Review

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APOE4 reprograms microglial lipid metabolism in Alzheimer's disease: Mechanisms and therapeutic implications

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SUMMARY: The apolipoprotein E ε4 (*APOE ε4*) allele, the strongest genetic risk factor for late-onset Alzheimer's disease (AD), induces cell-type-specific disturbances in brain lipid metabolism. Although impacting astrocytes and neurons, its most pronounced effects occur in microglia, where it causes energy metabolism deficits and promotes the formation of lipid droplet-accumulating microglia, triggering a cascade of neurodegenerative responses. This review comprehensively examines how microglial APOE4-driven lipid metabolic dysregulation exacerbates neuroinflammation and compromises phagocytic capacity, particularly in the clearance of amyloid-β, phosphorylated-tau, and pathological synapses. Mechanistically, microglial APOE4 activates neuroinflammation *via* LilrB3-mediated type I interferon signaling and induces lipid metabolic imbalance through PU.1/NF-κB-driven transcriptional reprogramming and ER stress-SREBP2 activation. These disturbances exacerbate neuroinflammation, promote lipid droplet accumulation and cholesterol overload, impair lysosomal function, and ultimately compromise microglial phagocytosis. The resulting disruption of neuron-microglia interactions further amplifies neurotoxicity in AD. Furthermore, this review summarizes emerging therapeutic strategies targeting APOE4-related pathway in microglia. By synthesizing these insights, this review highlights the multifaceted role of microglial APOE4 in AD pathology, with particular emphasis on the central role of lipid metabolism dysregulation, and provides new intervention ideas for reducing its damage to brain function.

Keywords: Alzheimer's disease, apolipoprotein E4, microglia, lipid metabolism, neuroinflammation, phagocytosis

1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease — responsible for 50-70% of dementia cases worldwide — and is characterized primarily by progressive cognitive dysfunction (*1*). As the global population ages, the prevalence of AD continues to increase, imposing a substantial burden on affected individuals and health care systems (*2*). The primary pathological features of AD include the abnormal accumulation of extracellular amyloid-β (Aβ) and phosphorylated tau (p-tau) protein in neurons. Concurrently, inflammatory responses, synaptic dysfunction, and neuronal loss are significant characteristics that cannot be overlooked in AD. Notably, significant changes in brain lipid peroxidation levels can be observed in the early stage of AD. These metabolic disorders of lipid components are closely related to the core pathological mechanisms of AD, including Aβ deposition, p-tau, oxidative stress, and mitochondrial dysfunction (*3*). These findings underscore the critical role of lipid metabolism imbalance in AD pathogenesis and provide important directions for identifying AD-biomarkers and discovering novel therapeutic strategies through lipidomics research.

An estimated 60-80% of the susceptibility to AD can be attributed to genetic factors, with the apolipoprotein E ε4 *(APOE*ε4) allele recognized as the primary genetic risk factor for late-onset AD (*4-6*). *APOE*ε4 carriers exhibit a greater risk of developing AD. Specifically, individuals with a single *APOE*ε4 allele face an approximately 3- to 4-fold greater risk of developing AD than noncarriers do, while those with two *APOE*ε4 alleles have a 9- to 15-fold greater risk (*7*). In addition to exacerbating Aβ accumulation, tau hyperphosphorylation, and synaptic loss, APOE4 severely disrupts cerebral lipid metabolism and lipid transport, leading to cellular dysfunction, neuroinflammation activation, and myelin impairment — all of which are hallmarks of AD progression. Consequently, investigating APOE4-related lipid metabolism dysregulation provides critical insights into the pathogenesis and therapeutic development of AD (*8-11*).

Microglia are resident immune cells in the central nervous system (CNS) that primarily perform immunosurveillance, neurotrophic support, and plasticity functions in the brain (*12*). At the onset of AD, microglia

recognize and phagocytose Aβ to prevent its aggregation. However, in the later stage of AD, neuroinflammation induced by reactive microglia promotes the deposition of Aβ and the formation of neurofibrillary tangles (NFTs). Additionally, reactive microglia phagocytose synapses and disrupt neuronal communication in AD (*13*). APOE4-related lipid metabolism disorders can induce metabolic reprogramming of microglia into a proinflammatory state, impairing their phagocytic function (*14,15*). This review first provides an overview of APOE4, and then analyzes APOE4-related lipid metabolism disorders at the cellular level, with particular emphasis on its impact on microglial lipid metabolism and subsequent effects on phagocytic and secretory functions during AD progression. Finally, we discuss emerging therapeutic strategies targeting APOE4-microglia interactions, highlighting their potential to restore microglial homeostasis and mitigate AD pathogenesis.

2. Overview of APOE4

2.1. Structure and function of APOE4

The *APOE* gene is located on chromosome 19 and encodes a secreted glycoprotein consisting of 299 amino acids with a molecular weight of approximately 34 kDa. Human *APOE* is polymorphic and comprises three distinct alleles: ε2, ε3, and ε4. The amino acid positions of the three isoforms encoded by the *APOE* allele differ at positions 112 and 158: Cys112/Cys158 for APOE2, Cys112/Arg158 for APOE3, and Arg112/Arg158 for APOE4 (*16-18*) (Figure 1A). The different APOE isoforms differ in their oligomerization tendency, structural stability, and binding affinity to lipids, receptors, and Aβ peptides. Structurally, APOE4 is the least stable isoform. It adopts a folded intermediate state characterized by a core α-helical structure, increased β-lamellar structure, and an enlarged hydrodynamic radius, collectively resulting in a "molten globule" state (*19,20*). This semi-folded configuration enhances the interaction of APOE4 with larger lipid-rich particles and Aβ deposits in the brain. Simultaneously, this "molten globule" state promotes the aggregation of lipid-deficient APOE4, impairing its lipid transport capacity and facilitating Aβ accumulation (*21,22*). This phenomenon

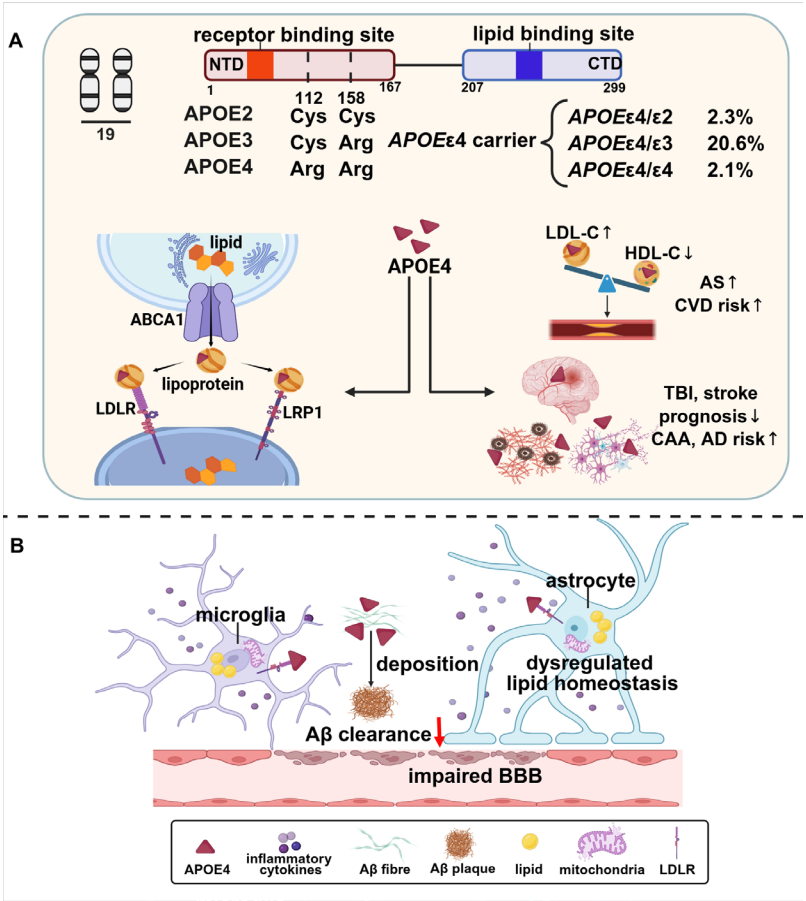

Figure 1. APOE4-mediated dysregulation and neurological implications. (A). Chromosomal location of the *APOE* gene and differences in different protein isoforms, the percentage of *APOEε4* gene carriers, and the association of APOE4 with multiple diseases. **(B)**. In AD, APOE4 promotes Aβ deposition and impairs Aβ clearance through receptor competition and BBB disruption. APOE4 drives astrocytes and microglia toward a pro-inflammatory phenotype and induces mitochondrial dysfunction. Importantly, APOE4 disrupts intracellular lipid metabolism, leading to pathological lipid droplet accumulation and accelerated AD progression. ABCA1, ATP-binding cassette transporters A1; LDLR, low-density lipoprotein receptor; LRP1, LDL receptor-related protein 1; AS, atherosclerosis; BBB, blood-brain barrier; CVD, cardiovascular disease; TBI, traumatic brain injury; CAA, cerebral amyloid angiopathy.

may represent a potential mechanism through which APOE4 contributes to the pathogenesis of AD.

Functionally, APOE participates in lipid metabolism and transport *via* lipoprotein particles. Lipidation occurs through two mechanisms: intracellular presecretory lipidation *via* the endoplasmic reticulum (ER)/Golgi pathway, and extracellular lipidation mediated by ATP-binding cassette transporter A1 (ABCA1) (*10,23,24*). ABCA1 is expressed in peripheral hepatocytes, macrophages, and intestinal epithelial cells to maintain systemic lipid homeostasis and in CNS glial cells and neurons to preserve lipid homeostasis in the brain, with its receptor proteins regulated by the retinoid X receptor (RXR) and liver X receptor (LXR) system (*25*). For lipid delivery, these lipoprotein particles facilitate intercellular lipid transport through receptor-mediated endocytosis involving low-density lipoprotein receptor (LDLR) and LDL receptor-related protein 1 (LRP1) (*26*). As an important lipid carrier, the APOE4 isoform has abnormal lipid metabolism properties, which leads to increased levels of low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C), thus promoting atherosclerosis and increasing the risk of cardiovascular diseases (*19,27*). Moreover, *APOE*ε4 is an important risk factor for AD and cerebral amyloid angiopathy because it affects lipid homeostasis in the CNS, and *APOE*ε4 carriers exhibit poorer outcomes following stroke and traumatic brain injury, as well as accelerated motor progression and cognitive decline in Parkinson's disease patients (*28-31*) (Figure 1A). Overall, APOE4 drives multisystem pathologies through dysregulated lipid metabolism, contributing to cardiovascular diseases, neurodegenerative disorders, and poor neurological recovery, highlighting its central role in disease mechanisms.

2.2. APOE4 and AD

The *APOE*ε4 allele represents the strongest genetic risk factor for late-onset AD, with carriers facing an increased risk of developing AD and often experiencing an earlier age of onset (*5,6,16*). The carrier rate of *APOE*ε4 in the general population is approximately 23.9%, with 2.1% *APOE*ε4/ε4, 20.6% *APOE*ε3/ε4, and 2.3% *APOE*ε2/ε4 (*32*) (Figure 1A). Notably, nearly all *APOE*ε4 homozygote carriers display AD-related pathologic features, making it crucial to explore the relationship between *APOE*ε4 and the risk of developing AD (*33*). Epidemiological studies have demonstrated that the prevalence of *APOE*ε4-associated AD risk is associated with racial and sexual dimorphism, with East Asians having the highest susceptibility, followed by non-Hispanic Whites, while non-Hispanic Blacks and Hispanics have a lower risk, and female carriers face a significantly greater risk than males do (*34,35*). Additionally, genetic modifications complicate the relationship between the *APOE*ε4 allele and AD risk. For instance, both Klotho-VS heterozygotes and *APOE*ε4-R251G can attenuate the *APOE*ε4-associated AD risk (*36-38*). Specific single-nucleotide polymorphisms, including rs10553596 in the *CASP*7 gene and rs4934-A/A in the *SERPINA*39 gene, also reduce the high risk of AD in *APOE*ε4 heterozygotes (*39*). Strikingly, comorbidities such as atherosclerosis, peripheral vascular disease, and diabetes mellitus increase the risk of cognitive decline in *APOE*ε4 carriers (*40*), suggesting that managing cognition-related risk factors in *APOE*ε4 carriers may represent a potential therapeutic approach.

