Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU26869

Lipid Droplets in Alzheimer's Disease: Roles and Implications

Haifan Yu

Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, China
1360284695@qq.com

Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder which becomes one of the most costly, fatal, and burdening diseases in this century. Lipid droplets (LDs), once considered passive storage organelles, are now recognized as dynamic structures involved in multiple biological process, with accumulating evidence suggesting the association between LDs and AD. This review systematically synthesizes findings from more than forty core studies published over the past decade, summarizing current knowledge on LD biogenesis and function, their accumulation in various brain cell types, and their dual role in either mitigating lipotoxicity or exacerbating neurodegeneration in AD. We propose bidirectional lipid trafficking between neurons and glial cells as a critical future research direction, postulating its important yet uncharacterized contribution to AD pathogenesis. Understanding LD dynamics and their cross-talk among brain cells may reveal innovative strategies for AD therapy.

Keywords: Lipid droplets, Alzheimer' s disease, Lipid trafficking

1. Introduction

Alzheimer's disease (AD) is swiftly converting into one of the most costly and fatal diseases in this century, which will triple the prevalence of dementia worldwide by 2050 [1]. AD is a progressive neurodegenerative disease distinguished by amyloid-beta (Aβ) deposition, tau pathology, dysfunctional synaptic transmission and neuronal loss. Lipid droplets (LDs), though identified by Alois Alzheimer in 1907, have not gained much attention since then. Recently, growing evidence have shown the convincible associations between AD and LDs accumulation, with increasing genes participated in lipid metabolism such as APOE (apolipoprotein E), ABCA7 (ATP-binding cassette, sub-family A, member 7), SORL1 (sortilin-related receptor 1) and CLU (clusterin) [2] considered as risky factors of AD. These results strongly indicate that dysregulated lipid metabolism plays an important, yet not fully understood, role in the AD pathogenesis.

LDs gather neutral lipids such as triglycerides (TGs) and cholesterol esters (CEs) in a wide range of cells. This dynamic organelle is not only essential for the punctual release of fatty acids (FAs) needed for lipids biosynthesis, energy production and cell signaling, but also protects cells from the accumulating lipotoxicity [3]. Contributing to 50% dry weight of the brain, lipids maintain its anatomic as well as functional hemostasis, while LDs are observed in both neurons and glial cells. Given this high lipid content, proper lipid storage and metabolism are essential for maintaining neuronal function. LDs were initially considered simple fat storage depots but are now recognized as

DOI: 10.54254/2753-8818/2025.AU26869

multifunctional organelles involved in different biological processes [4]. Considering LDs may play an important role in brain cells and the little attention they gain in AD study, there is no doubt that LDs will be a future research direction and potential therapeutic target for neurodegeneration. This review explores the biogenesis and function of LDs, their physiological and AD- related pathological functions in different brain cells, and lipid trafficking between these cells in AD pathology. Our work delineates the current mechanistic understanding by which LDs drive AD pathogenesis and identifies the existing uncertainties, which may point the way for future direction.

2. Function and biogenesis of lipid droplets

2.1. Biogenesis and regulation

The most empirically supported model for LDs biogenesis includes the lipid synthesis, LDs nucleation and cytoplasmic growth of neutral lipids from the endoplasmic reticulum (ER) [5], with several key enzymes and proteins regulating it. Basically, ER is the foundation of LDs biogenesis, accumulating neutral lipids in its membrane leaflets and forming lens-like structure which ultimately bud off into nascent LDs.

2.1.1. Lipid synthesis

As the most abundant neutral lipids in eukaryotes, TGs and CEs serve as mediators and modulators of numerous cellular processes, synthesized by esterified diacylglycerol catalyzed by diacylglycerol acyltransferases (DGAT) and acyl-CoA cholesterol O-acyltransferases (ACAT) separately. Crucially, genetic deletion of DGAT1 and DGAT2 in mice ablates the cytoplasmic LDs content, while exogenous expression of DGAT1 is sufficient for the restoration of LDs formation [5]. The results suggest the fundamental role of lipids synthesis in LDs biogenesis.

2.1.2. LDs nucleation

Nucleation represents the initiation of phase separation within a blend, such as mixtures of gases, liquids or solids. This phenomenon occurs when a reduction in the contact between dissimilar molecules within the mixture becomes energetically favorable. When these dissimilar molecules reach critical nucleation concentration (CNC), Neutral lipids within the ER bilayer can condense into a lens, which is critical for LDs formation [6]. Beyond the CNC, few TG clusters can outstrip the energy barrier that needed for nucleation and transfer to nascent LDs or blisters. Many proteins and lipids are involved in this whole process such as the Seipin, lipid droplet assembly factor 1 (LDAF1) and PLIN3 [7]. Further research is needed to explore the precise molecular interaction and regulation mechanism of lens formation.

