen-Blanchette U, Munch AE, Blum JA, Fine J, Neal MC, *et al*: Neurotoxic reactive astrocytes induce cell death via saturated lipids. Nature 599: 102-107, 2021.
11. Cameron EG, Nahmou M, Toth AB, Heo L, Tanasa B, Dalal R, Yan W, Nallagatla P, Xia X, Hay S, *et al*: A molecular switch for neuroprotective astrocyte reactivity. Nature 626: 574-582, 2024.
12. Debom GN, Rubenich DS and Braganhol E: Adenosinergic signaling as a key modulator of the glioma microenvironment and reactive astrocytes. Front Neurosci 15: 648476, 2021.
13. Acioglu C, Li L and Elkabes S: Contribution of astrocytes to neuropathology of neurodegenerative diseases. Brain Res 1758: 147291, 2021.
14. Kozachkov L, Kastanenka KV and Krotov D: Building transformers from neurons and astrocytes. Proc Natl Acad Sci USA 120: e2219150120, 2023.
15. Yamagata K: Lactate supply from astrocytes to neurons and its role in ischemic stroke-induced neurodegeneration. Neuroscience 481: 219-231, 2022.
16. Tewari BP, Woo AM, Prim CE, Chaunsali L, Patel DC, Kimbrough IF, Engel K, Browning JL, Campbell SL and Sontheimer H: Astrocytes require perineuronal nets to maintain synaptic homeostasis in mice. Nat Neurosci 27: 1475-1488, 2024.
17. Aldana BI, Zhang Y, Jensen P, Chandrasekaran A, Christensen SK, Nielsen TT, Nielsen JE, Hyttel P, Larsen MR, Waagepetersen HS and Freude KK: Glutamate-glutamine homeostasis is perturbed in neurons and astrocytes derived from patient ipsc models of frontotemporal dementia. Mol Brain 13: 125, 2020.
18. Qian K, Jiang X, Liu ZQ, Zhang J, Fu P, Su Y, Brazhe NA, Liu D and Zhu LQ: Revisiting the critical roles of reactive astrocytes in neurodegeneration. Mol Psychiatry 28: 2697-2706, 2023.
19. Yin F: Lipid metabolism and Alzheimer's disease: Clinical evidence, mechanistic link and therapeutic promise. FEBS J 290: 1420-1453, 2023.
20. Byrns CN, Perlegos AE, Miller KN, Jin Z, Carranza FR, Manchandra P, Beveridge CH, Randolph CE, Chaluvadi VS, Zhang SL, *et al*: Senescent glia link mitochondrial dysfunction and lipid accumulation. Nature 630: 475-483, 2024.

21. Nakamura A, Sakai S, Taketomi Y, Tsuyama J, Miki Y, Hara Y, Arai N, Sugiura Y, Kawaji H, Murakami M and Shichita T: PLA2G2E-mediated lipid metabolism triggers brain-autonomous neural repair after ischemic stroke. Neuron 111: 2995-3010 e9, 2023.
22. Chausse B, Kakimoto PA and Kann O: Microglia and lipids: How metabolism controls brain innate immunity. Semin Cell Dev Biol 112: 137-144, 2021.
23. Duquenne M, Folgueira C, Bourouh C, Millet M, Silva A, Clasadonte J, Imbernon M, Fernandois D, Martinez-Corral I, Kusumakshi S, *et al*: Leptin brain entry via a tanycytic LepR-EGFR shuttle controls lipid metabolism and pancreas function. Nat Metab 3: 1071-1090, 2021.
24. Mathiowetz AJ and Olzmann JA: Lipid droplets and cellular lipid flux. Nat Cell Biol 26: 331-345, 2024.
25. Ralhan I, Chang CL, Lippincott-Schwartz J and Ioannou MS: Lipid droplets in the nervous system. J Cell Biol 220: e202102136, 2021.
26. Mallick K, Paul S, Banerjee S and Banerjee S: Lipid droplets and neurodegeneration. Neuroscience 549: 13-23, 2024.
27. Windham IA, Powers AE, Ragusa JV, Wallace ED, Zanellati MC, Williams VH, Wagner CH, White KK and Cohen S: Apoe traffics to astrocyte lipid droplets and modulates triglyceride saturation and droplet size. J Cell Biol 223: e202305003, 2024.
28. Smolic T, Tavcar P, Horvat A, Cerne U, Haluzan Vasle A, Tratnjek L, Kreft ME, Scholz N, Matis M, Petan T, *et al*: Astrocytes in stress accumulate lipid droplets. Glia 69: 1540-1562, 2021.
29. Kim NS and Chung WS: Astrocytes regulate neuronal network activity by mediating synapse remodeling. Neurosci Res 187: 3-13, 2023.
30. de Ceglia R, Ledonne A, Litvin DG, Lind BL, Carriero G, Latagliata EC, Bindocci E, Di Castro MA, Savtchouk I, Vitali I, *et al*: Specialized astrocytes mediate glutamatergic gliotransmission in the CNS. Nature 622: 120-129, 2023.
31. Liu D, Liao P, Li H, Tong S, Wang B, Lu Y, Gao Y, Huang Y, Zhou H, Shi L, *et al*: Regulation of blood-brain barrier integrity by dmp1-expressing astrocytes through mitochondrial transfer. Sci Adv 10: eadk2913, 2024.