Extensive mechanistic investigations have substantiated the epidemiological evidence linking APOE4 to AD pathogenesis. In the amyloid pathway, APOE4 not only directly interacts with Aβ to promote its deposition in the CNS and accelerates the conversion of soluble Aβ to insoluble fibrils but also competitively binds to receptors such as LDLR, significantly inhibiting receptor-mediated Aβ clearance (*41-44*). APOE4-related blood-brain barrier (BBB) disruption also negatively affects Aβ clearance and precedes neuronal dysfunction, suggesting that vascular abnormalities may initiate neurodegeneration (*45,46*). In a nonamyloid-dependent pathway, APOE4 not only drives astrocytes and microglia toward a proinflammatory phenotype, impairing their immune function and exacerbating neuroinflammatory responses but also induces mitochondrial dysfunction, thereby impairing fatty acid oxidation (FAO) and disrupting the energy supply of the brain (*47-49*). Most importantly, APOE4 disrupts cholesterol and triglyceride transport and metabolism, altering cellular membrane lipid composition and inducing pathological lipid droplet (LD) accumulation (*50*). These lipid metabolic disturbances not only directly dysregulate Aβ metabolism but also impair endocytosis, lysosomal function, and brain energy homeostasis while promoting oxidative stress (*51,52*) (Figure 1B). In particular, an imbalance in cholesterol homeostasis can affect the formation of oligodendrocyte myelin, which in turn affects learning and memory ability (*53*). Although APOE4 critically contributes to AD progression through these multifaceted lipid metabolic disturbances, the underlying mechanisms exhibit cell-type specificity, which will be systematically examined in the following cellular-level analysis.

3. Lipid metabolic disturbances in diverse cell types mediated by APOE4

3.1. Astrocytes and neurons

Astrocytes serve as the primary source of APOE in the CNS, with its expression modulated by CCAAT/enhancer-binding protein β (C/EBPβ) and mitochondrial function (*54,55*). While astrocyte-derived APOE normally maintains lipid homeostasis, supports synaptic pruning, and preserves the integrity of the BBB, APOE4 astrocytes exacerbate neurodegenerative processes

through multiple synergistic pathways (*56,57*). Studies have shown that APOE4 astrocytes exhibit profound dysregulation of lipid metabolism, characterized by aberrant sterol regulatory element-binding protein 2 (SREBP2) activation, which increases de novo cholesterol synthesis despite lysosomal dysfunction-induced accumulation (*58*). This metabolic imbalance involves upregulated lipid metabolism genes but downregulated transport genes, potentially mediated by reduced peroxisome proliferator-activated receptor γ (PPARγ) expression (*9,56,59*). This pathological cholesterol accumulation disrupts lysosome-dependent mitophagy, leading to mitochondrial dysfunction and early AD energy deficits (*52*). In addition, APOE4 astrocytes also accumulate enlarged, oxidation-prone LDs enriched with unsaturated triglycerides while secreting poorly lipidated lipoproteins that inefficiently support neuronal lipid demands, which impairs synaptogenesis and neuronal viability (*60-62*). In addition to these lipid metabolic disorders, APOE4 astrocytes upregulate glypican-4 (GPC-4) expression, increase LRP1 membrane trafficking to promote tau propagation and hyperphosphorylation, and impair APOE4-mediated miRNA transfer to neurons, thereby disrupting neuronal metabolic and epigenetic regulation and ultimately contributing to synaptic dysfunction and memory deficits (*63,64*) (Figure 2A).

Neuronal APOE expression is increased during stress and aging, exerting early detrimental effects on synaptic function and neurodevelopment (*65,66*). At the metabolic level, APOE4 significantly interferes with neuronal function through lipid-dependent pathways. Excessive binding of APOE4 to LDLR leads to increased neuronal lipid uptake, resulting in lysosomal dysfunction, lipofuscin accumulation, and impaired autophagy, which subsequently triggers tau protein aggregation and brain cell death (*67*). Concurrently, APOE4-expressing neurons exhibit deficient fatty acid (FA) storage in LDs, leading to the pathological accumulation of free FAs and an increased risk of lipotoxicity (*61*). Although neighboring astrocytes take up these lipids, APOE4 impairs their transport and oxidation capacity, particularly in the hippocampus (*61,67*). Furthermore, APOE4 promotes ABCA1 degradation, reduces cholesterol efflux and activates mTORC1-mediated senescence pathways, ultimately impairing synaptic plasticity (*68*). Structurally,

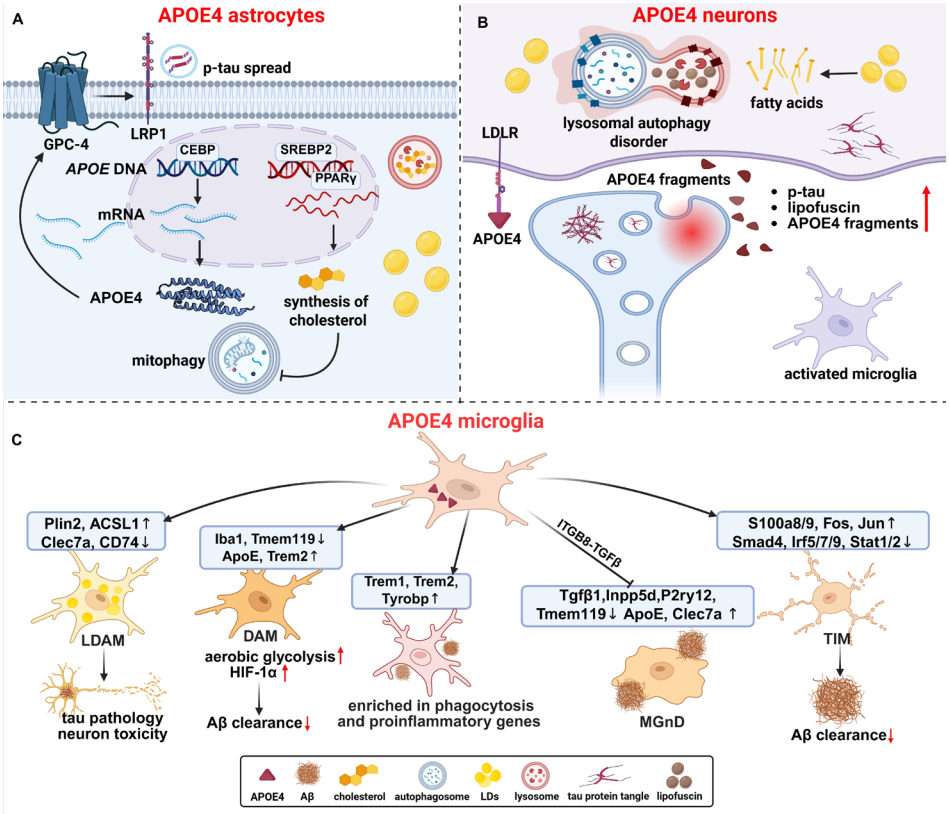

Figure 2. APOE4-mediated dysfunction of cellular lipid metabolism. (A). APOE4 astrocytes exhibit dysregulated lipid metabolism, characterized by SREBP2 activation, de novo cholesterol synthesis, and PPARγ suppression. Pathological cholesterol accumulation impairs mitophagy, leading to mitochondrial dysfunction. Additionally, APOE4 astrocytes specifically upregulates GPC-4, enhancing LRP1-mediated tau propagation. **(B).** APOE4 is hydrolyzed by neuron-specific proteases, producing neurotoxic fragments that exacerbate tau pathology and activate microglia. Metabolically, FAs are increased in APOE4 neurons, and hyperbinding of APOE4 to LDLR further increases lipid uptake in neurons, leading to lipid metabolism disorders, triggering lysosomal dysfunction, lipofuscin accumulation, and impaired autophagy-mediated tau protein aggregation. **C.** APOE4 microglia exhibit diverse phenotypic features, including LDAM, DAM, phagocytosis and pro-inflammatory phenotype, MGnD and TIM. SREBP2, sterol regulatory element-binding protein 2; GPC-4, glypican-4; FAs, fatty acids; LDAM, lipid-droplet-accumulating microglia; DAM, disease-associated microglia; MGnD, neurodegenerative microglia; TIM, terminally inflammatory microglia.

APOE4 undergoes neuron-specific proteolysis, generating neurotoxic fragments that destabilize the cytoskeleton and exacerbate tau pathology (*69*) (Figure 2B). APOE4 also selectively depletes GABAergic neurons, potentially disrupting neural network balance, while activating microglia through cell-nonautonomous mechanisms to amplify neuroinflammation (*70,71*). These findings establish that APOE4 links metabolic dysregulation to neurodegenerative processes by interfering with neuronal lipid homeostasis.

3.2. Microglia

Microglial APOE expression is significantly upregulated in response to injury and inflammation, demonstrating a close association with lipid metabolic dysregulation. Under physiological conditions, microglia maintain finely regulated lipid metabolic homeostasis, where the dynamic equilibrium between fatty acid synthesis (FAS) and FAO is essential for their immune surveillance functions (*15*). However, the *APOE*ε4 genotype disrupts this equilibrium, driving microglia toward a dysfunctional, proinflammatory lipid droplet-accumulating microglia (LDAM) phenotype (*72,73*). Specifically, APOE4 promotes de novo lipogenesis and LD accumulation by upregulating FAS while simultaneously suppressing autophagy-related genes to impair lipophagy (*73,74*). Additionally, APOE4 inhibits FAO *via* a dual mechanism — directly by inducing mitochondrial structural and functional damage that significantly reduces β-oxidation capacity, and indirectly by promoting microglial polarization toward a proinflammatory phenotype that downregulates FAO-related gene expression (*75,76*). This "enhanced synthesis-suppressed degradation" imbalance ultimately leads to the formation of pathological LDAM. In AD, microglia undergo dynamic lipid metabolic reprogramming. During the early stages, the triggering receptor expressed on myeloid cells 2 (TREM2)-APOE pathway mediates lipid uptake and FAO to support energy demands and facilitate Aβ clearance (*77*). However, chronic exposure to Aβ and tau pathology shifts the metabolism toward LD accumulation, resulting in LDAM (*73*). At the energy metabolism level, APOE4 microglia exhibit significant mitochondrial dysfunction, leading to reduced tricarboxylic acid cycle (TAC) efficiency and impaired FAO, in addition to hypoxia-inducible factor 1-α (HIF1α)-driven metabolic rewiring from oxidative phosphorylation to glycolysis (*78,79*). Intriguingly, a unique compensatory mechanism has been identified in microglia. In the context of AD, the expression of the glycolytic enzyme hexokinase 2 (HK2) is upregulated in microglia, and pharmacological inhibition of HK2 can subsequently activate lipoprotein lipase to increase lipid metabolism, thereby sustaining ATP production and promoting Aβ clearance (*80*). This glycolytic-lipid metabolic coupling appears to be microglia specific, as it has not been observed in other brain cells (*80*). These findings suggest that microglia respond to pathological stimuli through dynamic metabolic reprogramming mechanisms, but the *APOE*ε4 genotype drives microglia to a dysfunctional subtype by disrupting lipid metabolic balance and energy supply, ultimately exacerbating the neurodegenerative process.