2.1.3. Cytoplasmic growth of neutral lipids

After nucleation, the ER neutral lipids will bud into spherical LDs through overcoming the energy obstacle of their membrane leaflets deformation and transfer in the form of LDs [7]. To achieve this energy obstacle, several proteins and lipids are involved in the promotion of LDs budding through reducing the cytosolic surface tension [8]. Budded LDs may then develop via a process called Ostwald ripening in order to reach its full storage potential, facilitating the transit of neutral lipids from smaller, naiver LDs to larger, maturer and functionally complete LDs [9]. Besides,

DOI: 10.54254/2753-8818/2025.AU26869

phospholipids could be transferred from the ER to LDs through ORP5 proteins and promote cytoplasmic LDs growth [10], interpreting another modulator of LDs' growth.

The procedure mentioned below is the biogenesis of cytoplasmic LDs, which has been the most well characterized form of LDs so far. With the development of cell biology, we also recognized nuclear LDs and luminal LDs, but we haven't seen much correlation between the two types of LDs and AD. Recent studies have shown that LDs biogenesis is tightly linked to cellular stress responses [11]. For example, oxidative stress and ER stress can trigger LDs biogenesis as a protective mechanism against lipotoxicity.

2.2. Functional diversity

LDs are not merely passive lipid storage site but functional organelles that participate in multiple process such as ablating oxidate stress, preserving membrane hemostasis and degrading misfolded-proteins. For example, Evidence in human cancer cell shows that LDs formation is functioned as a protective mechanism to lower the ROS levels instead of enhancing it. Knockdown of endogenous expression of FABP3 and FABP7 (2 genes involved in uptake of fatty acids) significantly reduce the LDs formation and cancer cell proliferation during hypoxia, while genetic deletion of PLIN2 (LD formation associated gene) shows similar result. These cellular experiments suggest that lacking storage of fatty acids in LDs impairs the protection mechanism of ROS toxicity in cancer cells during hypoxia [12]. Current studies based on yeast model also purpose the interesting possibility that LDs can participate in protein maturation and modulate the folding condition of proteins by releasing a sterol-derived molecule that somehow functions as a chemical chaperone which play a role in promoting the refolding of misfolded proteins or in aiding their degradation pathways [13]. In many cell types, the major lipids stored in the droplet center correspond to TGs and CEs with a series of different FA side chains. These are important for supplying phospholipid precursors and cholesterol to cell membranes, which maintains the hemostasis of ER and serve as a constant supply for cell membrane [14].

Given these diverse roles, LDs may act as a potential crossing between proteins and lipids metabolism homeostasis. Abnormal changes happened in each step may lead to the consequence of breaking the Cellular material metabolism homeostasis. As a result, dysregulation of LDs dynamics can have profound implications for health and disease.

3. Link of lipid droplets with Alzheimer's disease

Currently, AD is characterized by senile plaques consist of deposited Aβ proteins and neurofibrillary tangles consist of hyperphosphorylated tau, but growing evidence shows that LDs accumulation is highly involved in the AD pathogenesis. LDs accumulation is found earlier than neurofibrillary tangles as well as senile plaques in both AD mouse models and the AD postmortem brains. More pathologic Aβ plaques deposition and neurofibrillary tangles formation are found in the LDs accumulating AD animal models [4], suggesting that AD pathogenesis could be exacerbated by dysfunctional lipid metabolism. Another study finds plasma of aged type 2 diabetes patients' cells lead to inhibited lipophagy and lipids accumulation in cultured microglia, with suppression of this pathway improve the cognitive function in mouse [15], interpreting LDs accumulation may contribute to cognitive impairment, which is also the major symptom of AD. However, LDs formation is not always a bad thing, the loss of functional tau proteins in glial cells could make them more sensitive to neuronal oxidate stress for disrupting normal LDs formation [16]. Recent study also shows protective alleles of AD upregulate neuronal CLU expression and promote neuron

DOI: 10.54254/2753-8818/2025.AU26869

excitability through facilitating lipid transport from neuron to glia, inducing LDs formation in astrocytes [17]. These changes then weaken the astrocytic function of glutamate uptake thereby affecting neuron excitability, showing a possible protective effect of the LDs in the AD.

The APOE gene mediate the lipid homeostasis and lipid transportation in brain, with the APOE4 variant as the riskiest genetic factor. Recent study revealed an unusual pathway that astrocytic APOE4 can traffic to LDs via ER–LD contacting membrane bridges instead of translocating into ER [18], modulating droplet size and leading to LDs accumulation in astrocytes, which then aggravate the AD pathology. Study on microglia also find transcriptomic changes in APOE4 microglia, showing genes involved in oxidative phosphorylation process are downregulated dramatically, which could contribute to dysfunctional FA oxidation and lead to lipids metabolism dysregulation. More LDs accumulation is observed in the APOE4 microglia compared to the APOE3 or APOE-Knockout microglia, causing more phosphorylated Tau (pTau) proteins and apoptosis in the neurons [19], which contribute to the memory loss and cognitive impairment in AD patients. These results indicate the necessity of LDs formation in AD pathogenesis.