32. Jayaram MA and Phillips JJ: Role of the microenvironment in glioma pathogenesis. Annu Rev Pathol 19: 181-201, 2024.
33. Giovannoni F and Quintana FJ: The role of astrocytes in CNS inflammation. Trends Immunol 41: 805-819, 2020.
34. Hou J, Bi H, Ge Q, Teng H, Wan G, Yu B, Jiang Q and Gu X: Heterogeneity analysis of astrocytes following spinal cord injury at single-cell resolution. FASEB J 36: e22442, 2022.
35. Chen ZP, Wang S, Zhao X, Fang W, Wang Z, Ye H, Wang M, Ke L, Huang T, Lv P, *et al*: Lipid-accumulated reactive astrocytes promote disease progression in epilepsy. Nat Neurosci 26: 542-554, 2023.
36. Veiga A, Abreu DS, Dias JD, Azenha P, Barsanti S and Oliveira JF: Calcium-dependent signaling in astrocytes: Downstream mechanisms and implications for cognition. J Neurochem 169: e70019, 2025.
37. Iovino L, Tremblay ME and Civiero L: Glutamate-induced excitotoxicity in Parkinson's disease: The role of glial cells. J Pharmacol Sci 144: 151-164, 2020.
38. Fang Y, Ding X, Zhang Y, Cai L, Ge Y, Ma K, Xu R, Li S, Song M, Zhu H, *et al*: Fluoxetine inhibited the activation of a1 reactive astrocyte in a mouse model of major depressive disorder through astrocytic 5-HT(2b)R/β-arrestin2 pathway. J Neuroinflammation 19: 23, 2022.
39. Chen Z, Yuan Z, Yang S, Zhu Y, Xue M, Zhang J and Leng L: Brain energy metabolism: Astrocytes in neurodegenerative diseases. CNS Neurosci Ther 29: 24-36, 2023.
40. Cheng X, Zhao M, Chen L, Huang C, Xu Q, Shao J, Wang HT, Zhang Y, Li X, Xu X, *et al*: Astrocytes modulate brain phosphate homeostasis via polarized distribution of phosphate uptake transporter PiT2 and exporter XPR1. Neuron 112: 3126-3142.e8, 2024.
41. Sharma V, Oliveira MM, Sood R, Khlaifia A, Lou D, Hooshmandi M, Hung TY, Mahmood N, Reeves M, Ho-Tieng D, *et al*: mRNA translation in astrocytes controls hippocampal long-term synaptic plasticity and memory. Proc Natl Acad Sci USA 120: e2308671120, 2023.
42. Guo F, Fan J, Liu JM, Kong PL, Ren J, Mo JW, Lu CL, Zhong QL, Chen LY, Jiang HT, *et al*: Astrocytic alkbh5 in stress response contributes to depressive-like behaviors in mice. Nat Commun 15: 4347, 2024.
43. Dewa KI, Arimura N, Kakegawa W, Itoh M, Adachi T, Miyashita S, Inoue YU, Hizawa K, Hori K, Honjoya N, *et al*: Neuronal DSCAM regulates the peri-synaptic localization of GLAST in bergmann glia for functional synapse formation. Nat Commun 15: 458, 2024.
44. Thakur S, Dhapola R, Sarma P, Medhi B and Reddy DH: Neuroinflammation in Alzheimer's disease: Current progress in molecular signaling and therapeutics. Inflammation 46: 1-17, 2023.
45. Zhang S, Li M, Qiu Y, Wu J, Xu X, Ma Q, Zheng Z, Lu G, Deng Z and Huang H: Enhanced VEGF secretion and blood-brain barrier disruption: Radiation-mediated inhibition of astrocyte autophagy via PI3K-AKT pathway activation. Glia 72: 568-587, 2024.
46. Bonvento G and Bolaños JP: Astrocyte-neuron metabolic cooperation shapes brain activity. Cell Metab 33: 1546-1564, 2021.
47. Arbring Sjöström T, Ivanov AI, Kiani N, Bernacka-Wojcik I, Samuelsson J, Saarela Unemo H, Xydias D, Vagiaki LE, Psilodimitrakopoulos S, Konidakis I, *et al*: Miniaturized iontronic micropipettes for precise and dynamic ionic modulation of neuronal and astrocytic activity. Small 21: e2410906, 2025.
48. Ferris HA, Perry RJ, Moreira GV, Shulman GI, Horton JD and Kahn CR: Loss of astrocyte cholesterol synthesis disrupts neuronal function and alters whole-body metabolism. Proc Natl Acad Sci USA 114: 1189-1194, 2017.
49. Tomas M, Duran JM, Lazaro-Dieguez F, Babia T, Renau-Piqueras J and Egea G: Fluorescent analogues of plasma membrane sphingolipids are sorted to different intracellular compartments in astrocytes; Harmful effects of chronic ethanol exposure on sphingolipid trafficking and metabolism. FEBS Lett 563: 59-65, 2004.
50. Zadoorian A, Du X and Yang H: Lipid droplet biogenesis and functions in health and disease. Nat Rev Endocrinol 19: 443-459, 2023.
51. Klemm RW and Carvalho P: Lipid droplets big and small: Basic mechanisms that make them all. Annu Rev Cell Dev Biol 40: 143-168, 2024.
52. Salo VT, Belevich I, Li S, Karhinen L, Vihinen H, Vigouroux C, Magre J, Thiele C, Holtta-Vuori M, Jokitalo E and Ikonen E: Seipin regulates ER-lipid droplet contacts and cargo delivery. EMBO J 35: 2699-2716, 2016.