As immune cells of the CNS, microglia can rapidly move and migrate extensively to perform immune surveillance and tissue repair functions. However, the *APOE*ε4 genotype significantly impairs these properties, resulting in reduced microglial mobility and reactivity, accompanied by marked morphological abnormalities that ultimately impair their immune surveillance and phagocytosis functions. Specifically, APOE4-expressing microglia exhibit irregular structural features, including enlarged cell bodies and nuclei, shortened processes, and a flattened, discoid shape (*9,81,82*). Advances in single-cell sequencing technology have further revealed that microglia exhibit different subtypes, mediated by the reprogramming of their cellular metabolism during development, growth, and disease. Among these, the LDAM subtype emerges as a canonical APOE4-driven pathological subtype characterized by dysregulated lipid metabolism, a proinflammatory state, and impaired phagocytic function (*72,73,81*). Disease-associated microglia (DAMs) exhibit high expression levels of genes involved in lipid metabolism and phagocytosis. APOE4-expressing microglia exhibit metabolic features consistent with those of DAMs, with increased aerobic glycolysis and Hif1a expression but impaired Aβ uptake (*9,78*). Moreover, a subset of microglia enriched in phagocytic and proinflammatory genes has been identified in *APOE*ε4 carriers, clustering around neuroinflammatory plaques and driving the conversion of microglia to phagocytic and proinflammatory phenotypes *via* the APOE–TREM2–TYROBP axis (*83*). In neurodegenerative diseases, the TREM2–APOE pathway mediates the transition of microglia into neurodegenerative microglia (MGnD), which exert a neuroprotective effect by eliminating apoptotic neurons (*84*). However, APOE4 exacerbates neurodegeneration by activating ITGB8–TGFβ signaling, upregulating the expression of homeostatic checkpoint molecules such as Inpp5d, and inhibiting MGnD function (*85*). Additionally, terminal inflammatory microglia (TIMs), another APOE4-associated exhausted subtype, display profound Aβ clearance deficits in both AD patients and mouse models (*86*) (Figure 2C). In conclusion, these findings demonstrate that APOE4 exacerbates neurodegenerative progression through multiple mechanisms, orchestrating the production of diverse subtypes of dysfunctional microglia that exhibit metabolic disturbances, inflammatory dysregulation, and phagocytic impairment.

4. Microglial APOE4 and AD

4.1. APOE4 in microglia exacerbates abnormal lipid metabolism

AD was initially described by the identification of numerous glial cells displaying lipid vacuoles in the brains of patients, highlighting the significant role of abnormal lipid metabolism in glial cells in the pathogenesis of AD (*87*). In particular, abnormal lipid metabolism in microglia not only exacerbates Aβ and tau pathology but is also directly associated with cognitive impairment in AD. Recent studies have shown that APOE4 induces the phosphorylation of eIF2α in microglia, activates the integrated stress response, and promotes the release of harmful lipids and synaptic loss (*88*).

4.1.1. POE4 in microglia and intracellular lipid droplet accumulation

The critical metabolic shift in the formation of microglial LDs involves a decrease in free FAs and an increase in triglycerides (*89*). This shift represents a defensive response that maintains lipid homeostasis and neutralizes lipid-mediated neurotoxicity by buffering excess free FAs and cholesterol. However, the lipid homeostasis of APOE4 microglia is often disrupted. Research has shown that *APOE*ε4 carriers and their induced pluripotent stem cell (iPSC)-derived microglia tend to accumulate LDs. This phenomenon may be linked to the stress-related responses promoted by microglial APOE4, which downregulates complement and lysosomal pathways, while excessive oxidative stress significantly contributes to LD accumulation (*81*). Furthermore, the binding of fibrillar Aβ to TREM2 receptors on the surface of microglia activates the PI3K–Akt–mTOR signaling pathway, leading to the overexpression of LD-related genes, including *ACSL*1 and *PLIN*2. This overexpression enhances triglyceride synthesis and promotes LD formation, especially in patients with AD carrying *APOE*ε4/ε4 (*73,90*). Notably, the number of LDs is negatively correlated with cognitive function but positively correlated with the levels of Aβ plaques and tau pathology, suggesting a role for LDs in AD progression. ATAC-seq and RNA-seq analyses revealed that enhancer regions in LD-rich APOE4 microglia are highly enriched in protein upstream of .1 (PU.1) and nuclear factor kappa-B (NF-κB) family factors. PU.1 regulates genes involved in LD formation, while NF-κB increases proinflammatory gene expression and induces the transformation of microglia into a proinflammatory phenotype involved in neuroinflammation, disrupting the neural microenvironment (*73*). LDAM often accumulate near Aβ plaques, impair lysosomal function, affect phagocytosis, and may accelerate the spread of plaques. Moreover, excessive proinflammatory cytokines and ROS are released, promoting neuronal lipogenesis. Abnormally increased lipids can be transported to microglia *via* APOE to synthesize LDs, thus forming a vicious cycle (*72*) (Figure 3). Surprisingly, in AD model mice, the accumulation of human iPSC-derived microglial LDs largely depends on microglial reactivity and proximity to plaques, which are impaired by the TREM2-R47H mutation. Specifically, TREM2 R47H-mutant microglia exhibited reduced LD accumulation *in vivo*, decreased plaque reactivity, and decreased plaque-associated APOE secretion, whereas the same mutation exacerbated LD accumulation *in vitro*, highlighting the critical regulatory role of the environmental context in microglial function (*91,92*).

These findings highlight how APOE4 disrupts the delicate balance of microglial lipid metabolism, transforming a potentially protective LD formation process into a maladaptive response that promotes AD progression through impaired phagocytosis, sustained neuroinflammation, and the creation of a neurotoxic lipid microenvironment. The microenvironment-dependent phenotypes observed in chimeric models further emphasize the critical interplay between cell-intrinsic metabolic reprogramming and the pathological brain milieu in shaping microglial dysfunction (*91*).

4.1.2. APOE4 microglia and abnormal cholesterol metabolism

Cholesterol is an indispensable lipid in cellular membranes and is essential for maintaining membrane fluidity and integrity (*93*). Numerous analyses of clinical data have revealed abnormal cholesterol accumulation in the cores of mature Aβ plaques, with elevated cholesterol levels in the brain often associated with AD-related cognitive decline and exacerbation of clinical symptoms. In particular, dysregulated cholesterol metabolism in microglia is thought to be a major driver of senescence pathologies in AD (*94,95*). APOE, a cholesterol transport protein, is vital for the survival and phagocytic function of microglia. However, microglial APOE4 disrupts cholesterol homeostasis and alters cholesterol transport-related signaling pathways, impairing myelination and subsequently affecting cognitive function (*51,53*). Evidence indicates that cholesterol overload occurs in APOE4 microglia, potentially because of increased synthesis driven by the stress–ER Ca^{2+}–SREBP2 pathway. Specifically, microglial APOE4 induces ER stress, leading to Ca^{2+} depletion in the ER and activation of the SREBP2 transcription factor. This activation promotes the transcription of key genes, such as *HMGCR* and *SQLE*, which regulate the cholesterol biosynthesis pathway (*96*). Furthermore, microglial APOE4 may impair ABCA1 recycling, lysosomal function, and cholesterol efflux and metabolism, leading to the accumulation of intracellular cholesterol that ultimately reduces the capacity for Aβ degradation (*51,97*) (Figure 3). In addition to Aβ clearance, cholesterol may significantly influence Aβ plaque formation because of its uneven distribution in the cell membrane, where it

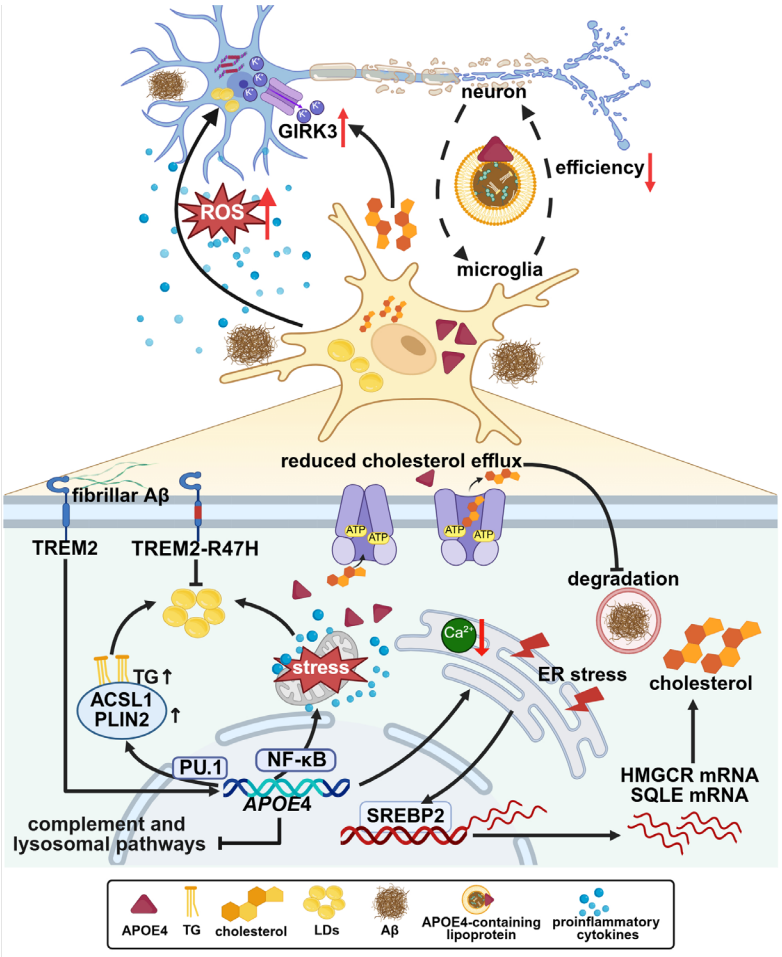

Figure 3. Microglial APOE4-mediated dysregulation of lipid metabolism in AD. Microglial APOE4-mediated upregulation of triglyceride synthesis exacerbates the accumulation of LDs under Aβ stimulation, whereas TREM2-R47H reduces intracellular LDs accumulation. In addition, microglial APOE4 promotes cholesterol synthesis *via* the ER stress-ER Ca^{2+}-SREBP2 pathway and impairs cholesterol efflux, affecting Aβ degradation in lysosomes. The accumulation of extracellular cholesterol increased GIRK3 and decreased neuronal excitability. Microglial APOE4 also decreased lipid transport efficiency and disrupted lipid metabolic coupling in neurons. Ultimately, phagocytosis-impaired APOE4 microglia release pro-inflammatory cytokines and ROS that promote neuronal lipogenesis and translocation to microglia, creating a vicious cycle. ACSL, acyl-CoA synthetase long-chain; ER, endoplasmic reticulum; GIRK3, G protein-gated inwardly rectifying potassium channel 3; ROS, reactive oxygen species; LDs, lipid droplets; TREM2, triggering receptor expressed on myeloid cells 2.

aggregates with sphingolipids and scaffolding proteins to form lipid rafts. These rafts are involved in the cleavage of amyloid precursor proteins and the generation of Aβ by α-, β-, and γ-secretases. Disruption of cholesterol homeostasis can lead to abnormal accumulation and release of Aβ, promoting plaque formation (*98,99*).

Recent studies have demonstrated that using LXR agonists, overexpressing ABCA1, or activating TRPV1 can increase cholesterol efflux and reduce the accumulation of cholesteryl esters in microglia, thereby ameliorating APOE4-related neurodegeneration (*51,96,100*). These findings suggest that APOE4 disrupts cholesterol homeostasis in microglia through multiple mechanisms, including enhanced cholesterol biosynthesis *via* the ER stress pathway and impaired efflux *via* ABCA1 dysfunction. The resulting cholesterol overload not only impairs Aβ clearance and promotes plaque formation, but also contributes to broader neurodegenerative processes by disrupting myelin integrity and synaptic function. Importantly, therapeutic strategies targeting cholesterol metabolism have shown promise in alleviating APOE4-driven pathology, highlighting the central role of cholesterol dysregulation in AD pathogenesis (*51,68,96,100*).

4.1.3. APOE4-mediated dysregulation of lipid metabolism in microglia disrupts communication between neurons and microglia

Microglia serve as sentinels in the neural network, and their interactions with neurons are regulated by a complex array of intercellular signaling mechanisms, including purinergic signaling, cytokines, neurotransmitters, and neuropeptides (*101,102*). However, APOE4 alters purinergic signaling and lipid metabolism in microglia, which in turn affects their communication with neurons. It has been demonstrated that APOE4 induces a pronounced accumulation of LDs in microglia, which not only

impairs their phagocytosis and clearance of pathological proteins but also disrupts their interactions with neurons (*8,72,103*). Mechanistic studies revealed that APOE4 drives these pathological processes through multiple convergent pathways. It compromises the lipid uptake efficiency of microglia, leading to extracellular lipid accumulation and enhanced proinflammatory signaling, ultimately attenuating their ability to monitor neuronal network activity — a phenomenon closely aligned with the aberrant neural network activity observed in AD patients. In addition, APOE4 shifts microglial energy metabolism from oxidative phosphorylation toward glycolysis, further exacerbating intracellular lipid accumulation (*103,104*). This metabolic dysregulation triggers a cascade of pathological consequences. The most immediate manifestation is impaired lipid reuptake by APOE4 microglia, resulting in extracellular cholesterol accumulation that induces significant hyperpolarization of neuronal resting membrane potentials and upregulation of G protein-coupled inwardly rectifying potassium channels (GIRK3), collectively reducing neuronal excitability (*103*) (Figure 3). More critically, LDAM secrete toxic factors that not only promote abnormal p-tau deposition in neurons but also activate apoptotic pathways (*73*). Concurrently, proinflammatory cytokines released by LDAM drive intracellular LD accumulation in neurons, exacerbating neuronal damage. Interestingly, neurons are not passive recipients but actively regulate microglial lipid metabolism through AMPK-mediated suppression of lipogenesis and activation of lipophagy, thereby modulating lipid flux to microglia and demonstrating a sophisticated bidirectional regulatory mechanism (*105*).