4. Ad-related physiological and pathological function of lipid droplets in different types of brain cells

4.1. Neurons

Physiologically, neurons exhibit low TG concentrations, with limited in vivo evidence demonstrating LDs accumulation in it [20]. Under normal conditions, neurons have relatively few LDs, as they preferentially oxidize FAs for energy and reconstruct cellular membranes by turning over TGs constantly to synthesis phospholipids. However, neuronal LDs accumulation could be enhanced by cellular stress, aging and treatment of high fatty acid in vitro. Neurons are relatively vulnerable to neutral lipids accumulation because of lacking antioxidant protecting system contrast to other glial cells in the brain [4]. Pathologic neutral lipids accumulation can potentially contribute to neurodegeneration due to the increasing reactive oxygen species (ROS) generation induced by dysregulated fatty acid catabolism. The AD protective genes involved in lipid synthesis pathway reduce the neuronal LDs accumulation and increase the neuronal excitability through CLU expression [17], which explores the protective mechanism of reducing neuronal LDs accumulation in AD pathology.

LDs in neurons also participate in synaptic plasticity by supplying lipids for membrane remodeling. For example, energetic storage capacity in neuronal lipid bilayer is enhanced in the form of long-term potentiation (LTP) as a result of electrical stimulation, enabling neuronal learning process and long-term memory formation [21]. LDs play an important role in this procedure as it can supply phospholipids to reconstruct the neuronal membrane and keep its' hemostasis, breaking the balance of lipid metabolism may impair the LTP and memory storage in neurodegeneration diseases.

4.2. Astrocytes

Astrocytes, the most abundant cell type in the CNS, also the main lipid supplier in the brain, store fatty acids in LDs and release them via lipolysis for neuronal energy metabolism. Lipids play a crucial role in astrocytic function, such as producing energy, membrane hemostasis and consisting intercellular signal pathway. Since most of the lipoproteins can't permeate the blood brain barrier (BBB), the lipids synthesized in astrocyte are functional importantly to neurons and other glia.

DOI: 10.54254/2753-8818/2025.AU26869

Excess FAs from neuron membranes may lead to the LDs accumulation in astrocytes via FAs binding protein (FABP), while the dietary FAs cross the BBB may have a synergetic effect [22], serving as buffer pools for either toxic or energy-producing FAs in CNS.

Additionally, there is growing evidence that astrocytic stored lipids in LDs have a significant physiological and protective meaning in the CNS. The main purpose for astrocyte to form LDs is to provide fuel for beta-oxidate, supplying alternative energy for the cells. Under cell stress, however, the low glucose condition in astrocytes switch the main energy source from carbohydrate to lipids [23], which promotes the LDs accumulation in astrocyte. LDs in astrocytes modulate inflammatory responses by sequestering oxidized lipids that would otherwise activate pro-inflammatory pathways. For example, it has been shown that conjugated linoleic acid could modify the secretion of TNF-α, RANTES, and IL-1β in cell-cultured astrocytes [24].

Clinically, impaired lipid hemostasis in AD' s early phase, especially LDs accumulation in brain cells, has been confirmed by abundant experimental evidence. As the most important modulator of lipid metabolism in brain, astrocytes demonstrate metabolic shift and LDs accumulation induced by APOE4 during AD pathogenesis [25]. A recent study reveals that deficient oxidative phosphorylation in astrocytes triggers lipid metabolic dysregulation and reactive astrogliosis, which henceforth inhibits the biogenesis of lipids demanded for oligodendrocyte-mediated myelin turnover, activating microglial neuroinflammation as well as aggravating cognitive impairment in AD patients [26]. Since we discuss both the physiologically protective and pathologically destructive roles of LDs accumulation in astrocytes. It is still mysterious how do the LDs accumulating astrocytes switch from a protector in CNS to the main promoter in AD pathology, which may shed light on the mechanism of starting the early stage of AD.

4.3. Microglia

Functioning as the principal resident immune cells within the CNS, microglia express a diverse array of receptors sensitive to fluctuations in lipidomic composition. The increased formation of LDs in microglia indicate activated phagocytosis or pathological conditions, affecting their physiological roles, containing capabilities of immune defense, phagocytosis, and polarization adversely. For instance, lack of adipose triglyceride lipase (ATGL), resulting in decreased intracellular free fatty acids (FFAs) concentrations and increased accumulation of LDs, weaken the phagocytosis function and defense capabilities of microglia [27]. Microglia have several main sources for LDs formation, comprising the phagocytosis of dead cells or pathogens, lipoprotein particles and neuron-derived lipids [28]. When the lipids are overloaded in microglia, the impairment of phagocytosis may serve as negative feedback to limit the excessive lipids accumulation.

