Comment

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Association between abnormal lipid metabolism and Alzheimer's disease: New research has revealed significant findings on the APOE4 genotype in microglia

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SUMMARY *APOE4* is widely recognized as a genetic risk factor for Alzheimer's disease (AD), implicated in 60–80% of all AD cases. Recent research suggests that microglia carrying the *APOE4* genotype display abnormal lipid metabolism and accumulate lipid droplets, which may exacerbate the pathology of AD. Microglia play a critical role in immune surveillance within the central nervous system and are responsible for removing harmful particles and preserving neuronal function. The *APOE4* genotype causes abnormal lipid metabolism in microglia, resulting in excessive accumulation of lipid droplets. This accumulation not only impairs the phagocytic and clearance capabilities of microglia but also disrupts their interactions with neurons, resulting in disorganization and neurodegenerative alterations at the neuronal network level. In addition, the presence of *APOE4* modifies the metabolic landscape of microglia, particularly affecting purinergic signaling and lipid metabolism, thereby exacerbating the pathological processes of AD. In conclusion, the accumulation of lipid droplets and abnormal lipid metabolism may be critical mechanisms in the progression of AD in microglia carrying the *APOE4* genotype.

Keywords Alzheimer's disease, lipid metabolism, apolipoprotein E, microglia, *APOE4*

Alzheimer's disease (AD) is a neurodegenerative disorder that gradually impairs cognitive function and affects tens of millions of people worldwide (*1*). Genetic studies have shown that 60–80% of the risk of developing AD is dependent on genetic factors (*2*). Over 40 genetic risk loci associated with AD have been identified, including the *APOE* gene (*1,3*). *APOE* is a gene responsible for lipid and cholesterol-related metabolism and transport, as well as neuronal maintenance and repair in the central nervous system. It has three major alleles: *APOE2*, *APOE3*, and *APOE4*. Studies have found that *APOE4* is significantly associated with an increased risk of developing AD. This allele promotes amyloid plaque deposition and neuronal damage (*4*), which may be related to abnormal lipid metabolism.

Abnormal lipid metabolism and lipid droplet accumulation have been observed in the microglia of individuals with AD with the *APOE4* genotype. Research has shown that under conditions related to aging and disease, microglia accumulate lipid droplets (*5,6*). This accumulation is more pronounced in *APOE4* human induced pluripotent stem cells (iPSCs)-derived microglia compared to *APOE3* microglia (*7*). Haney *et al*. (2024) reported that microglia associated with lipid-droplet-accumulating microglia (LDAM) were found in AD patients with the *APOE4/4* genotype, and these cells displayed significantly increased expression in amyloid plaque regions (*7*). In their study, Claes *et al*. transplanted xenograft microglia (xMG) derived from human iPSCs into the brain of an amyloid mouse model. They observed a similar accumulation of large numbers of lipid droplets around amyloid plaques (6). Global transcriptomic analysis revealed that *APOE4*-driven abnormalities in human-specific lipid metabolism caused dysregulation of lipid metabolism in microglia (*8*).

In AD, APOE4 leads to abnormal lipid metabolism and lipid droplet accumulation in microglia. This may be due to alterations in lipid and cholesterol metabolism and transport, inflammation, oxidative stress, and other factors. Global transcriptomic analysis revealed that APOE4 was linked to increased cholesterol synthesis and decreased catabolism/exocytosis (*8*). ApoE4 was found to be less capable of effluxing cholesterol and phosphatidylcholine (PC) compared to ApoE2 and ApoE3 (*9*). A study found that *APOE4* microglia had impaired lipid reuptake, resulting in cholesterol overload

in the culture medium (*10*). ApoE4 caused disruption of intracellular lipid homeostasis in neuroglia, leading to increased unsaturation of fatty acids and accumulation of intracellular lipid droplets (*11,12*).

ApoE4 enhances microglia MHC-II-dependent antigen presentation and T cell activation while also promoting inflammatory responses in microglia (*12*). Moreover, the expression of ApoE4 in microglia leads to downregulation of complement and lysosomal pathways and promotes stress-related responses (*13*). Studies have shown that in a model of frontotemporal lobe dementia with chronic neuroinflammation, microglia containing lipid droplets were found in the hippocampus and thalamus (*5,14*). Neurons produce lipids due to elevated reactive oxygen species (ROS), which are then transferred to glial cells to form lipid droplets (*15*). Lipid droplets were detected in microglia of adult mice in which ROS were induced with rotenone as well (*16*). Inflammation and oxidative stress may be significant factors in the accumulation of lipid droplets in microglia. According to gene pathway analysis, microglia that are rich in lipid droplets exhibit impaired phagocytosis, produce ROS, and release pro-inflammatory cytokines. This could potentially exacerbate the accumulation of lipid droplets in microglia (*5*).