These findings provide novel insights into the pathogenesis of neurodegenerative diseases. APOE4 disrupts metabolic coupling between neurons and microglia by impairing microglial lipid transport capacity, which is characterized by decreased APOE-containing lipoprotein particles and reduced lipidation levels, ultimately leading to neural network dysfunction (*106*). Building upon this understanding, current research is focused on developing innovative therapeutic strategies to increase APOE4-mediated lipid transport efficiency. By restoring metabolic homeostasis and restoring neural network stability, these interventions represent promising avenues for AD treatment.

4.2. Microglial APOE4 promotes neuroinflammation

Neuronal death caused by neuroinflammation in AD is far greater than that caused by Aβ plaques and NFTs, establishing neuroinflammation as a hallmark pathological feature of AD (*107-110*). Microglia, the central orchestrators of this inflammatory cascade, release a plethora of cytokines, including tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β), which are crucial for modulating the inflammatory cascade. Importantly, microglial APOE4 has a bidirectional interaction between lipid metabolism disorders and neuroinflammation: it both directly activates inflammatory pathways and aggravates neuroinflammation by disrupting lipid homeostasis (*72,73,75,111*).

First, microglial APOE4 directly activates inflammatory pathways through multiple mechanisms. Zhou *et al.* reported that APOE4 binds to LilrB3 on the surface of microglia to upregulate the expression of relevant type I interferon-stimulating genes, including *IFITM*3, *BST*2, *MX*1, *ISG*15, and *STAT*1. This transition drives microglia to enter a proinflammatory state, hinders their phagocytic function, and contributes to Aβ deposition (*75*). In addition to this receptor-mediated pathway, APOE4 also intrinsically primes microglia toward inflammation. In the basal state, APOE4-expressing microglia exhibit an obvious proinflammatory effect, which manifests as increased activation of the NLRP3 inflammasome and excessive production of reactive oxygen species (ROS), leading to cellular immune dysfunction. This proinflammatory phenotype is further exacerbated by immune stimulation such as lipopolysaccharide (LPS) and interferon-gamma (IFN-γ), which promote the secretion of inflammatory factors such as TNF-α, IL-1β, NOS2 and MCP1 in large amounts, especially in female mice. More importantly, microglial $nAPOE_{41-151}$ significantly increases the expression of the proinflammatory cytokine TNF-α by inhibiting Cxorf56, thus leading to the formation of a full-spectrum inflammatory amplifying pathway from the basal state to the immune-activated state (*112-114*). All of the above findings indicate that microglial APOE4 activates neuroinflammation and affects microglial function. Second, APOE4-induced lipid dysregulation further amplifies this inflammatory response. Metabolic reprogramming of APOE4-expressing microglia enhances glycolysis, inhibits TAC, and directs carbon flux toward lipid synthesis (*78*). This results in the accumulation of pathological LDs and increased release of proinflammatory lipid mediators, including prostaglandins and arachidonic acid metabolites, activating neuroinflammatory pathways (*78*). Moreover, lipid peroxides and cholesterol accumulated by APOE4 microglia activate the NF-κB signaling axis, creating a self-reinforcing cycle of cytokine production and metabolic dysfunction (*73*). On the other hand, accumulated lipids enhance Major Histocompatibility Complex Class II (MHC-II)-dependent antigen presentation, thereby hyperactivating T cells and contributing to neuroinflammation (*100*). It has also been reported that APOE4 microglia secrete more oxysterol 25-hydroxycholesterol (25-HC) and IL-1β following LPS treatment, with 25-HC further significantly increasing IL-1β secretion; these findings highlight a lipid-driven mechanism through which APOE4 sustains chronic neuroinflammation (*111*) (Figure 4A). Collectively, APOE4 microglia-mediated lipid metabolism disturbances trigger cell membrane dysfunction

and the release of inflammatory mediators, which activate microglia while impairing their Aβ clearance capacity, ultimately promoting neuronal apoptosis. The accumulation of Aβ deposits and inflammation further exacerbate lipid metabolic dysregulation, creating a spatially specific self-reinforcing cycle. This bidirectional crosstalk mechanism reveals how APOE4 promotes neurodegenerative progression through "metabolism-inflammation" interplay.

Notably, therapeutic strategies targeting this lipid-inflammation axis have shown promising neuroprotective effects. Pharmacological agents such as acyl-CoA cholesterol Acyltransferase (ACAT) inhibitors demonstrate dual functionality by enhancing cholesterol efflux while concurrently suppressing NF-κB-mediated cytokine release (*115*). This metabolic reprogramming attenuates both neuroinflammation and lipid accumulation, effectively breaking the vicious cycle that drives disease progression.

4.3. Microglial APOE4 inhibits the clearance of pathological proteins

Microglial phagocytosis plays a pivotal role in maintaining CNS homeostasis by eliminating neurotoxic substances, including Aβ and p-tau, and participating in neural circuit remodeling. However, the *APOE*ε4 genotype substantially impairs this critical function through multifaceted mechanisms during AD pathogenesis. Under physiological conditions, the TREM2-dependent lipid metabolic network coordinates cholesterol efflux through the LXR/PPARγ pathway, maintains phago-lysosomal cycling, and activates microglia to phagocytose diffuse Aβ, compressing it into dense Aβ plaques that are less toxic and prevent its further spread in the brain (*44,116,117*).

The presence of APOE4 disrupts this sophisticated regulation through several interconnected pathways. It induces mitochondrial dysfunction while simultaneously compromising pseudopod extension capacity because of altered membrane fluidity from abnormal lipid accumulation, coupled with downregulated TREM2 expression, collectively impairing phagocytic capacity (*74,118*). Furthermore, APOE4 increases the likelihood of forming fibrillar aggregates within microglia that serve as nucleation sites for Aβ plaque formation and specifically suppresses $Aβ_{42}$ clearance by disrupting ITGB8–TGFβ signaling, as demonstrated by animal studies showing that selective ablation of microglial APOE4 expression restores their phagocytic function and markedly reduces the plaque burden (*42,85*). Interestingly, in female AD patients carrying *APOE*ε4, APOE4-expressing neutrophils upregulate the expression of IL-17F, which interacts with microglial IL-17RA to disrupt Aβ clearance, ultimately impacting cognitive function. Interrupting the IL-17F/IL-17RA signaling pathway ameliorates cognitive deficits and reduces Aβ deposition in AD (*119*) (Figure 4B). These findings systematically elucidate how APOE4 synergistically impairs microglial phagocytosis through multiple mechanisms such as lipid metabolism disorders to affect Aβ pathology.

Microglial phagocytosis also contributes to the propagation of tau pathology. In general, reactive microglia exert neuroprotective effects by actively engulfing tau proteins and tau-laden synapses and neurons for clearance (*120*). However, APOE4 fundamentally alters this homeostatic mechanism by

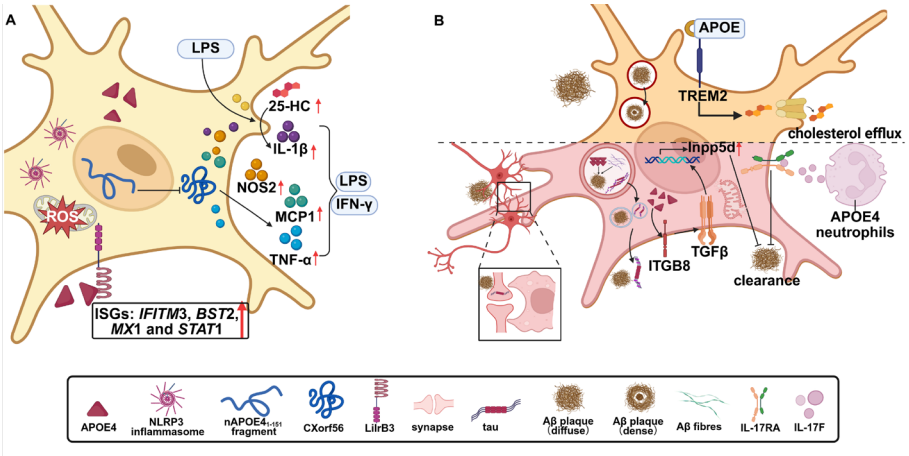

Figure 4. Microglial APOE4 promotes neuroinflammation and inhibits the clearance of pathological proteins in AD. (A). Microglial APOE4 promotes neuroinflammation by interacting with LilrB3 to upregulate ISGs, or inhibiting Cxorf56 to enhance TNF-α secretion in AD. In addition, NLRP3 inflammasomes and ROS were increased in APOE4 microglia, and more inflammatory factors were secreted in response to LPS and IFN-γ stimulation, further confirming the involvement of APOE4 in microglia-mediated neuroinflammation. **(B)**. Upper part: APOE accumulates around Aβ plaques, compacting diffuse Aβ into less toxic core plaques and restricting their dissemination within the brain. Lower part: microglial APOE4 inhibits Aβ clearance, promotes Aβ plaque formation, reduces tau degradation, and facilitates tau spread *via* exosomes. Meanwhile, APOE4 microglia enhance synaptic phagocytosis near Aβ plaques, correlating with cognitive decline. ISGs, interferon-stimulating genes; LPS, lipopolysaccharide; IFN-γ, interferon-gamma.

initiating a cascade of pathological events. APOE4-driven lipid metabolic dysregulation induces intracellular LD accumulation, which compromises plasma membrane integrity and severely impairs endosomal–lysosomal system functionality (*15,68,121*). This organelle dysfunction directly attenuates the processing and degradation capacity of tau proteins, leading to abnormal intracellular accumulation of p-tau (*51*). The accumulated pathological p-tau subsequently undergoes exosome-mediated release, thereby facilitating its intercellular propagation (*51,122*). Neuroimaging studies have consistently demonstrated significantly enhanced p-tau accumulation in APOE4 carriers, while the ameliorative effects of the APOE4-R136S homozygous mutation on tau pathology provide compelling genetic evidence for the pivotal role of APOE4 in regulating tau protein metabolism (*123,124*). In particular, aggregates of Aβ and tau near synapses have been shown to recruit microglia to phagocytose pathological synapses, thereby exacerbating synaptic dysfunction in AD. Increased phagocytosis of synapses by microglia was observed in the brains of AD patients carrying *APOE*ε4, which was particularly pronounced near Aβ plaques (*125,126*) (Figure 4B). Reactivation of transient receptor potential vanilloid 1 (TRPV1) has been shown to ameliorate cerebral lipid metabolic dysregulation, reduce LD accumulation, and attenuate microglial synaptic pruning, thereby ameliorating tau pathology and memory impairment (*96,100*). These findings reveal that APOE4 not only aggravates the impairment of Aβ/tau clearance, but also actively promotes pathological protein propagation and synaptic damage through dysregulation of the metabolism–phagocytosis pathway, suggesting that targeting the lipid metabolic reprogramming of APOE4 microglia may be a key strategy to attenuate AD progression.

APOE4 exacerbates AD progression through multifaceted mechanisms that disrupt microglial lipid homeostasis, thereby affecting neuroinflammation and the clearance of pathological proteins (*127,128*). APOE4-induced lipid metabolic dysregulation and mitochondrial dysfunction impair lysosomal degradation capacity, significantly compromising the clearance of Aβ and tau aggregates by microglia (*74*). Concurrently, aberrant lipid metabolism activates inflammatory signaling pathways, promoting excessive secretion of proinflammatory factors and establishing a persistent neuroinflammatory microenvironment. This inflammatory cascade further disrupts microglial function, ultimately resulting in neuronal death. These pathological alterations mutually reinforce each other, establishing a vicious cycle of "lipid metabolic dysregulation–neuroinflammation–functional impairment" (*14,15,72,73,78,100,111*). Consequently, therapeutic strategies targeting APOE4-mediated microglial lipid metabolic pathways, simultaneously suppressing inflammatory responses and restoring phagocytic function, may offer novel intervention approaches for AD treatment.