53. Fu L, Zhang J, Wang Y, Wu H, Xu X, Li C, Li J, Liu J, Wang H, Jiang X, *et al*: LET-767 determines lipid droplet protein targeting and lipid homeostasis. J Cell Biol 223: e202311024, 2024.
54. Harris CA, Haas JT, Streeper RS, Stone SJ, Kumari M, Yang K, Han X, Brownell N, Gross RW, Zechner R and Farese RV Jr: DGAT enzymes are required for triacylglycerol synthesis and lipid droplets in adipocytes. J Lipid Res 52: 657-667, 2011.
55. Rao MJ and Goodman JM: Seipin: Harvesting fat and keeping adipocytes healthy. Trends Cell Biol 31: 912-923, 2021.
56. Wang H, Nikain C, Fortounas KI, Amengual J, Tufanli O, La Forest M, Yu Y, Wang MC, Watts R, Lehner R, *et al*: FITM2 deficiency results in ER lipid accumulation, ER stress, and reduced apolipoprotein B lipidation and VLDL triglyceride secretion in vitro and in mouse liver. Mol Metab 90: 102048, 2024.
57. Xu L, Li L, Wu L, Li P and Chen F: CIDE proteins and their regulatory mechanisms in lipid droplet fusion and growth. FEBS Lett 598: 1154-1169, 2024.
58. Zhang L, Zhou Y, Yang Z, Jiang L, Yan X, Zhu W, Shen Y, Wang B, Li J and Song J: Lipid droplets in central nervous system and functional profiles of brain cells containing lipid droplets in various diseases. J Neuroinflammation 22: 7, 2025.
59. Khaddaj R, Stribny J, Cottier S and Schneiter R: Perilipin 3 promotes the formation of membrane domains enriched in diacylglycerol and lipid droplet biogenesis proteins. Front Cell Dev Biol 11: 1116491, 2023.
60. Ferreira JV, Ahmed Y, Heunis T, Jain A, Johnson E, Raschle M, Ernst R, Vanni S and Carvalho P: Pex30-dependent membrane contact sites maintain ER lipid homeostasis. J Cell Biol 224: e202409039, 2025.
61. Li D, Zhang J and Liu Q: Brain cell type-specific cholesterol metabolism and implications for learning and memory. Trends Neurosci 45: 401-414, 2022.
62. Feringa FM and van der Kant R: Cholesterol and Alzheimer's disease; From risk genes to pathological effects. Front Aging Neurosci 13: 690372, 2021.
63. Li X, Zhang J, Li D, He C, He K, Xue T, Wan L, Zhang C and Liu Q: Astrocytic ApoE reprograms neuronal cholesterol metabolism and histone-acetylation-mediated memory. Neuron 109: 957-970, 2021.
64. Litvinchuk A, Suh JH, Guo JL, Lin K, Davis SS, Bien-Ly N, Tycksen E, Tabor GT, Remolina Serrano J, Manis M, *et al*: Amelioration of Tau and Apoe4-linked glial lipid accumulation and neurodegeneration with an LXR agonist. Neuron 112: 384-403 e8, 2024.

65. Yang A, Alrosan AZ, Sharpe LJ, Brown AJ, Callaghan R and Gelissen IC: Regulation of ABCG4 transporter expression by sterols and LXR ligands. Biochim Biophys Acta Gen Subj 1865: 129769, 2021.
66. Arenas F, Garcia-Ruiz C and Fernandez-Checa JC: Intracellular cholesterol trafficking and impact in neurodegeneration. Front Mol Neurosci 10: 382, 2017.
67. Adachi C, Otsuka S and Inoue T: Cholesterol-induced robust Ca oscillation in astrocytes required for survival and lipid droplet formation in high-cholesterol condition. iScience 25: 105138, 2022.
68. Zhu X, Owen JS, Wilson MD, Li H, Griffiths GL, Thomas MJ, Hiltbold EM, Fessler MB and Parks JS: Macrophage abca1 reduces myd88-dependent toll-like receptor trafficking to lipid rafts by reduction of lipid raft cholesterol. J Lipid Res 51: 3196-3206, 2010.
69. Sapoń K, Mańka R, Janas T and Janas T: The role of lipid rafts in vesicle formation. J Cell Sci 136: jcs260887, 2023.
70. Cheng C, Tu J, Hu Z, Chen Y, Wang Y, Zhang T, Zhang C, Li C, Wang Y and Niu C: SREBP2/Rab11s/GLUT1/6 network regulates proliferation and migration of glioblastoma. Pathol Res Pract 240: 154176, 2022.
71. Vanherle S, Loix M, Miron VE, Hendriks JJA and Bogie JFJ: Lipid metabolism, remodelling and intercellular transfer in the CNS. Nat Rev Neurosci 26: 214-231, 2025.
72. Benatzy Y, Palmer MA, Lütjohann D, Ohno RI, Kampschulte N, Schebb NH, Fuhrmann DC, Snodgrass RG and Brüne B: Alox15b controls macrophage cholesterol homeostasis via lipid peroxidation, erk1/2 and srebp2. Redox Biol 72: 103149, 2024.
73. Kuo A and Hla T: Regulation of cellular and systemic sphingolipid homeostasis. Nat Rev Mol Cell Biol 25: 802-821, 2024.
74. Pan X, Dutta D, Lu S and Bellen HJ: Sphingolipids in neurodegenerative diseases. Front Neurosci 17: 1137893, 2023.
75. Robles-Martinez L, Morin KH and Nikolova-Karakashian M: Ceramide homeostasis in hepatic lipid droplets. Biochem Soc Trans 53: 509-518, 2025.