Microglial LDs are also linked to immune responses. LDs may function as the signaling platform which modulate the immune response. Activation of toll receptors, one of the most important receptors for innate immune pathogens, could induce LDs accumulation in microglia through upregulation of lipid-synthesis enzymes, which may then exacerbate neuroinflammation [29]. Intriguningly, recent study has found that CRISPER-knockout (CRISPER-KO) of an AD risk gene-S100A1, which is a downstream modulator of the lipopolysaccharide (LPS) and toll-like receptor 4 (TLR4) response in macrophages, could reduce the LDs in microglia [19]. These lipid-laden microglia upregulate the pro-inflammation pathway as the response to the innate immune triggers, such as virus or bacteria [30].

Accumulating evidence implicates dysregulated LDs accumulation within microglia as a significant contributor to the AD pathogenesis. The Aβ proteins exposure is sufficient to induce the

DOI: 10.54254/2753-8818/2025.AU26869

LDs accumulation in microglia [31], which impair phagocytosis function and aggravate the tau pathology in AD patients. Increased microglial LDs accumulation has been observed in mouse brains with serve pTau pathology, which can be exacerbated by neuronal AMP-activated protein kinase (AMPK) depletion [32]. DGAT2, a key gene involved in lipid biosynthesis and LDs formation, is upregulated in both the 5xFAD mice model and AD patients' s brains, with enhanced microglial uptake of Aβ as well as decreased plaque load observed in AD mouse models after pharmacological treatment of DGAT2 [31], suggesting reducing LDs formation could be a potential therapeutic target of AD.

4.4. Oligodendrocytes

The main function of oligodendrocytes is to mediate the myelin wrapping around the axons, which ensure rapid electrical conduction of neurons. Oligodendrocytes rely on LDs for myelin sheath maintenance, as myelin is highly enriched in lipids. Seipin is one of the key proteins involved in LDs formation. Recent study has found that deficient Seipin dysregulates physiologic differentiation of the oligodendrocyte precursor cells, which subsequently decreases oligodendrocytes numbers, producing less myelin proteins and diminishing thickness of myelin. Behavioral tests indicate impaired motor coordination and spatial cognition in mice [33]. This suggests that disruption of LDs homeostasis in oligodendrocytes can lead to myelin degeneration, a feature observed in early AD. Higher LDs have also been reported in immature precursors contrasted with mature oligodendrocytes [4], indicating that LDs in oligodendrocyte may contribute to the myelin maturation in our central neuronal system. But the mechanism of how LDs affect the myelin maturation still remains unknown, and more experiments are needed to confirm the correlation between LDs in oligodendrocytes and AD.

In conclusion, Aβ deposition and neuron inflammation may induce LDs accumulation in astrocytes during the early stage of AD, disrupting lipid homeostasis in CNS. As the disease progresses, Aβ or other innate immune triggers could induce LDs accumulation in microglia, causing transcriptomic changes and dysfunctional phagocytosis which exacerbate neuron inflammation and Aβ pathology. LDs-accumulating glial cells ultimately drive neuronal lipotoxicity and tau pathology, aggravating AD-associated cognitive impairment or memory loss.