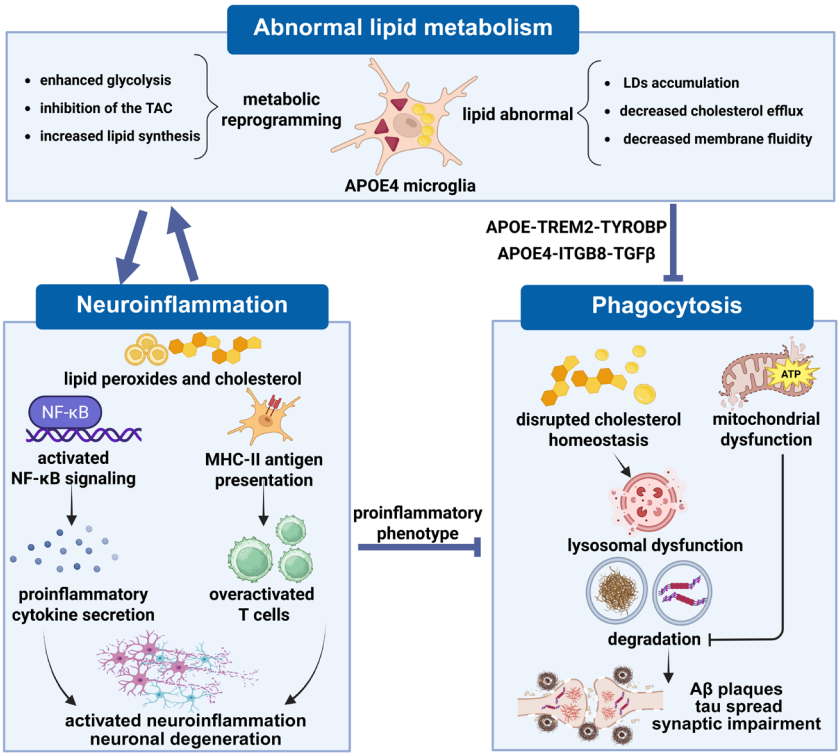

Figure 5. Summary of the role of microglial APOE4 in AD. APOE4-driven abnormal lipid metabolism of microglia is the core, which further aggravates neuroinflammation, eventually affects the immune phagocytosis of microglia, and accelerates the pathological process of AD.

5. Promising therapeutic strategies targeting microglial APOE4

Despite decades of research into treatments for AD, the therapeutic landscape remains limited. This review summarizes advances in microglia- and APOE4-related AD therapy (Table 1). In terms of metabolic regulation, lipid metabolism disorders can be alleviated by inhibition of cholesterol synthesis by TRPV1, promotion of cholesterol efflux by an LXR agonist (CS-6253), or enhancement of APOE4 lipidation by an RXR agonist (bexarotene) (*96,100,129-131*). Notably, pharmacological inhibition of diacylglycerol O-acyltransferase 2 (DGAT2) in microglia has been demonstrated to suppress triglyceride biosynthesis and subsequent LD accumulation, whereas genetic ablation of perilipin 2 (PLIN2) promotes LD degradation and attenuates neuroinflammation (*132,133*). These results suggest that targeting lipid metabolism is a promising therapeutic strategy for ameliorating pathological progression in AD. In the context of neuroinflammation, dimethyl malonate (DMM) reduces HIF1α expression in the microglia of AD model mice, promotes an anti-inflammatory phenotype, and attenuates neuroinflammation (*134*). Given that microglial APOE4 is associated with the upregulation of the NLRP3 inflammasome, modulation of the NLRP3 inflammasome is also a viable option to mitigate neuroinflammation (*114*). NLRP3 inhibitors, such as JC-124, dihydromyricetin (DHM), DAPPD, and dapansutrile (OLT1177), have shown potential in curbing neuroinflammation and enhancing Aβ clearance (*135-138*). Additionally, the ubiquitin ligase COP1 is another target for AD therapy because it modulates CEBP levels and attenuates proinflammatory gene expression in microglia (*139*). Strikingly, traditional herbal compounds, such as resveratrol and curcumin, have demonstrated the ability to inhibit microglia-associated neuroinflammation as potential therapeutic agents (*140-142*). The interaction between lipid metabolism and neuroinflammation is ultimately reflected in microglial dysfunction. For example, rutin sodium (NaR) and the 5-HT2A receptor antagonist desloratadine increase the expression of phagocytic receptors on the surface of microglia, and NaR promotes a shift in oxidative phosphorylation to generate the ATP required for efficient Aβ clearance (*143,144*). Furthermore, the AMPKα1 activator DW14006, and the TREM2 activator AL002c (NCT03635047, NCT04592874) have been shown to increase microglial phagocytosis of Aβ (*145-148*). Although some progress has been made in the study of microglial dysfunction as a therapeutic target for AD in animal models and at the cellular level, translating these findings into effective therapies in humans remains challenging.

Therapeutic strategies targeting the *APOE*ε4 allele have also been important focuses in AD research. Studies have reported that small-molecule mimetics such as $A\beta_{12\text{-}28}$p and the APOE mimic CN-105 reduce Aβ plaques and tau pathology by disrupting the interaction between APOE4 and Aβ (*149-151*). Recent research underscores the significant benefits of reducing APOE4 levels in AD. In a mouse model expressing human APOE4, immunotherapy with the anti-human APOE antibody HAE-4 has been shown to decrease the number of Aβ plaques and tau protein while inhibiting the expression of proinflammatory genes (*152,153*). Moreover, another promising approach involves the delivery of the human *APOE*ε2 gene *via* adeno-associated virus (AAV), which has been shown to prevent or even reverse the deleterious effects of APOE4 on brain amyloid pathology, with intracisternal delivery being the most effective method (*154,155*). LX1001, a drug targeting the *APOE*ε4 allele, has recently completed testing in phase I/II clinical trials. They have reported positive results regarding a dose-dependent increase in APOE2 protein expression and reductions in disease-associated tau protein biomarkers (*156,157*). The advent of CRISPR-Cas9 gene editing technology offers the potential to convert APOE4 to other isoforms, although this approach is accompanied by technical, ethical, and safety challenges (*9,158*).

Despite growing interest in microglial dysfunction and APOE4 as therapeutic targets for AD, no effective drugs currently exist to specifically correct APOE4-driven lipid metabolic abnormalities in microglia. Emerging evidence suggests that APOE4 exerts cell-type-specific pathogenic effects and that intervening with APOE4 in specific cell types can yield more precise results while alleviating the potentially toxic side effects associated with full-scale interventions targeting APOE4 (*159*). The critical role of microglial APOE4 in AD underscores its significance as a research focus, and future studies may provide breakthroughs in the treatment of AD.

6. Conclusion

AD is a progressive neurodegenerative disorder with complex pathogenic mechanisms. The *APOEε4* allele, the most significant genetic risk factor for AD, primarily mediates its pathological effects through microglial dysfunction, in which dysregulated lipid metabolism emerges as a pivotal pathogenic driver. Increasing evidence indicates that *APOEε4* disrupts microglial lipid homeostasis by impairing cholesterol efflux and promoting excessive LD formation, consequently (1) inducing proinflammatory cytokine secretion to activate microglia and aggravate neuroinflammation; (2) impairing phagocytic function by hindering energy metabolism, membrane fluidity and lysosomal activity; and (3) disrupting neuron–microglia crosstalk through lipid-mediated signaling pathways. The activation of neuroinflammation further aggravates abnormal lipid metabolism and affects the immune function of microglia. This pathogenic triad — lipid dysregulation,

Table 1. Promising therapeutic strategies targeting microglial APOE4 in Alzheimer's disease

Target Pathway	Therapeutic Agent	Mechanisms	Effects Observed	Note	*Ref.*
Lipid Metabolism	TRPV1/capsaicin	Inhibits SREBP-2, enhances autophagy activity	Alleviates cholesterol biosynthesis in APOE4 microglia; reduces APOE4 microglial phagocytosis of synapses	Specific to APOE4 microglia	(*96,100*)
	LXR agonist (GW3965), CS-6253	Increases cholesterol efflux in glial cells	Reduces lipid accumulation in glial cells; attenuates tau pathology	Specific to APOE4 microglia	(*51,129,131*)
	Bexarotene	Increases APOE4 lipidation	Reduces Aβ and p-tau accumulation; reverses cognitive and neuronal impairments	Specific to APOE4 Clinical trial: NCT01782742	(*130*)
Neuro-inflammation	JC-124, Dihydromyricetin, DAPPD, Dapansutrile (OLT1177)	NLRP3 inflammasome inhibitor	Suppresses neuroinflammation; promotes Aβ clearance; attenuates cognitive deficits	Targeting the NLRP3 inflammasome	(*135-138*)
	Ubiquitin ligase COP1	Modulates C/EBP levels and inhibits pro-inflammatory gene expression in microglia	Reduces microglial activation and neurotoxicity; suppresses neuroinflammation	Specific to microglia	(*139*)
	Resveratrol, Curcumin	Traditional Chinese Herbal medicine	Reduces neuroinflammation; neuroprotective	Specific to microglia	(*140-142*)
	Dimethyl Malonate	Inhibits succinate dehydrogenase (SDH) and HIF-1α expression in microglia	Enhances mitochondrial function; suppresses neuroinflammation	Specific to microglia	(*134*)
Phagocytosis	Sodium Rutin (NaR), Desloratadine	Increase the expression of phagocytic receptors in microglia	Enhances microglial phagocytosis of Aβ	Specific to microglia	(*143,144*)
	DW14006	Upregulates CD36 and modulates AMPKα1/IκB/NFκB signaling in microglia	Enhances microglial phagocytosis of Aβ; suppresses neuroinflammation	Specific to microglia	(*145*)
	AL002c	TREM2 activator	Reduces Aβ plaques and neurite dystrophy; tempers microglial inflammatory response	phase I clinical trial: NCT03635047; phase II clinical trial: NCT04592874	(*146-148*)
APOE4	Aβ12-28p, CN-105	disrupt the interaction between APOE and Aβ	Reduces Aβ pathology	Specific to APOE4	(*149-151*)
	HAE-4	Anti-human APOE4 antibody	Reduces Aβ plaques; inhibits tau propagation and neuritic dystrophy	Specific to APOE4	(*152,153*)
	LX1001	Increases APOE2 levels in the brain of APOE4 homozygous patients *via* AAV	Ameliorates tau pathology	Clinical trial: NCT03634007	(*156,157*)
	CRISPR-Cas9	Gene editing for APOE modification	Potential to convert APOE4 to other isoforms	technical, ethical, and safety challenges	(*158*)

sustained neuroinflammation and impaired phagocytosis — forms a self-perpetuating cycle that exacerbates AD progression. Current therapeutic strategies for this axis include restoring the homeostasis of lipid metabolism in microglia, reducing neuroinflammation, enhancing immune phagocytosis by microglia, and reducing the expression of APOE4. Future research should aim to elucidate the molecular mechanisms underlying APOE4-mediated lipid metabolism disorders in microglia, develop lipidomic signatures as predictive biomarkers for APOE4-targeted interventions, and design integrated treatment approaches that synergistically address multiple pathological cascades in AD.