76. Di Scala C, Yahi N, Boutemeur S, Flores A, Rodriguez L, Chahinian H and Fantini J: Common molecular mechanism of amyloid pore formation by Alzheimer's beta-amyloid peptide and alpha-synuclein. Sci Rep 6: 28781, 2016.
77. Di Scala C, Troadec JD, Lelievre C, Garmy N, Fantini J and Chahinian H: Mechanism of cholesterol-assisted oligomeric channel formation by a short Alzheimer β-amyloid peptide. J Neurochem 128: 186-195, 2014.
78. Chahinian H, Yahi N and Fantini J: Glutamate, gangliosides, and the synapse: Electrostatics at work in the brain. Int J Mol Sci 25: 8583, 2024.
79. Corbit KC, Trakul N, Eves EM, Diaz B, Marshall M and Rosner MR: Activation of Raf-1 signaling by protein kinase C through a mechanism involving Raf kinase inhibitory protein. J Biol Chem 278: 13061-13068, 2003.
80. Shim M, San TT, Shin B, Lee H, Han SB, Lee DK and Kim HJ: Histone demethylase inhibitor KDM5-C70 regulates metabolomic and lipidomic programming during an astrocyte differentiation of rat neural stem cell. Sci Rep 15: 5409, 2025.
81. Thieren L, Zanker HS, Droux J, Dalvi U, Wyss MT, Waag R, Germain PL, von Ziegler LM, Looser ZJ, Hosli L, *et al*: Astrocytic GLUT1 deletion in adult mice enhances glucose metabolism and resilience to stroke. Nat Commun 16: 4190, 2025.
82. Mi Y, Qi G, Vitali F, Shang Y, Raikes AC, Wang T, Jin Y, Brinton RD, Gu H and Yin F: Loss of fatty acid degradation by astrocytic mitochondria triggers neuroinflammation and neurodegeneration. Nat Metab 5: 445-465, 2023.
83. Astarita G, Jung K, Berchtold NC, Nguyen VQ, Gillen DL, Head E, Cotman CW and Piomelli D: Deficient liver biosynthesis of docosahexaenoic acid correlates with cognitive impairment in alzheimer's disease. PLoS One 5: e12538, 2010.
84. Nguyen LN, Ma D, Shui G, Wong P, Cazenave-Gassiot A, Zhang X, Wenk MR, Goh EL and Silver DL: Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. Nature 509: 503-506, 2014.
85. Pelerin H, Jouin M, Lallemand MS, Alessandri JM, Cunnane SC, Langelier B and Guesnet P: Gene expression of fatty acid transport and binding proteins in the blood-brain barrier and the cerebral cortex of the rat: Differences across development and with different DHA brain status. Prostaglandins Leukot Essent Fatty Acids 91: 213-220, 2014.
86. Kim ID, Ju H, Minkler J, Jiang R, Singh A, Sharma R, Febbraio M and Cho S: Endothelial cell CD36 mediates stroke-induced brain injury via BBB dysfunction and monocyte infiltration in normal and obese conditions. J Cereb Blood Flow Metab 43: 843-855, 2023.
87. Geng Z, Peng F, Cheng Z, Su J, Song J, Han X, Li R, Li X, Cui R and Li B: Astrocytic FABP7 alleviates depression-like behaviors of chronic unpredictable mild stress mice by regulating neuroinflammation and hippocampal spinogenesis. FASEB J 39: e70606, 2025.
88. Su Y and Yuan Q: Mitochondrial fatty acid oxidase CPT1A ameliorates postoperative cognitive dysfunction by regulating astrocyte ferroptosis. Brain Res 1850: 149424, 2025.
89. Ochiai Y, Uchida Y, Ohtsuki S, Tachikawa M, Aizawa S and Terasaki T: The blood-brain barrier fatty acid transport protein 1 (FATP1/SLC27A1) supplies docosahexaenoic acid to the brain, and insulin facilitates transport. J Neurochem 141: 400-412, 2017.
90. Li YC, Fu JT and Tzeng SF: Exposure to lipid mixture induces intracellular lipid droplet formation and impairs mitochondrial functions in astrocytes. Neurochem Int 178: 105792, 2024.
91. Liang KX, Chen A, Kianian A, Kristiansen CK, Yangzom T, Furriol J, Hoyland LE, Ziegler M, Krakenes T, Tzoulis C, *et al*: Activation of neurotoxic astrocytes due to mitochondrial dysfunction triggered by POLG mutation. Int J Biol Sci 20: 2860-2880, 2024.
92. Kong J, Ji Y, Jeon YG, Han JS, Han KH, Lee JH, Lee G, Jang H, Choe SS, Baes M and Kim JB: Spatiotemporal contact between peroxisomes and lipid droplets regulates fasting-induced lipolysis via PEX5. Nat Commun 11: 578, 2020.
93. Kuijpers M, Kochlamazashvili G, Stumpf A, Puchkov D, Swaminathan A, Lucht MT, Krause E, Maritzen T, Schmitz D and Haucke V: Neuronal autophagy regulates presynaptic neurotransmission by controlling the axonal endoplasmic reticulum. Neuron 110: 734, 2022.
94. Pu M, Zheng W, Zhang H, Wan W, Peng C, Chen X, Liu X, Xu Z, Zhou T, Sun Q, *et al*: ORP8 acts as a lipophagy receptor to mediate lipid droplet turnover. Protein Cell 14: 653-667, 2023.