DOI: 10.54254/2753-8818/2025.AU26869

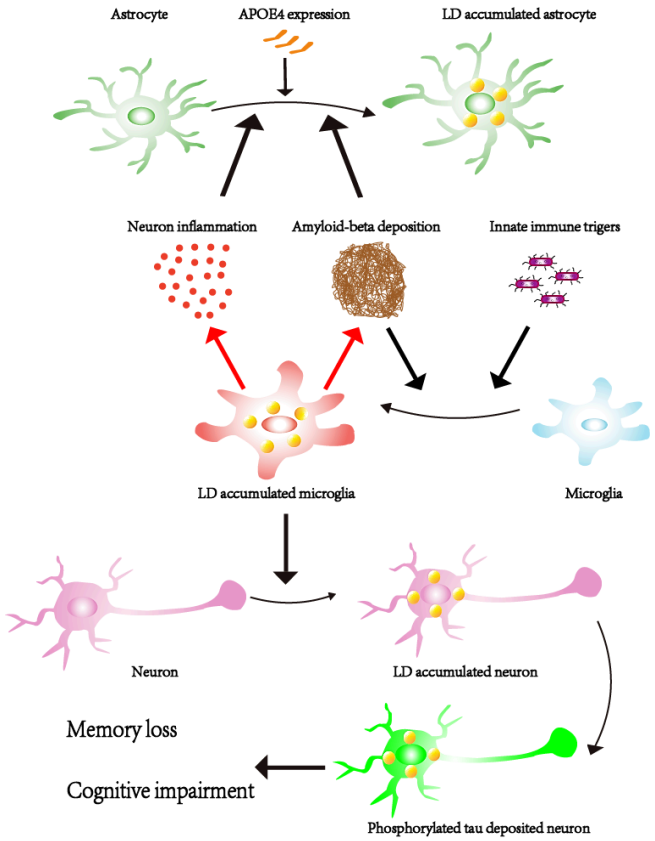

Figure 1. AD-related pathological function of LDs in different brain cells

5. Bidirectional lipid trafficking between neurons and glial cells in AD

Bidirectional lipid trafficking between neurons and glial cells in AD are becoming more and more important as the study develop. We discuss the lipid metabolic dysregulation among different types of brain cells during AD pathology, and the deterioration of it leads to the abnormal lipid transport between brain cells. Since the abnormal lipid transport can induce the lipid accumulation or LDs formation from one cell to another, this makes it not only a crucial mechanism for disease deterioration but also a potential treatment target for neurodegenerative disease. Here we will introduce the lipid transport in neuron-astrocyte and neuron-microglia, which is also shown in Figure2.

5.1. Neuron-astrocyte lipid trafficking

The lipid trafficking between astrocytes and neurons is a well-characterized process. With protein mass spectrometry, researchers confirm the significant upregulation of APOE proteins in purified reactive astrocytes media, suggesting concentrated APOE expression in pathology-induced astrocyte and potentially crucial function of it [34]. APOE is necessary for the formation of lipoprotein particles, which is the major mechanism for lipid trafficking [35], while high expression of APOE suggest high secretion of lipoprotein particles. However, combinatorial exposure to a wide range of extracellular factors, including growth factors, cytokines and hormones under multiple pathologic conditions induce the astrocytes transfer into another transcriptional type-reactive astrocytes, which could cause both destructive and protective effects on the CNS [36]. An interesting study finds that the IL-1 induced reactive astrocyte could secret toxic lipoprotein particles and increase the cell death

DOI: 10.54254/2753-8818/2025.AU26869

of oligodendrocytes or neurons in vitro, while the APOE-antibodies could reverse the astrocyte-induced cell death [34], interpreting the possibility that lipid transport induces the neuron-toxicity during pathologic conditions such as AD. Another research reveals that the specific expression of APOE in astrocytes is adequate to reverse the pathological state of fibrillar amyloid - beta (fAβ) and trigger a reactive response in microglia [37]. These recent studies support the perspective that astrocyte may play a central role in APOE mediated amyloid plaque pathology as well as lipid dysfunction in AD pathology.

Besides, the discovery of lipids trafficking from neurons to glial cells has gained more and more attention recently. Not only carbohydrate oxidation but also lipid metabolism is coupled in both the glial cells and neurons [35]. Neurons produce extra toxic FFAs in response to oxidate stress. Since neurons have a poor ability to form LDs and protect the cells from lipotoxicity, they need to transfer these fatty acids into the glia cells around it, which is mostly astrocyte. While the knock-down of APOE could reduce the lipids trafficking from neuron to glial cells, indicating the APOE also highly involved in this procedure [4]. Decreased FA sequestering in LDs as well as diminished lipid transport efficiency could explain the APOE-induced neuronal dysfunction, causing energy metabolic impairment and neurite outgrowth in neurons [26]. Recent studies prove that neuron-to-glia lipid transport pathway induced by ROS is highly regulated by several AD-associated genes including VPS26 and ABCA1, while loss of these genes reduce the LDs formation in astrocyte, which is neuroprotective [38]. An endolysosomal protein-TTYH1 enriched in astrocyte facilitates autophagic flux and LD degradation process, while the depletion of this gene leads to impaired protective function in LDs and increasing neuro-derived lipotoxicity [39], suggesting a potential pathologic pathway in AD brains. Correspondingly, the AD protective alleles reduce the neuronal LDs accumulation but induce LDs formation in astrocyte through CLU expression [17], which means enhancing neuron to astrocyte lipid transport might be the mechanism of AD protective alleles. Further experiments will be needed to explore the exact molecular pathway of the lipid transport between astrocyte and neuron, hoping to find some molecular target for the AD treatment.

5.2. Neuron-microglia lipid trafficking

LDs accumulation in microglia raises increasing attention nowadays. Termed as LD-accumulating microglia (LDAM), the microglia of aged mouse accumulate LDs and exhibit transcriptional changes, while the same type of microglia has also been seen in AD patients' brain sections [19]. Intriguingly, in Haney's study, they find co-culture of the microglia with LDs accumulation and neurons may induce LDs in these neurons with the same type of lipids as the LDs in microglia. Subsequent research reveals that activated microglia prompt neuronal LDs accumulation. Moreover, it identifies lactic acid from microglia as a principal modulator of this mechanism [40]. These findings indicate a potential unknown pathway that transfer the lipids from LDAM to neurons, which can be neurotoxic. Further studies are essential to explore that pathway and confirm the molecular mechanism of it.