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References

1. 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023; 19:1598-1695.
2. Jia L, Quan M, Fu Y, *et al*. Dementia in China: Epidemiology, clinical management, and research advances. Lancet Neurol. 2020; 19:81-92.
3. Kao YC, Ho PC, Tu YK, Jou IM, Tsai KJ. Lipids and Alzheimer's disease. Int J Mol Sci. 2020; 21:1505.
4. Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, Fiske A, Pedersen NL. Role of genes and environments for explaining Alzheimer disease. Arc Gen Psychiatry. 2006; 63:168-174.
5. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261:921-923.
6. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM. Alzheimer's disease. Lancet. 2021; 397:1577-1590.
7. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997; 278:1349-1356.
8. Hu X, Ma YN, Xia Y. Association between abnormal lipid metabolism and Alzheimer's disease: New research has revealed significant findings on the APOE4 genotype in microglia. Biosci Trends. 2024; 18:195-197.
9. Lin YT, Seo J, Gao F, *et al*. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. Neuron. 2018; 98:1141-1154.e7.
10. Windham IA, Cohen S. The cell biology of APOE in the brain. Trends Cell Biol. 2024; 34:338-348.
11. Yang LG, March ZM, Stephenson RA, Narayan PS. Apolipoprotein E in lipid metabolism and neurodegenerative disease. Trends Endocrinol Metab. 2023; 34:430-445.
12. Eyo UB, Wu LJ. Microglia: Lifelong patrolling immune cells of the brain. Prog Neurobiol. 2019; 179:101614.
13. Guo S, Wang H, Yin Y. Microglia polarization from M1 to M2 in Neurodegenerative diseases. Front Aging Neurosci. 2022; 14:815347.
14. Dias D, Portugal CC, Relvas J, Socodato R. From genetics to neuroinflammation: The impact of ApoE4 on microglial function in Alzheimer's disease. Cells. 2025; 14:243.
15. Chausse B, Kakimoto PA, Kann O. Microglia and lipids: How metabolism controls brain innate immunity. Semin Cell Dev Biol. 2021; 112:137-144.
16. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A. 1993; 90:1977-1981.
17. McIntosh AM, Bennett C, Dickson D, Anestis SF, Watts DP, Webster TH, Fontenot MB, Bradley BJ. The apolipoprotein E (APOE) gene appears functionally monomorphic in chimpanzees (Pan troglodytes). PloS One. 2012; 7:e47760.
18. Weisgraber KH, Rall SC, Jr., Mahley RW. Human E apoprotein heterogeneity. Cysteine-arginine interchanges in the amino acid sequence of the apo-E isoforms. J Biol Chem. 1981; 256:9077-9083.
19. Hatters DM, Peters-Libeu CA, Weisgraber KH. Apolipoprotein E structure: insights into function. Trends Biochem Sci. 2006; 31:445-454.
20. Morrow JA, Hatters DM, Lu B, Hochtl P, Oberg KA, Rupp B, Weisgraber KH. Apolipoprotein E4 forms a molten globule. A potential basis for its association with disease. J Biol Chem. 2002; 277:50380-50385.
21. Chetty PS, Mayne L, Lund-Katz S, Englander SW, Phillips MC. Helical structure, stability, and dynamics in human apolipoprotein E3 and E4 by hydrogen exchange and mass spectrometry. Proc Natl Acad Sci U S A. 2017; 114:968-973.
22. Rawat V, Wang S, Sima J, Bar R, Liraz O, Gundimeda U, Parekh T, Chan J, Johansson JO, Tang C, Chui HC, Harrington MG, Michaelson DM, Yassine HN. ApoE4 alters ABCA1 membrane trafficking in astrocytes. J Neurosci. 2019; 39:9611-9622.
23. Zannis VI, McPherson J, Goldberger G, Karathanasis SK, Breslow JL. Synthesis, intracellular processing, and signal peptide of human apolipoprotein E. J Biol Chem. 1984; 259:5495-5499.
24. Wahrle SE, Jiang H, Parsadanian M, Legleiter J, Han X, Fryer JD, Kowalewski T, Holtzman DM. ABCA1 is required for normal central nervous system ApoE levels and for lipidation of astrocyte-secreted apoE. J Biol Chem. 2004; 279:40987-40993.
25. Fitz NF, Nam KN, Koldamova R, Lefterov I. Therapeutic targeting of nuclear receptors, liver X and retinoid X receptors, for Alzheimer's disease. Br J Pharmacol. 2019; 176:3599-3610.
26. Herz J, Bock HH. Lipoprotein receptors in the nervous system. Annu Rev Biochem. 2002; 71:405-434.

27. Zhao XN, Sun Q, Cao YQ, Ran X, Cao Y. Association between apolipoprotein gene polymorphisms and hyperlipidemia: A meta-analysis. BMC Genom Data. 2021; 22:14.
28. Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Ann Neurol. 1995; 38:254-259.
29. Rong X, Chen J, Pan D, Wang Y, Zhang C, Tang Y. Association between Apolipoprotein E genotype and functional outcome in acute ischemic stroke. Aging. 2023; 15:108-118.
30. Teasdale GM, Nicoll JA, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. Lancet. 1997; 350:1069-1071.
31. Kim R, Park S, Yoo D, Jun JS, Jeon B. Impact of the apolipoprotein E ε4 allele on early Parkinson's disease progression. Parkinsonism Relat Disord. 2021; 83:66-70.
32. Wang YY, Ge YJ, Tan CC, Cao XP, Tan L, Xu W. The proportion of APOE4 carriers among non-demented individuals: A pooled analysis of 389,000 community-dwellers. J Alzheimers Dis. 2021; 81:1331-1339.
33. Fortea J, Pegueroles J, Alcolea D, Belbin O, Dols-Icardo O, Vaqué-Alcázar L, Videla L, Gispert JD, Suárez-Calvet M, Johnson SC, Sperling R, Bejanin A, Lleó A, Montal V. APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. Nat Med. 2024; 30:1284-1291.
34. Belloy ME, Andrews SJ, Le Guen Y, Cuccaro M, Farrer LA, Napolioni V, Greicius MD. APOE genotype and Alzheimer disease risk across age, sex, and population ancestry. JAMA Neurol. 2023; 80:1284-1294.
35. Payami H, Zareparsi S, Montee KR, Sexton GJ, Kaye JA, Bird TD, Yu CE, Wijsman EM, Heston LL, Litt M, Schellenberg GD. Gender difference in apolipoprotein E-associated risk for familial Alzheimer disease: a possible clue to the higher incidence of Alzheimer disease in women. Am J Hum Genet. 1996; 58:803-811.
36. Dubal DB, Yokoyama JS. Longevity gene KLOTHO and Alzheimer disease-A better fate for individuals who carry APOE ε4. JAMA Neurol. 2020; 77:798-800.
37. Le Guen Y, Belloy ME, Grenier-Boley B, *et al*. Association of rare APOE missense variants V236E and R251G with risk of Alzheimer disease. JAMA Neurol. 2022; 79:652-663.
38. Belloy ME, Napolioni V, Han SS, Le Guen Y, Greicius MD. Association of Klotho-VS heterozygosity with risk of Alzheimer disease in individuals who carry APOE4. JAMA Neurol. 2020; 77:849-862.
39. Huq AJ, Fransquet P, Laws SM, Ryan J, Sebra R, Masters CL, Winship IM, James PA, Lacaze P. Genetic resilience to Alzheimer's disease in APOE ε4 homozygotes: A systematic review. Alzheimers Dement. 2019; 15:1612-1623.
40. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA. 1999; 282:40-46.
41. Kanekiyo T, Xu H, Bu G. ApoE and Aβ in Alzheimer's disease: Accidental encounters or partners? Neuron. 2014; 81:740-754.
42. Kaji S, Berghoff SA, Spieth L, *et al*. Apolipoprotein E aggregation in microglia initiates Alzheimer's disease pathology by seeding β-amyloidosis. Immunity. 2024; 57:2651-2668.e12.
43. Chen Y, Strickland MR, Soranno A, Holtzman DM. Apolipoprotein E: Structural insights and links to Alzheimer disease pathogenesis. Neuron. 2021; 109:205-221.
44. Baligács N, Albertini G, Borrie SC, Serneels L, Pridans C, Balusu S, De Strooper B. Homeostatic microglia initially seed and activated microglia later reshape amyloid plaques in Alzheimer's disease. Nat Commun. 2024; 15:10634.
45. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, Holtzman DM, Betsholtz C, Armulik A, Sallstrom J, Berk BC, Zlokovic BV. Apolipoprotein E controls cerebrovascular integrity *via* cyclophilin A. Nature. 2012; 485:512-516.
46. Jackson RJ, Meltzer JC, Nguyen H, Commins C, Bennett RE, Hudry E, Hyman BT. APOE4 derived from astrocytes leads to blood-brain barrier impairment. Brain. 2022; 145:3582-3593.
47. Schmukler E, Solomon S, Simonovitch S, Goldshmit Y, Wolfson E, Michaelson DM, Pinkas-Kramarski R. Altered mitochondrial dynamics and function in APOE4-expressing astrocytes. Cell Death Dis. 2020; 11:578.
48. Farmer BC, Kluemper J, Johnson LA. Apolipoprotein E4 alters astrocyte fatty acid metabolism and lipid droplet formation. Cells. 2019; 8:182.
49. Parhizkar S, Holtzman DM. APOE mediated neuroinflammation and neurodegeneration in Alzheimer's disease. Semin Immunol. 2022; 59:101594.
50. Sienski G, Narayan P, Bonner JM, *et al*. APOE4 disrupts intracellular lipid homeostasis in human iPSC-derived glia. Sci Transl Med. 2021; 13:eaaz4564.
51. Litvinchuk A, Suh JH, Guo JL, *et al*. Amelioration of Tau and ApoE4-linked glial lipid accumulation and neurodegeneration with an LXR agonist. Neuron. 2024; 112:384-403.e8.
52. Lee H, Cho S, Kim MJ, *et al*. ApoE4-dependent lysosomal cholesterol accumulation impairs mitochondrial homeostasis and oxidative phosphorylation in human astrocytes. Cell Rep. 2023; 42:113183.
53. Blanchard JW, Akay LA, Davila-Velderrain J, *et al*. APOE4 impairs myelination *via* cholesterol dysregulation in oligodendrocytes. Nature. 2022; 611:769-779.
54. Xia Y, Wang ZH, Zhang J, Liu X, Yu SP, Ye KX, Wang JZ, Ye K, Wang XC. C/EBPβ is a key transcription factor for APOE and preferentially mediates ApoE4 expression in Alzheimer's disease. Mol Psychiatry. 2021; 26:6002-6022.
55. Wynne ME, Ogunbona O, Lane AR, *et al*. APOE expression and secretion are modulated by mitochondrial dysfunction. ELife. 2023; 12:e85779.
56. de Leeuw SM, Kirschner AWT, Lindner K, Rust R, Budny V, Wolski WE, Gavin AC, Nitsch RM, Tackenberg C. APOE2, E3, and E4 differentially modulate cellular homeostasis, cholesterol metabolism, and inflammatory response in isogenic iPSC-derived astrocytes. Stem Cell Reports. 2022; 17:110-126.
57. Chung WS, Verghese PB, Chakraborty C, Joung J, Hyman BT, Ulrich JD, Holtzman DM, Barres BA. Novel allele-dependent role for APOE in controlling the rate of synapse pruning by astrocytes. Proc Natl Acad Sci U S A. 2016; 113:10186-10191.
58. Tcw J, Qian L, Pipalia NH, *et al*. Cholesterol and matrisome pathways dysregulated in astrocytes and microglia. Cell. 2022; 185:2213-2233.e25.
59. Staurenghi E, Leoni V, Lo Iacono M, Sottero B, Testa G, Giannelli S, Leonarduzzi G, Gamba P. ApoE3 *vs.* ApoE4 astrocytes: A detailed analysis provides new insights