95. Smolic T, Zorec R and Vardjan N: Pathophysiology of lipid droplets in neuroglia. Antioxidants (Basel) 11: 22, 2021.
96. Han X, Liu Y, Dai Y, Xu T, Hu Q, Yi X, Rui L, Hu G and Hu J: Neuronal SH2B1 attenuates apoptosis in an MPTP mouse model of Parkinson's disease via promoting PLIN4 degradation. Redox Biol 52: 102308, 2022.
97. Schweiger M, Schreiber R, Haemmerle G, Lass A, Fledelius C, Jacobsen P, Tornqvist H, Zechner R and Zimmermann R: Adipose triglyceride lipase and hormone-sensitive lipase are the major enzymes in adipose tissue triacylglycerol catabolism. J Biol Chem 281: 40236-40241, 2006.
98. Grabner GF, Xie H, Schweiger M and Zechner R: Lipolysis: Cellular mechanisms for lipid mobilization from fat stores. Nat Metab 3: 1445-1465, 2021.
99. Li Q, Liu P, Zhu X, Zhou C, Hu Y, Cao S, Li H, Zou X, Gao S, Cao X, *et al*: NG-497 alleviates microglia-mediated neuroinflammation in a MTNR1A-dependent manner. Inflammation 48: 2663-2676, 2025.
100. Morant-Ferrando B, Jimenez-Blasco D, Alonso-Batan P, Agulla J, Lapresa R, Garcia-Rodriguez D, Yunta-Sanchez S, Lopez-Fabuel I, Fernandez E, Carmeliet P, *et al*: Fatty acid oxidation organizes mitochondrial supercomplexes to sustain astrocytic ROS and cognition. Nat Metab 5: 1290-1302, 2023.
101. Yang D, Wang X, Zhang L, Fang Y, Zheng Q, Liu X, Yu W, Chen S, Ying J and Hua F: Lipid metabolism and storage in neuroglia: Role in brain development and neurodegenerative diseases. Cell Biosci 12: 106, 2022.
102. Li J, Jiang W, Cai Y, Ning Z, Zhou Y, Wang C, Chung SK, Huang Y, Sun J, Deng M, *et al*: Astrocytic endothelin-1 overexpression impairs learning and memory ability in ischemic stroke via altered hippocampal neurogenesis and lipid metabolism. Neural Regen Res 19: 650-656, 2024.
103. Majchrzak M, Stojanović O, Ajjaji D, Ben M'barek K, Omrane M, Thiam AR and Klemm RW: Perilipin membrane integration determines lipid droplet heterogeneity in differentiating adipocytes. Cell Rep 43: 114093, 2024.
104. Shimano H and Sato R: SREBP-regulated lipid metabolism: Convergent physiology-divergent pathophysiology. Nat Rev Endocrinol 13: 710-730, 2017.
105. Han X, Zhu J, Zhang X, Song Q, Ding J, Lu M, Sun S and Hu G: Plin4-dependent lipid droplets hamper neuronal mitophagy in the MPTP/p-induced mouse model of Parkinson's disease. Front Neurosci 12: 397, 2018.
106. Kimmel AR and Sztalryd C: The perilipins: Major cytosolic lipid droplet-associated proteins and their roles in cellular lipid storage, mobilization, and systemic homeostasis. Annu Rev Nutr 36: 471-509, 2016.

107. Xu SF, Pang ZQ, Fan YG, Zhang YH, Meng YH, Bai CY, Jia MY, Chen YH, Wang ZY and Guo C: Astrocyte-specific loss of lactoferrin influences neuronal structure and function by interfering with cholesterol synthesis. Glia 70: 2392-2408, 2022.
108. Yang C, Wang X, Wang J, Wang X, Chen W, Lu N, Siniossoglou S, Yao Z and Liu K: Rewiring neuronal glycerolipid metabolism determines the extent of axon regeneration. Neuron 105: 276-292. e5, 2020.
109. Brandebura AN, Paumier A, Onur TS and Allen NJ: Astrocyte contribution to dysfunction, risk and progression in neurodegenerative disorders. Nat Rev Neurosci 24: 23-39, 2023.
110. Mauch DH, Nägler K, Schumacher S, Göritz C, Müller EC, Otto A and Pfrieger FW: CNS synaptogenesis promoted by glia-derived cholesterol. Science 294: 1354-1357, 2001.
111. Christopherson KS, Ullian EM, Stokes CC, Mullowney CE, Hell JW, Agah A, Lawler J, Mosher DF, Bornstein P and Barres BA: Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Cell 120: 421-433, 2005.
112. Kucukdereli H, Allen NJ, Lee AT, Feng A, Ozlu MI, Conatser LM, Chakraborty C, Workman G, Weaver M, Sage EH, *et al*: Control of excitatory CNS synaptogenesis by astrocyte-secreted proteins hevin and SPARC. Proc Natl Acad Sci USA 108: E440-E449, 2011.
113. Allen NJ, Bennett ML, Foo LC, Wang GX, Chakraborty C, Smith SJ and Barres BA: Astrocyte glypicans 4 and 6 promote formation of excitatory synapses via GluA1 AMPA receptors. Nature 486: 410-414, 2012.
114. Jin S, Chen X, Tian Y, Jarvis R, Promes V and Yang Y: Astroglial exosome hepaCAM signaling and ApoE antagonization coordinates early postnatal cortical pyramidal neuronal axon growth and dendritic spine formation. Nat Commun 14: 5150, 2023.
115. Zhang X, Chen C and Liu Y: Navigating the metabolic maze: Anomalies in fatty acid and cholesterol processes in Alzheimer's astrocytes. Alzheimers Res Ther 16: 63, 2024.