Microglia can uptake the excessive FFAs or lipoprotein particles secreted by stressed neurons to reduce the lipotoxicity. Nevertheless, the microglia in AD brains demonstrate impaired phagocytosis as the amyloid-β proteins affect the microglia through APOE4-LILRB4 combination [41]. As a result, these neurotoxic lipids accumulate with the disease develop, contributing to the memory loss or cognitive impairment in AD patients. It is also reported that APOE4 induces a lipid-accumulated state that renders microglial calcium activity as the response of neuronal electrical signals. They successfully identified that APOE4 microglia disrupts the coordinated electrical physiology among neurons and glial cells via decreasing phagocytosis of extracellular FAs and lipoproteins [42].

DOI: 10.54254/2753-8818/2025.AU26869

TREM2, one of the star-molecular in macrophage studies, regulates crucial cellular metabolic pathways such as lipid metabolism and oxidative phosphorylation, triggering the APOE subsequent signal activation which could lead to LDs accumulation and pro-inflammation effect [28]. This comes up with a potential pathway that the neurons or astrocytes could secret the APOE through lipoprotein particles, which could then affect the clearance function and lipid homeostasis of microglia by binding with the LILRB4 or TREM2 receptors. But still, many details have not been confirmed in this speculation and more further experiments are needed to identify the mechanism of the lipids' crosstalk between neurons and glia cells.

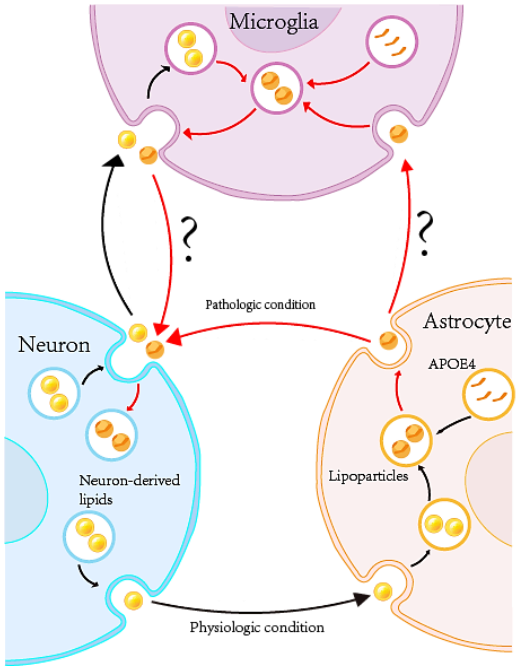

Figure 2. Lipid trafficking during physiologic and AD-pathologic conditions

6. Conclusion

In summary, LDs play a dual role in AD—protecting cells from lipotoxicity while potentially exacerbating neurodegeneration and neuroinflammation. In this review article, we look back the latest studies about the biogenesis process of LDs, the correlation of LDs and AD, the physiological and pathological function of LDs in brain cells and the lipid trafficking between different brain cells. This area has not gained much attention until now, and more details need to be further investigated. Although accumulating evidence reveals the LDs might play a significant role in AD pathogenesis, only a small number of clinical trials targeting LDs formation are currently underway. The further study on LD dynamics and lipid transport among different brain cell types may provide novel therapeutic strategies for AD.

References

[1] Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. Lancet. 2021; 397(10284): 1577-1590. doi: 10.1016/S0140-6736(20)32205-4

[2] Giri M., Zhang M., Lu Y. Genes associated with Alzheimer's disease: An overview and current status. Clin. Interv. Aging. 2016; 11: 665–681. doi: 10.2147/CIA.S105769.

[3] Olzmann JA, Carvalho P. Dynamics and functions of lipid droplets. Nat Rev Mol Cell Biol. 2019; 20(3): 137-155. doi: 10.1038/s41580-018-0085-z