Single-nucleus RNA sequencing (snRNA-seq) of frontal cortex tissues revealed differential expression of genes associated with lipid metabolism, including *ACSL1*, *DPYD*, and *NAMPT*, in microglial cells of AD patients with the *APOE4/4* genotype compared to the control (*7*). Of these genes, *ACSL1* differed the most in microglial cells (*7*).

ACSL1 is an enzyme associated with lipid droplets that promotes their formation (*17,18*). Inhibition of the adipogenic gene *ACSL1* resulted in a reduction of lipid droplets in *APOE4* microglia and restoration of the purinergic signalling pathway. These findings suggest that ACSL1 expression, triglyceride synthesis, and lipid droplet accumulation are induced in an APOE4-dependent manner in AD.

The abnormal lipid metabolism and droplet accumulation observed in microglia of the *APOE4* genotype in AD have significant implications for an organism. Microglia are immune cells in the central nervous system responsible for clearing microbes, dead cells, redundant synapses, protein aggregates, and other potentially harmful particles (*19,20*). Recent research has shown that microglia with lipid droplets, known as LDAM, have a severe phagocytosis defect compared to microglia without lipid droplets in the aging brain. This is closely associated with increased lipid storage (*5*). Microglia carrying the *APOE4* allele exhibit a decreased ability to scavenge, especially for lipid-rich myelin debris, resulting in impaired myelin regeneration (*21*). Moreover, ApoE4 triggers lipid accumulation, leading to reduced surveillance of neuronal activity by microglia, ultimately resulting in disorganization at the neuronal network level (*10*). As immune cells of the brain, microglia participate in surveillance. Microglia prevent the invasion of foreign pathogens and regulate neuronal activities. The presence of *APOE4* alters the metabolic network of microglia, particularly affecting purinergic signaling and lipid metabolism. These alterations can change the surveillance status of microglia, impacting not only brain regions but also directly affecting neuronal activity, ultimately resulting in neurodegenerative changes (*10*) (Figure 1).

The current work has reviewed the effects of abnormal lipid metabolism and lipid droplet accumulation on an organism as observed in AD

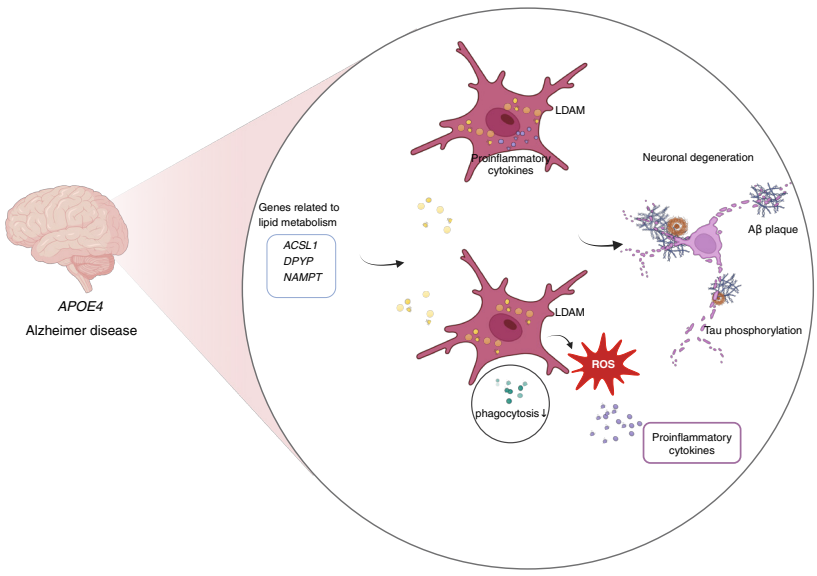

Figure 1. A schematic representation of lipid metabolism in AD microglia with the *APOE4* genotype. *Abbreviations*: ACSL1, acyl-CoA synthetase long-chain family member 1; AD, Alzheimer's disease; APOE4, apolipoprotein E4; DPYP, dihydropyrimidine dehydrogenase; LDAM, lipid-droplet-accumulating microglia; NAMPT, Nicotinamide phosphoribosyltransferase; ROS, reactive oxygen species.

microglia with the *APOE4* genotype. Microglia play a critical role in immune surveillance in the central nervous system and are responsible for eliminating harmful particles and maintaining neuronal function. Abnormal lipid metabolism induced by the *APOE4* genotype in microglia has been found to lead to excessive accumulation of lipid droplets. The presence of lipid droplets affected not only the phagocytosis and clearance ability of microglia but also their interactions with neurons, leading to disorganization at the neuronal network level and neurodegenerative changes. In addition, the presence of *APOE4* altered the metabolic network of microglia, and particularly purinergic signaling and lipid metabolism, further exacerbating pathological changes. In conclusion, abnormal lipid metabolism and lipid droplet accumulation may be important mechanisms in the progression of AD in microglia with the *APOE4* genotype. These findings provide new insights and research directions into the pathogenic mechanism and treatment of AD.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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