116. Ioannou MS, Jackson J, Sheu SH, Chang CL, Weigel AV, Liu H, Pasolli HA, Xu CS, Pang S, Matthies D, *et al*: Neuron-astrocyte metabolic coupling protects against activity-induced fatty acid toxicity. Cell 177: 1522-1535.e14, 2019.
117. Lindner K, Beckenbauer K, van Ek LC, Titeca K, de Leeuw SM, Awwad K, Hanke F, Korepanova AV, Rybin V, van der Kam EL, *et al*: Isoform- and cell-state-specific lipidation of ApoE in astrocytes. Cell Rep 38: 110435, 2022.
118. Leng F and Edison P: Neuroinflammation and microglial activation in Alzheimer disease: Where do we go from here? Nat Rev Neurol 17: 157-172, 2021.
119. Liu M, Xu Z, Wang L, Zhang L, Liu Y, Cao J, Fu Q, Liu Y, Li H, Lou J, *et al*: Cottonseed oil alleviates ischemic stroke injury by inhibiting the inflammatory activation of microglia and astrocyte. J Neuroinflammation 17: 270, 2020.
120. Doring C, Regen T, Gertig U, van Rossum D, Winkler A, Saiepour N, Bruck W, Hanisch UK and Janova H: A presumed antagonistic LPS identifies distinct functional organization of TLR4 in mouse microglia. Glia 65: 1176-1185, 2017.
121. Robb JL, Boisjoly F, Machuca-Parra AI, Coursan A, Manceau R, Majeur D, Rodaros D, Bouyakdan K, Greffard K, Bilodeau JF, *et al*: Blockage of ATGL-mediated breakdown of lipid droplets in microglia alleviates neuroinflammatory and behavioural responses to lipopolysaccharides. Brain Behav Immun 123: 315-333, 2025.
122. Marschallinger J, Iram T, Zardeneta M, Lee SE, Lehallier B, Haney MS, Pluvinage JV, Mathur V, Hahn O, Morgens DW, *et al*: Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. Nat Neurosci 23: 194-208, 2020.
123. Pan RY, He L, Zhang J, Liu X, Liao Y, Gao J, Liao Y, Yan Y, Li Q, Zhou X, *et al*: Positive feedback regulation of microglial glucose metabolism by histone H4 lysine 12 lactylation in Alzheimer's disease. Cell Metab 34: 634-648.e6, 2022.
124. Zhang X, Zhang Y, Wang B, Xie C, Wang J, Fang R, Dong H, Fan G, Wang M, He Y, *et al*: Pyroptosis-mediator GSDMD promotes Parkinson's disease pathology via microglial activation and dopaminergic neuronal death. Brain Behav Immun 119: 129-145, 2024.
125. Tcw J, Qian L, Pipalia NH, Chao MJ, Liang SA, Shi Y, Jain BR, Bertelsen SE, Kapoor M and Marcora E, *et al*: Cholesterol and matrisome pathways dysregulated in astrocytes and microglia. Cell 185: 2213-2233 e25, 2022.
126. Wang X, Li X, Zuo X, Liang Z, Ding T, Li K, Ma Y, Li P, Zhu Z, Ju C, *et al*: Photobiomodulation inhibits the activation of neurotoxic microglia and astrocytes by inhibiting Lcn2/JAK2-STAT3 crosstalk after spinal cord injury in male rats. J Neuroinflammation 18: 256, 2021.
127. Jung BK, Park Y, Yoon B, Bae JS, Han SW, Heo JE, Kim DE and Ryu KY: Reduced secretion of LCN2 (lipocalin 2) from reactive astrocytes through autophagic and proteasomal regulation alleviates inflammatory stress and neuronal damage. Autophagy 19: 2296-2317, 2023.
128. Shin HJ, Kim KE, Jeong EA, An HS, Lee SJ, Lee J and Roh GS: Amyloid β oligomer promotes microglial galectin-3 and astrocytic lipocalin-2 levels in the hippocampus of mice fed a high-fat diet. Biochem Biophys Res Commun 667: 10-17, 2023.
129. Xiao R, Pan J, Yang M, Liu H, Zhang A, Guo X and Zhou S: Regulating astrocyte phenotype by Lcn2 inhibition toward ischemic stroke therapy. Biomaterials 317: 123102, 2025.
130. Sun Y, Wei K, Liao X, Wang J, Gao L and Pang B: Lipid metabolism in microglia: Emerging mechanisms and therapeutic opportunities for neurodegenerative diseases (review). Int J Mol Med 56: 139, 2025.
131. Wang Y, Wang W, Su L, Ji F, Zhang M, Xie Y, Zhang T and Jiao J: BACH1 changes microglial metabolism and affects astrogenesis during mouse brain development. Dev Cell 59: 108-124. e7, 2024.
132. Asadollahi E, Trevisiol A, Saab AS, Looser ZJ, Dibaj P, Ebrahimi R, Kusch K, Ruhwedel T, Möbius W, Jahn O, *et al*: Oligodendroglial fatty acid metabolism as a central nervous system energy reserve. Nat Neurosci 27: 1934-1944, 2024.
133. Molina-Gonzalez I, Holloway RK, Jiwaji Z, Dando O, Kent SA, Emelianova K, Lloyd AF, Forbes LH, Mahmood A, Skripuletz T, *et al*: Astrocyte-oligodendrocyte interaction regulates central nervous system regeneration. Nat Commun 14: 3372, 2023.