DOI: 10.54254/2753-8818/2025.AU26869

[4] Ralhan I, Chang CL, Lippincott-Schwartz J, Ioannou MS. Lipid droplets in the nervous system. J Cell Biol. 2021; 220(7): e202102136. doi: 10.1083/jcb.202102136
[5] Gao M, Huang X, Song B-L, Yang H. The biogenesis of lipid droplets: lipids take center stage. Prog. Lipid Res. 2019; 75: 100989. doi: 10.1016/j.plipres.2019.100989.
[6] Choudhary V, Ojha N, Golden A, Prinz WA. A conserved family of proteins facilitates nascent lipid droplet budding from the ER. J Cell Biol. 2015 Oct 26; 211(2): 261-71. doi: 10.1083/jcb.201505067. PMID: 26504167; PMCID: PMC4621845.
[7] Thiam AR, Ikonen E. Lipid Droplet Nucleation. Trends Cell Biol. 2021; 31(2): 108-118. doi: 10.1016/j.tcb.2020.11.006
[8] Chorlay A, Monticelli L, Veríssimo Ferreira J, et al. Membrane Asymmetry Imposes Directionality on Lipid Droplet Emergence from the ER. Dev Cell. 2019; 50(1): 25-42.e7. doi: 10.1016/j.devcel.2019.05.003
[9] Deslandes F, Thiam AR, Forêt L. Lipid Droplets Can Spontaneously Bud Off from a Symmetric Bilayer. Biophys J. 2017; 113(1): 15-18. doi: 10.1016/j.bpj.2017.05.045
[10] Du X, Zhou L, Aw YC, et al. ORP5 localizes to ER-lipid droplet contacts and regulates the level of PI(4)P on lipid droplets. J Cell Biol. 2020; 219(1): e201905162. doi: 10.1083/jcb.201905162
[11] Henne WM, Reese ML, Goodman JM. The assembly of lipid droplets and their roles in challenged cells. EMBO J. 2019; 38(9): e101816. doi: 10.15252/embj.2019101816
[12] Bensaad K, Favaro E, Lewis CA, et al. Fatty acid uptake and lipid storage induced by HIF-1α contribute to cell growth and survival after hypoxia-reoxygenation. Cell Rep. 2014; 9(1): 349-365. doi: 10.1016/j.celrep.2014.08.056
[13] Moldavski O, Amen T, Levin-Zaidman S, et al. Lipid Droplets Are Essential for Efficient Clearance of Cytosolic Inclusion Bodies. Dev Cell. 2015; 33(5): 603-610. doi: 10.1016/j.devcel.2015.04.015
[14] Velázquez AP, Tatsuta T, Ghillebert R, Drescher I, Graef M. Lipid droplet-mediated ER homeostasis regulates autophagy and cell survival during starvation. J Cell Biol. 2016; 212(6): 621-631. doi: 10.1083/jcb.201508102
[15] Li Q, Zhao Y, Guo H, et al. Impaired lipophagy induced-microglial lipid droplets accumulation contributes to the buildup of TREM1 in diabetes-associated cognitive impairment. Autophagy. 2023; 19(10): 2639-2656. doi: 10.1080/15548627.2023.2213984
[16] Goodman LD, Ralhan I, Li X, et al. Tau is required for glial lipid droplet formation and resistance to neuronal oxidative stress. Nat Neurosci. 2024; 27(10): 1918-1933. doi: 10.1038/s41593-024-01740-1
[17] Zhao X, Li Y, Zhang S, et al. Alzheimer's disease protective allele of Clusterin modulates neuronal excitability through lipid-droplet-mediated neuron-glia communication. Mol Neurodegener. 2025; 20(1): 51. Published 2025 May 3. doi: 10.1186/s13024-025-00840-1
[18] Windham IA, Powers AE, Ragusa JV, et al. APOE traffics to astrocyte lipid droplets and modulates triglyceride saturation and droplet size. J Cell Biol. 2024; 223(4): e202305003. doi: 10.1083/jcb.202305003
[19] Haney MS, Pálovics R, Munson CN, et al. APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia. Nature. 2024; 628(8006): 154-161. doi: 10.1038/s41586-024-07185-7
[20] Yang C, Wang X, Wang J, et al. Rewiring Neuronal Glycerolipid Metabolism Determines the Extent of Axon Regeneration. Neuron. 2020; 105(2): 276-292.e5. doi: 10.1016/j.neuron.2019.10.009
[21] Scott HL, Bolmatov D, Premadasa UI, et al. Cations Control Lipid Bilayer Memcapacitance Associated with Long-Term Potentiation. ACS Appl Mater Interfaces. 2023; 15(37): 44533-44540. doi: 10.1021/acsami.3c09056
[22] Pan Y, Scanlon MJ, Owada Y, Yamamoto Y, Porter CJ, Nicolazzo JA. Fatty Acid-Binding Protein 5 Facilitates the Blood-Brain Barrier Transport of Docosahexaenoic Acid. Mol Pharm. 2015; 12(12): 4375-4385. doi: 10.1021/acs.molpharmaceut.5b00580
[23] Weightman Potter PG, Vlachaki Walker JM, Robb JL, et al. Basal fatty acid oxidation increases after recurrent low glucose in human primary astrocytes. Diabetologia. 2019; 62(1): 187-198. doi: 10.1007/s00125-018-4744-6
[24] Saba F, Sirigu A, Pillai R, et al. Downregulation of inflammatory markers by conjugated linoleic acid isomers in human cultured astrocytes. Nutr Neurosci. 2019; 22(3): 207-214. doi: 10.1080/1028415X.2017.1367130
[25] Yin F. Lipid metabolism and Alzheimer's disease: clinical evidence, mechanistic link and therapeutic promise. FEBS J. 2023; 290(6): 1420-1453. doi: 10.1111/febs.16344
[26] Mi Y, Qi G, Vitali F, et al. Loss of fatty acid degradation by astrocytic mitochondria triggers neuroinflammation and neurodegeneration. Nat Metab. 2023; 5(3): 445-465. doi: 10.1038/s42255-023-00756-4
[27] Chandak PG, Radovic B, Aflaki E, et al. Efficient phagocytosis requires triacylglycerol hydrolysis by adipose triglyceride lipase. J Biol Chem. 2010; 285(26): 20192-20201. doi: 10.1074/jbc.M110.107854
[28] Krasemann S, Madore C, Cialic R, et al. The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases. Immunity. 2017; 47(3): 566-581.e9. doi: 10.1016/j.immuni.2017.08.008