into differences in cholesterol homeostasis. Antioxidants (Basel). 2022; 11:2168.
60. Zhao J, Davis MD, Martens YA, Shinohara M, Graff-Radford NR, Younkin SG, Wszolek ZK, Kanekiyo T, Bu G. APOE ε4/ε4 diminishes neurotrophic function of human iPSC-derived astrocytes. Hum Mol Genet. 2017; 26:2690-2700.
61. Qi G, Mi Y, Shi X, Gu H, Brinton RD, Yin F. ApoE4 impairs neuron-astrocyte coupling of fatty acid metabolism. Cell Rep. 2021; 34:108572.
62. Windham IA, Powers AE, Ragusa JV, Wallace ED, Zanellati MC, Williams VH, Wagner CH, White KK, Cohen S. APOE traffics to astrocyte lipid droplets and modulates triglyceride saturation and droplet size. J Cell Biol. 2024; 223:e202305003.
63. Li X, Zhang J, Li D, He C, He K, Xue T, Wan L, Zhang C, Liu Q. Astrocytic ApoE reprograms neuronal cholesterol metabolism and histone-acetylation-mediated memory. Neuron. 2021; 109:957-970.e8.
64. Saroja SR, Gorbachev K, Julia T, Goate AM, Pereira AC. Astrocyte-secreted glypican-4 drives APOE4-dependent tau hyperphosphorylation. Proc Natl Acad Sci U S A. 2022; 119:e2108870119.
65. Zalocusky KA, Najm R, Taubes AL, *et al*. Neuronal ApoE upregulates MHC-I expression to drive selective neurodegeneration in Alzheimer's disease. Nat Neurosci. 2021; 24:786-798.
66. Koutsodendris N, Blumenfeld J, Agrawal A, Traglia M, Grone B, Zilberter M, Yip O, Rao A, Nelson MR, Hao Y, Thomas R, Yoon SY, Arriola P, Huang Y. Neuronal APOE4 removal protects against tau-mediated gliosis, neurodegeneration and myelin deficits. Nat Aging. 2023; 3:275-296.
67. Guo JL, Braun D, Fitzgerald GA, *et al*. Decreased lipidated ApoE-receptor interactions confer protection against pathogenicity of ApoE and its lipid cargoes in lysosomes. Cell. 2025; 188:187-206.e26.
68. Wang S, Li B, Li J, *et al*. Cellular senescence induced by cholesterol accumulation is mediated by lysosomal ABCA1 in APOE4 and AD. Mol Neurodegener. 2025; 20:15.
69. Mahley RW. Apolipoprotein E: From cardiovascular disease to neurodegenerative disorders. J Mol Med (Berl). 2016; 94:739-746.
70. Wang C, Najm R, Xu Q, Jeong DE, Walker D, Balestra ME, Yoon SY, Yuan H, Li G, Miller ZA, Miller BL, Malloy MJ, Huang Y. Gain of toxic apolipoprotein E4 effects in human iPSC-derived neurons is ameliorated by a small-molecule structure corrector. Nat Med. 2018; 24:647-657.
71. Rao A, Chen N, Kim MJ, *et al*. Microglia depletion reduces human neuronal APOE4-related pathologies in a chimeric Alzheimer's disease model. Cell Stem Cell. 2025; 32:86-104.e7.
72. Marschallinger J, Iram T, Zardeneta M, *et al*. Author Correction: Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. Nat Neurosci. 2020; 23:294.
73. Haney MS, Pálovics R, Munson CN, *et al*. APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia. Nature. 2024; 628:154-161.
74. Bassal R, Rivkin-Natan M, Rabinovich A, Michaelson DM, Frenkel D, Pinkas-Kramarski R. APOE4 impairs autophagy and Aβ clearance by microglial cells. Inflamm Res. 2025; 74:61.
75. Zhou J, Wang Y, Huang G, Yang M, Zhu Y, Jin C, Jing D, Ji K, Shi Y. LilrB3 is a putative cell surface receptor of APOE4. Cell Res. 2023; 33:116-130.
76. Mauerer R, Walczak Y, Langmann T. Comprehensive mRNA profiling of lipid-related genes in microglia and macrophages using taqman arrays. Methods Mol Biol. 2009; 580:187-201.
77. Wang Q, Lu M, Zhu X, Gu X, Zhang T, Xia C, Yang L, Xu Y, Zhou M. The role of microglia immunometabolism in neurodegeneration: Focus on molecular determinants and metabolic intermediates of metabolic reprogramming. Biomed Pharmacother. 2022; 153:113412.
78. Lee S, Devanney NA, Golden LR, *et al*. APOE modulates microglial immunometabolism in response to age, amyloid pathology, and inflammatory challenge. Cell Rep. 2023; 42:112196.
79. Liu L, Zhang K, Sandoval H, Yamamoto S, Jaiswal M, Sanz E, Li Z, Hui J, Graham BH, Quintana A, Bellen HJ. Glial lipid droplets and ROS induced by mitochondrial defects promote neurodegeneration. Cell. 2015; 160:177-190.
80. Leng L, Yuan Z, Pan R, *et al*. Microglial hexokinase 2 deficiency increases ATP generation through lipid metabolism leading to β-amyloid clearance. Nat Metab. 2022; 4:1287-1305.
81. Liu CC, Wang N, Chen Y, *et al*. Cell-autonomous effects of APOE4 in restricting microglial response in brain homeostasis and Alzheimer's disease. Nat Immunol. 2023; 24:1854-1866.
82. Muth C, Hartmann A, Sepulveda-Falla D, Glatzel M, Krasemann S. Phagocytosis of apoptotic cells is specifically upregulated in ApoE4 expressing microglia *in vitro*. Front Cellular Neurosci. 2019; 13:181.
83. Serrano-Pozo A, Li Z, Noori A, Nguyen HN, Mezlini A, Li L, Hudry E, Jackson RJ, Hyman BT, Das S. Effect of APOE alleles on the glial transcriptome in normal aging and Alzheimer's disease. Nat Aging. 2021; 1:919-931.
84. Krasemann S, Madore C, Cialic R, *et al*. The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in Neurodegenerative diseases. Immunity. 2017; 47:566-581.e9.
85. Yin Z, Rosenzweig N, Kleemann KL, *et al*. APOE4 impairs the microglial response in Alzheimer's disease by inducing TGFβ-mediated checkpoints. Nat Immunol. 2023; 24:1839-1853.
86. Millet A, Ledo JH, Tavazoie SF. An exhausted-like microglial population accumulates in aged and APOE4 genotype Alzheimer's brains. Immunity. 2024; 57:153-170.e6.
87. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde". Clin Anat. 1995; 8:429-431.
88. Flury A, Aljayousi L, Park HJ, *et al*. A neurodegenerative cellular stress response linked to dark microglia and toxic lipid secretion. Neuron. 2025; 113:554-571.e14.
89. Prakash P, Manchanda P, Paouri E, *et al*. Amyloid β induces lipid droplet-mediated microglial dysfunction *via* the enzyme DGAT2 in Alzheimer's disease. bioRxiv : the preprint server for biology. 2023; *https://www.biorxiv.org/content/10.1101/2023.06.04.543525v2.full.pdf*
90. Zhao Y, Wu X, Li X, *et al*. TREM2 is a receptor for β-amyloid that mediates microglial function. Neuron. 2018; 97:1023-1031.e7.
91. Claes C, Danhash EP, Hasselmann J, Chadarevian JP,

Shabestari SK, England WE, Lim TE, Hidalgo JLS, Spitale RC, Davtyan H, Blurton-Jones M. Plaque-associated human microglia accumulate lipid droplets in a chimeric model of Alzheimer's disease. Mol Neurodegener. 2021; 16:50.
92. Andreone BJ, Przybyla L, Llapashtica C, Rana A, Davis SS, van Lengerich B, Lin K, Shi J, Mei Y, Astarita G, Di Paolo G, Sandmann T, Monroe KM, Lewcock JW. Alzheimer's-associated PLCγ2 is a signaling node required for both TREM2 function and the inflammatory response in human microglia. Nat Neurosci. 2020; 23:927-938.
93. Zhang J, Liu Q. Cholesterol metabolism and homeostasis in the brain. Protein Cell. 2015; 6:254-264.
94. Li B, Wang S, Kerman B, Hugo C, Shwab EK, Shu C, Chiba-Falek O, Arvanitakis Z, Yassine H. Microglia states are susceptible to senescence and cholesterol dysregulation in Alzheimer's disease. 2024; *https://www.biorxiv.org/content/10.1101/2024.11.18.624141v1*
95. Komatsu C, Komatsu RS. Alzheimer's Disease (AD): High cholesterol is associated with lower Mini-Mental State Exam (MMSE) scores. Alzheimer's & Dementia. 2023; 19. *https://doi.org/10.1002/alz.065868*
96. Lu J, Wu K, Sha X, Lin J, Chen H, Yu Z. TRPV1 alleviates APOE4-dependent microglial antigen presentation and T cell infiltration in Alzheimer's disease. Transl Neurodegener. 2024; 13:52.
97. Lee CY, Tse W, Smith JD, Landreth GE. Apolipoprotein E promotes β-amyloid trafficking and degradation by modulating microglial cholesterol levels. J Biol Chem. 2012; 287:2032-2044.
98. Egawa J, Pearn ML, Lemkuil BP, Patel PM, Head BP. Membrane lipid rafts and neurobiology: Age-related changes in membrane lipids and loss of neuronal function. J Physiol. 2016; 594:4565-4579.
99. Rudajev V, Novotny J. Cholesterol-dependent amyloid β production: Space for multifarious interactions between amyloid precursor protein, secretases, and cholesterol. Cell Biosci. 2023; 13:171.
100. Wang C, Lu J, Sha X, Qiu Y, Chen H, Yu Z. TRPV1 regulates ApoE4-disrupted intracellular lipid homeostasis and decreases synaptic phagocytosis by microglia. Exp Mol Med. 2023; 55:347-363.
101. Cserép C, Schwarcz AD, Pósfai B, László ZI, Kellermayer A, Környei Z, Kisfali M, Nyerges M, Lele Z, Katona I, Ádám D. Microglial control of neuronal development *via* somatic purinergic junctions. Cell Rep. 2022; 40:111369.
102. Marinelli S, Basilico B, Marrone MC, Ragozzino D. Microglia-neuron crosstalk: Signaling mechanism and control of synaptic transmission. Semin Cell Dev Biol. 2019; 94:138-151.
103. Victor MB, Leary N, Luna X, *et al*. Lipid accumulation induced by APOE4 impairs microglial surveillance of neuronal-network activity. Cell Stem Cell. 2022; 29:1197-1212.e8.
104. Young JE, Jayadev S. Neighborhood matters: Altered lipid metabolism in APOE4 microglia causes problems for neurons. Cell Stem Cell. 2022; 29:1159-1160.
105. Li Y, Munoz-Mayorga D, Nie Y, Kang N, Tao Y, Lagerwall J, Pernaci C, Curtin G, Coufal NG, Mertens J, Shi L, Chen X. Microglial lipid droplet accumulation in tauopathy brain is regulated by neuronal AMPK. Cell Metab. 2024; 36:1351-1370.e8.
106. Huynh TV, Wang C, Tran AC, Tabor GT, Mahan TE, Francis CM, Finn MB, Spellman R, Manis M, Tanzi RE, Ulrich JD, Holtzman DM. Lack of hepatic apoE does not influence early Aβ deposition: observations from a new APOE knock-in model. Mol Neurodegener. 2019; 14:37.
107. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol. 2021; 17:157-172.
108. Zhang R, Ding RQ, Wang Q, Zhang LK, Fan XC, Guo FY, Chen XM, Jiang C, Cao J, Wang JM, Zang WD, Wang J. Inflammation in intracerebral hemorrhage: A bibliometric perspective. Brain Hemorrhages. 2024; 5:107-116.
109. Goel P, Chakrabarti S, Goel K, Bhutani K, Chopra T, Bali S. Neuronal cell death mechanisms in Alzheimer's disease: An insight. Front Mol Neurosci. 2022; 15:937133.
110. Amelimojarad M, Amelimojarad M, Cui X. The emerging role of brain neuroinflammatory responses in Alzheimer's disease. Front Aging Neurosci. 2024; 16:1391517.
111. Wong MY, Lewis M, Doherty JJ, Shi Y, Cashikar AG, Amelianchik A, Tymchuk S, Sullivan PM, Qian M, Covey DF, Petsko GA, Holtzman DM, Paul SM, Luo W. 25-Hydroxycholesterol amplifies microglial IL-1β production in an apoE isoform-dependent manner. J Neuroinflammation. 2020; 17:192.
112. Pollock TB, Mack JM, Day RJ, Isho NF, Brown RJ, Oxford AE, Morrison BE, Hayden EJ, Rohn TT. A fragment of apolipoprotein E4 leads to the downregulation of a CXorf56 homologue, a novel ER-associated protein, and activation of BV2 microglial cells. Oxid Med Cell Longev. 2019; 2019:5123565.
113. Mhatre-Winters I, Eid A, Han Y, Tieu K, Richardson JR. Sex and APOE genotype alter the basal and induced inflammatory states of primary microglia from APOE targeted replacement mice. Int J Mol Sci. 2022; 23:9829.
114. Liu XT, Chen X, Zhao N, Geng F, Zhu MM, Ren QG. Synergism of ApoE4 and systemic infectious burden is mediated by the APOE-NLRP3 axis in Alzheimer's disease. Psychiatry Clin Neurosci. 2024; 78:517-526.
115. Huynh TN, Fikse EN, De La Torre AL, Havrda MC, Chang CCY, Chang TY. Inhibiting the cholesterol storage enzyme ACAT1/SOAT1 in aging apolipoprotein E4 mice alters their brains' inflammatory profiles. Int J Mol Sci. 2024; 25:13690.
116. Fitz NF, Nam KN, Wolfe CM, Letronne F, Playso BE, Iordanova BE, Kozai TDY, Biedrzycki RJ, Kagan VE, Tyurina YY, Han X, Lefterov I, Koldamova R. Phospholipids of APOE lipoproteins activate microglia in an isoform-specific manner in preclinical models of Alzheimer's disease. Nat Commun. 2021; 12:3416.
117. Bogie JF, Jorissen W, Mailleux J, Nijland PG, Zelcer N, Vanmierlo T, Van Horssen J, Stinissen P, Hellings N, Hendriks JJ. Myelin alters the inflammatory phenotype of macrophages by activating PPARs. Acta Neuropathol Commun. 2013; 1:43.
118. Park JC, Han JW, Lee W, *et al*. Microglia Gravitate toward Amyloid Plaques Surrounded by Externalized Phosphatidylserine *via* TREM2. Adv Sci (Weinh). 2024; 11:e2400064.
119. Rosenzweig N, Kleemann KL, Rust T, *et al*. Sex-dependent APOE4 neutrophil-microglia interactions drive cognitive impairment in Alzheimer's disease. Nat Med. 2024; 30:2990-3003.
120. Vogels T, Murgoci AN, Hromádka T. Intersection of pathological tau and microglia at the synapse. Acta Neuropathol Commun. 2019; 7:109.
121. Wu X, Miller JA, Lee BTK, Wang Y, Ruedl C. Reducing microglial lipid load enhances β amyloid phagocytosis in an Alzheimer's disease mouse model. Sci Adv. 2025;