134. Birolini G, Verlengia G, Talpo F, Maniezzi C, Zentilin L, Giacca M, Conforti P, Cordiglieri C, Caccia C, Leoni V, *et al*: SREBP2 gene therapy targeting striatal astrocytes ameliorates Huntington's disease phenotypes. Brain 144: 3175-3190, 2021.
135. Tiwari V and Simons M: Lipid metabolism and neuroinflammation: What is the link? J Exp Med 222: e20241232, 2025.
136. Li M, Li Z, Yao Y, Jin WN, Wood K, Liu Q, Shi FD and Hao J: Astrocyte-derived interleukin-15 exacerbates ischemic brain injury via propagation of cellular immunity. Proc Natl Acad Sci USA 114: E396-E405, 2017.
137. Lee HG, Lee JH, Flausino LE and Quintana FJ: Neuroinflammation: An astrocyte perspective. Sci Transl Med 15: eadi7828, 2023.
138. Morkholt AS, Trabjerg MS, Oklinski MKE, Bolther L, Kroese LJ, Pritchard CEJ, Huijbers IJ and Nieland JDV: CPT1A plays a key role in the development and treatment of multiple sclerosis and experimental autoimmune encephalomyelitis. Sci Rep 9: 13299, 2019.
139. Castellani G, Croese T, Peralta Ramos JM and Schwartz M: Transforming the understanding of brain immunity. Science 380: eabo7649, 2023.
140. Sanmarco LM, Wheeler MA, Gutierrez-Vazquez C, Polonio CM, Linnerbauer M, Pinho-Ribeiro FA, Li Z, Giovannoni F, Batterman KV, Scalisi G, *et al*: Gut-licensed IFNγ(+) NK cells drive LAMP1(+)TRAIL(+) anti-inflammatory astrocytes. Nature 590: 473-479, 2021.
141. Miwa S, Kashyap S, Chini E and von Zglinicki T: Mitochondrial dysfunction in cell senescence and aging. J Clin Invest 132: e158447, 2022.
142. Byrns CN, Saikumar J and Bonini NM: Glial AP1 is activated with aging and accelerated by traumatic brain injury. Nat Aging 1: 585-597, 2021.
143. Sheng L, Shields EJ, Gospocic J, Sorida M, Ju L, Byrns CN, Carranza F, Berger SL, Bonini N and Bonasio R: Ensheathing glia promote increased lifespan and healthy brain aging. Aging Cell 22: e13803, 2023.
144. Madji Hounoum B, Mavel S, Coque E, Patin F, Vourc'h P, Marouillat S, Nadal-Desbarats L, Emond P, Corcia P, Andres CR, *et al*: Wildtype motoneurons, ALS-linked SOD1 mutation and glutamate profoundly modify astrocyte metabolism and lactate shuttling. Glia 65: 592-605, 2017.
145. Zelic M, Blazier A, Pontarelli F, Lamorte M, Huang J, Tasdemir-Yilmaz OE, Ren Y, Ryan SK, Shapiro C, Morel C, *et al*: Single-cell transcriptomic and functional studies identify glial state changes and a role for inflammatory RIPK1 signaling in ALS pathogenesis. Immunity 58: 961-979, e8 2025.
146. He D, Xu H, Zhang H, Tang R, Lan Y, Xing R, Li S, Christian E, Hou Y, Lorello P, *et al*: Disruption of the IL-33-ST2-AKT signaling axis impairs neurodevelopment by inhibiting microglial metabolic adaptation and phagocytic function. Immunity 55: 159-173.e9, 2022.

147. Zengeler KE, Hollis A, Deutsch T, Samuels JD, Ennerfelt H, Moore KA, Steacy EJ, Sabapathy V, Sharma R, Patel MK, *et al*: Inflammasome signaling in astrocytes modulates hippocampal plasticity. Immunity 58: 1519-1535 e11, 2025.
148. Chen ZP, Zhao X, Wang S, Cai R, Liu Q, Ye H, Wang MJ, Peng SY, Xue WX, Zhang YX, *et al*: GABA-dependent microglial elimination of inhibitory synapses underlies neuronal hyperexcitability in epilepsy. Nat Neurosci 28: 1404-1417, 2025.
149. Faustino AF, Martins IC, Carvalho FA, Castanho MA, Maurer-Stroh S and Santos NC: Understanding dengue virus capsid protein interaction with key biological targets. Sci Rep 5: 10592, 2015.
150. Haney MS, Palovics R, Munson CN, Long C, Johansson PK, Yip O, Dong W, Rawat E, West E, Schlachetzki JCM, *et al*: APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia. Nature 628: 154-161, 2024.
151. Wang S, Li B, Cai Z, Hugo C, Li J, Sun Y, Qian L, Remaley AT, Tcw J, Chui HC, *et al*: Cellular senescence induced by cholesterol accumulation is mediated by lysosomal ABCA1 in APOE4 and AD. Res Sq [Preprint] rs.3.rs-4373201, 2024.
152. Wang N, Pan Y, Starling SC, Haskell DH, Quintero AC, Kawatani K, Inoue Y, Shue F, Ma X, Aikawa T, *et al*: Neuronal ABCA7 deficiency aggravates mitochondrial dysfunction and neurodegeneration in Alzheimer's disease. Alzheimers Dement 21: e70112, 2025.
153. Wang X, Chen S, Xia X, Du Y, Wei Y, Yang W, Zhang Y, Song Y, Lei T, Huang Q and Gao H: Lysosome-targeting protein degradation through endocytosis pathway triggered by polyvalent nano-chimera for AD therapy. Adv Mater 37: e2411061, 2025.