DOI: 10.54254/2753-8818/2025.AU26869

[29] Pereira-Dutra FS, Teixeira L, de Souza Costa MF, Bozza PT. Fat, fight, and beyond: The multiple roles of lipid droplets in infections and inflammation. J Leukoc Biol. 2019; 106(3): 563-580. doi: 10.1002/JLB.4MR0119-035R
[30] Xin W, Pan Y, Wei W, et al. TGF-β1 Decreases Microglia-Mediated Neuroinflammation and Lipid Droplet Accumulation in an In Vitro Stroke Model. Int J Mol Sci. 2023; 24(24): 17329. Published 2023 Dec 10. doi: 10.3390/ijms242417329
[31] Prakash P, Manchanda P, Paouri E, et al. Amyloid-β induces lipid droplet-mediated microglial dysfunction via the enzyme DGAT2 in Alzheimer's disease. Immunity. 2025; 58(6): 1536-1552.e8. doi: 10.1016/j.immuni.2025.04.029
[32] Li Y, Munoz-Mayorga D, Nie Y, et al. Microglial lipid droplet accumulation in tauopathy brain is regulated by neuronal AMPK. Cell Metab. 2024; 36(6): 1351-1370.e8. doi: 10.1016/j.cmet.2024.03.014
[33] Cui W, Yang J, Tu C, et al. Seipin deficiency-induced lipid dysregulation leads to hypomyelination-associated cognitive deficits via compromising oligodendrocyte precursor cell differentiation. Cell Death Dis. 2024; 15(5): 350. Published 2024 May 21. doi: 10.1038/s41419-024-06737-z
[34] Barber CN, Raben DM. Lipid Metabolism Crosstalk in the Brain: Glia and Neurons. Front Cell Neurosci. 2019; 13: 212. Published 2019 May 21. doi: 10.3389/fncel.2019.00212
[35] Linnerbauer M, Rothhammer V. Protective Functions of Reactive Astrocytes Following Central Nervous System Insult. Front Immunol. 2020; 11: 573256. Published 2020 Sep 30. doi: 10.3389/fimmu.2020.573256
[36] Guttenplan KA, Weigel MK, Prakash P, et al. Neurotoxic reactive astrocytes induce cell death via saturated lipids. Nature. 2021; 599(7883): 102-107. doi: 10.1038/s41586-021-03960-y
[37] Preman P, Moechars D, Fertan E, et al. APOE from astrocytes restores Alzheimer's Aβ-pathology and DAM-like responses in APOE deficient microglia. EMBO Mol Med. 2024; 16(12): 3113-3141. doi: 10.1038/s44321-024-00162-7
[38] Moulton MJ, Barish S, Ralhan I, et al. Neuronal ROS-induced glial lipid droplet formation is altered by loss of Alzheimer's disease-associated genes. Proc Natl Acad Sci U S A. 2021; 118(52): e2112095118. doi: 10.1073/pnas.2112095118
[39] Bhupana JN, Pabon A, Leung HH, et al. Endolysosomal processing of neuron-derived signaling lipids regulates autophagy and lipid droplet degradation in astrocytes. Nat Commun. 2025; 16(1): 5073. Published 2025 May 31. doi: 10.1038/s41467-025-60402-3
[40] Lan Z, Lv S, Ge Z, Zhao B, Li L, Li C. Lactic acid regulates lipid droplet aggregation through a microglia-neuron axis in neuroinflammation. J Lipid Res. 2024; 65(10): 100629. doi: 10.1016/j.jlr.2024.100629
[41] Hou J, Chen Y, Cai Z, et al. Antibody-mediated targeting of human microglial leukocyte Ig-like receptor B4 attenuates amyloid pathology in a mouse model. Sci Transl Med. 2024; 16(741): eadj9052. doi: 10.1126/scitranslmed.adj9052
[42] Victor MB, Leary N, Luna X, et al. Lipid accumulation induced by APOE4 impairs microglial surveillance of neuronal-network activity. Cell Stem Cell. 2022; 29(8): 1197-1212.e8. doi: 10.1016/j.stem.2022.07.005