11:eadq6038.
122. Asai H, Ikezu S, Tsunoda S, Medalla M, Luebke J, Haydar T, Wolozin B, Butovsky O, Kügler S, Ikezu T. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nat Neurosci. 2015; 18:1584-1593.
123. Ferrari-Souza JP, Lussier FZ, Leffa DT, *et al*. APOEε4 associates with microglial activation independently of Aβ plaques and tau tangles. Sci Adv. 2023; 9:eade1474.
124. Nelson MR, Liu P, Agrawal A, *et al*. The APOE-R136S mutation protects against APOE4-driven Tau pathology, neurodegeneration and neuroinflammation. Nat Neurosci. 2023; 26:2104-2121.
125. Tzioras M, McGeachan RI, Durrant CS, Spires-Jones TL. Synaptic degeneration in Alzheimer disease. Nat Rev Neurol. 2023; 19:19-38.
126. Tzioras M, Daniels MJD, Davies C, *et al*. Human astrocytes and microglia show augmented ingestion of synapses in Alzheimer's disease *via* MFG-E8. Cell Rep Med. 2023; 4:101175.
127. Chen Y, Jin H, Chen J, Li J, Găman MA, Zou Z. The multifaceted roles of apolipoprotein E4 in Alzheimer's disease pathology and potential therapeutic strategies. Cell Death Discov. 2025; 11:312.
128. Jung ES, Choi H, Mook-Jung I. Decoding microglial immunometabolism: A new frontier in Alzheimer's disease research. Mol Neurodegener. 2025; 20:37.
129. Valencia-Olvera AC, Balu D, Bellur S, McNally T, Saleh Y, Pham D, Ghura S, York J, Johansson JO, LaDu MJ, Tai L. A novel apoE-mimetic increases brain apoE levels, reduces Aβ pathology and improves memory when treated before onset of pathology in male mice that express APOE3. Alzheimers Res Ther. 2023; 15:216.
130. Boehm-Cagan A, Michaelson DM. Reversal of apoE4-driven brain pathology and behavioral deficits by bexarotene. J Neurosci. 2014; 34:7293-7301.
131. Boehm-Cagan A, Bar R, Liraz O, Bielicki JK, Johansson JO, Michaelson DM. ABCA1 agonist reverses the ApoE4-driven cognitive and brain pathologies. J Alzheimers Dis. 2016; 54:1219-1233.
132. 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; 58:1536-1552.e8.
133. Loix M, Wouters E, Vanherle S, Dehairs J, McManaman JL, Kemps H, Swinnen JV, Haidar M, Bogie JFJ, Hendriks JJA. Perilipin-2 limits remyelination by preventing lipid droplet degradation. Cell Mol Life Sci. 2022; 79:515.
134. Sangineto M, Ciarnelli M, Cassano T, Radesco A, Moola A, Bukke VN, Romano A, Villani R, Kanwal H, Capitanio N, Duda L, Avolio C, Serviddio G. Metabolic reprogramming in inflammatory microglia indicates a potential way of targeting inflammation in Alzheimer's disease. Redox Biol. 2023; 66:102846.
135. Yin J, Zhao F, Chojnacki JE, Fulp J, Klein WL, Zhang S, Zhu X. NLRP3 inflammasome inhibitor ameliorates amyloid pathology in a mouse model of Alzheimer's disease. Mol Neurobiol. 2018; 55:1977-1987.
136. Feng J, Wang JX, Du YH, Liu Y, Zhang W, Chen JF, Liu YJ, Zheng M, Wang KJ, He GQ. Dihydromyricetin inhibits microglial activation and neuroinflammation by suppressing NLRP3 inflammasome activation in APP/PS1 transgenic mice. CNS Neurosci Ther. 2018; 24:1207-1218.
137. Park MH, Lee M, Nam G, *et al*. N,N'-Diacetyl-p-phenylenediamine restores microglial phagocytosis and improves cognitive defects in Alzheimer's disease transgenic mice. Proc Natl Acad Sci U S A. 2019; 116:23426-23436.
138. Lonnemann N, Hosseini S, Marchetti C, Skouras DB, Stefanoni D, D'Alessandro A, Dinarello CA, Korte M. The NLRP3 inflammasome inhibitor OLT1177 rescues cognitive impairment in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A. 2020; 117:32145-32154.
139. Ndoja A, Reja R, Lee SH, Webster JD, Ngu H, Rose CM, Kirkpatrick DS, Modrusan Z, Chen YJ, Dugger DL, Gandham V, Xie L, Newton K, Dixit VM. Ubiquitin ligase COP1 suppresses neuroinflammation by degrading c/EBPβ in microglia. Cell. 2020; 182:1156-1169.e12.
140. Feng L, Zhang L. Resveratrol suppresses Aβ-induced microglial activation through the TXNIP/TRX/NLRP3 signaling pathway. DNA Cell Biol. 2019; 38:874-879.
141. Abozaid OAR, Sallam MW, El-Sonbaty S, Aziza S, Emad B, Ahmed ESA. Resveratrol-selenium nanoparticles alleviate neuroinflammation and neurotoxicity in a rat model of Alzheimer's disease by regulating Sirt1/miRNA-134/GSK3β expression. Biol Trace Elem Res. 2022; 200:5104-5114.
142. Qiao P, Ma J, Wang Y, Huang Z, Zou Q, Cai Z, Tang Y. Curcumin prevents neuroinflammation by inducing microglia to transform into the M2-phenotype *via* CaMKKβ-dependent activation of the AMP-activated protein kinase signal pathway. Curr Alzheimer Res. 2020; 17:735-752.
143. Lu J, Zhang C, Lv J, Zhu X, Jiang X, Lu W, Lu Y, Tang Z, Wang J, Shen X. Antiallergic drug desloratadine as a selective antagonist of 5HT(2A) receptor ameliorates pathology of Alzheimer's disease model mice by improving microglial dysfunction. Aging cell. 2021; 20:e13286.
144. Pan RY, Ma J, Kong XX, Wang XF, Li SS, Qi XL, Yan YH, Cheng J, Liu Q, Jin W, Tan CH, Yuan Z. Sodium rutin ameliorates Alzheimer's disease-like pathology by enhancing microglial amyloid-β clearance. Sci Adv. 2019; 5:eaau6328.
145. Lv J, Wang W, Zhu X, Xu X, Yan Q, Lu J, Shi X, Wang Z, Zhou J, Huang X, Wang J, Duan W, Shen X. DW14006 as a direct AMPKα1 activator improves pathology of AD model mice by regulating microglial phagocytosis and neuroinflammation. Brain Behav Immun. 2020; 90:55-69.
146. Wang S, Mustafa M, Yuede CM, *et al*. Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. J Exp Med. 2020; 217:e20200785.
147. A Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Single and Multiple Doses of AL002 in Healthy Participants and in Participants With Mild to Moderate Alzheimer's Disease. 2018; *https://clinicaltrials.gov/study/NCT03635047*
148. A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of AL002 in Participants With Early Alzheimer's Disease. AbbVie, ed. 2020; *https://clinicaltrials.gov/study/NCT04592874*
149. Kuszczyk MA, Sanchez S, Pankiewicz J, Kim J, Duszczyk M, Guridi M, Asuni AA, Sullivan PM, Holtzman DM, Sadowski MJ. Blocking the interaction between apolipoprotein E and Aβ reduces intraneuronal accumulation of Aβ and inhibits synaptic degeneration.

Am J Pathol. 2013; 182:1750-1768.
150. Krishnamurthy K, Cantillana V, Wang H, Sullivan PM, Kolls BJ, Ge X, Lin Y, Mace B, Laskowitz DT. ApoE mimetic improves pathology and memory in a model of Alzheimer's disease. Brain Res. 2020; 1733:146685.
151. Liu S, Breitbart A, Sun Y, Mehta PD, Boutajangout A, Scholtzova H, Wisniewski T. Blocking the apolipoprotein E/amyloid β interaction in triple transgenic mice ameliorates Alzheimer's disease related amyloid β and tau pathology. J Neurochem. 2014; 128:577-591.
152. Gratuze M, Jiang H, Wang C, Xiong M, Bao X, Holtzman DM. APOE antibody inhibits Aβ-associated Tau seeding and spreading in a mouse model. Ann Neurol. 2022; 91:847-852.
153. Xiong M, Jiang H, Serrano JR, Gonzales ER, Wang C, Gratuze M, Hoyle R, Bien-Ly N, Silverman AP, Sullivan PM, Watts RJ, Ulrich JD, Zipfel GJ, Holtzman DM. APOE immunotherapy reduces cerebral amyloid angiopathy and amyloid plaques while improving cerebrovascular function. Sci Transl Med. 2021; 13:eabd7522.
154. Zhao L, Gottesdiener AJ, Parmar M, Li M, Kaminsky SM, Chiuchiolo MJ, Sondhi D, Sullivan PM, Holtzman DM, Crystal RG, Paul SM. Intracerebral adeno-associated virus gene delivery of apolipoprotein E2 markedly reduces brain amyloid pathology in Alzheimer's disease mouse models. Neurobiol Aging. 2016; 44:159-172.
155. Rosenberg JB, Kaplitt MG, De BP, *et al*. AAVrh.10-mediated APOE2 central nervous system gene therapy for APOE4-associated Alzheimer's disease. Hum Gene Ther Clin Dev. 2018; 29:24-47.
156. A 52-Week, Multicenter, Phase 1/2 Open-label Study to Evaluate the Safety of LX1001 in Participants With APOE4 Homozygote Alzheimer's Disease.Alzheimer's Drug Discovery F, Weill Medical College of Cornell U, eds.), 2018; *https://clinicaltrials.gov/study/NCT03634007*
157. Long-Term Follow-Up to Evaluate the Safety of LX1001 in Participants With APOE4 Homozygote Alzheimer's Disease. 2022; *https://clinicaltrials.gov/study/NCT05400330*
158. Li T, Yang Y, Qi H, Cui W, Zhang L, Fu X, He X, Liu M, Li PF, Yu T. CRISPR/Cas9 therapeutics: Progress and prospects. Signal Transduct Target Ther. 2023; 8:36.
159. Blumenfeld J, Yip O, Kim MJ, Huang Y. Cell type-specific roles of APOE4 in Alzheimer disease. Nat Rev Neurosci. 2024; 25:91-110.

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