154. Xu X, Xuan S, Chen S, Liu D, Xiao Q and Tu J: Increased excitatory amino acid transporter 2 levels in basolateral amygdala astrocytes mediate chronic stress-induced anxiety-like behavior. Neural Regen Res 20: 1721-1734, 2025.
155. Stephenson RA, Sepulveda J, Johnson KR, Lita A, Gopalakrishnan J, Acri DJ, Beilina A, Cheng L, Yang LG, Root JT, *et al*: Triglyceride metabolism controls inflammation and microglial phenotypes associated with APOE4. Cell Rep 44: 115961, 2025.
156. Liu L, Zhang K, Sandoval H, Yamamoto S, Jaiswal M, Sanz E, Li Z, Hui J, Graham BH, Quintana A and Bellen HJ: Glial lipid droplets and ROS induced by mitochondrial defects promote neurodegeneration. Cell 160: 177-190, 2015.
157. Jernberg JN, Bowman CE, Wolfgang MJ and Scafidi S: Developmental regulation and localization of carnitine palmitoyltransferases (CPTs) in rat brain. J Neurochem 142: 407-419, 2017.
158. Dressman JW, Bayram MF, Angel PM, Drake RR and Mehta AS: Single-cell multiomic MALDI-MSI analysis of lipids and N-glycans through affinity array capture. Anal Chem 97: 12493-12502, 2025.
159. Endle H, Horta G, Stutz B, Muthuraman M, Tegeder I, Schreiber Y, Snodgrass IF, Gurke R, Liu ZW, Sestan-Pesa M, *et al*: AgRP neurons control feeding behaviour at cortical synapses via peripherally derived lysophospholipids. Nat Metab 4: 683-692, 2022.
160. Bitar L, Uphaus T, Thalman C, Muthuraman M, Gyr L, Ji H, Domingues M, Endle H, Groppa S, Steffen F, *et al*: Inhibition of the enzyme autotaxin reduces cortical excitability and ameliorates the outcome in stroke. Sci Transl Med 14: eabk135, 2022.
161. Xia J, Yang L, Huang C, Deng S, Yang Z, Zhang Y, Zhang C and Song C: Omega-3 polyunsaturated fatty acid eicosapentaenoic acid or docosahexaenoic acid improved ageing-associated cognitive decline by regulating glial polarization. Mar Drugs 21: 398, 2023.
162. Zgorzynska E, Stulczewski D, Dziedzic B, Su KP and Walczewska A: Docosahexaenoic fatty acid reduces the pro-inflammatory response induced by IL-1β in astrocytes through inhibition of NF-κb and AP-1 transcription factor activation. BMC Neurosci 22: 4, 2021.
163. Konttinen H, Gureviciene I, Oksanen M, Grubman A, Loppi S, Huuskonen MT, Korhonen P, Lampinen R, Keuters M, Belaya I, *et al*: PPARβ/δ-agonist GW0742 ameliorates dysfunction in fatty acid oxidation in PSEN1δE9 astrocytes. Glia 67: 146-159, 2019.
164. Chehaibi K, le Maire L, Bradoni S, Escola JC, Blanco-Vaca F and Slimane MN: Effect of PPAR-β/δ agonist GW0742 treatment in the acute phase response and blood-brain barrier permeability following brain injury. Transl Res 182: 27-48, 2017.
165. Spencer M, Kulbe JR, Venkatesh V, Laird A, Ford M, O'Brien S, Boustani A, Schlachetzki JCM and Fields JA: Caloric restriction mimetic 2-deoxyglucose alters metabolic and transcriptomic phenotype in association with changes in chromatin accessibility in human astrocytes. Sci Rep 15: 19368, 2025.
166. Kratzer A, Buchebner M, Pfeifer T, Becker TM, Uray G, Miyazaki M, Miyazaki-Anzai S, Ebner B, Chandak PG, Kadam RS, *et al*: Synthetic LXR agonist attenuates plaque formation in apoE-/- mice without inducing liver steatosis and hypertriglyceridemia. J Lipid Res 50: 312-326, 2009.
167. Goodman LD, Ralhan I, Li X, Lu S, Moulton MJ, Park YJ, Zhao P, Kanca O, Ghaderpour Taleghani ZS, Jacquemyn J, *et al*: Tau is required for glial lipid droplet formation and resistance to neuronal oxidative stress. Nat Neurosci 27: 1918-1933, 2024.
168. Cheng X, Geng F, Pan M, Wu X, Zhong Y, Wang C, Tian Z, Cheng C, Zhang R, Puduvalli V, *et al*: Targeting DGAT1 ameliorates glioblastoma by increasing fat catabolism and oxidative stress. Cell Metab 32: 229-242 e8, 2020.
169. Lee H, Wheeler MA and Quintana FJ: Function and therapeutic value of astrocytes in neurological diseases. Nat Rev Drug Discov 21: 339-358, 2022.
170. van Deijk AF, Camargo N, Timmerman J, Heistek T, Brouwers JF, Mogavero F, Mansvelder HD, Smit AB and Verheijen MH: Astrocyte lipid metabolism is critical for synapse development and function in vivo. Glia 65: 670-682, 2017.
171. Lee JA, Hall B, Allsop J, Alqarni R and Allen SP: Lipid metabolism in astrocytic structure and function. Semin Cell Dev Biol 112: 123-136, 2021.

Copyright © 2025 Wang et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.