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# *ApoE4 Influence Alzheimer's Disease Through Various Molecular Mechanisms*

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***Abstract.*** Alzheimer's disease (AD) is a neurodegenarative disease. β-amyloid(Aβ) deposition and abnormal tau phosphorylation are the major features. The ε4 allele of apolipoprotein E(ApoE4) is an important genetic factor in late-onset AD(LOAD). Due to the abnormal salt bridge between Arg112 and Glu255, the structure of ApoE4 is unstable and easy to generate toxic fragments to disrupt various molecular pathways in AD. ApoE4 accelerates the amyloid pathology progression by promoting Aβ aggregation while simultaneously inhibiting Aβ clearance. ApoE4 also induces tau hyperphosphorylation to promote neurofibrillary tangle (NFTs) formation, causes lipid metabolism disorder and microglia prolonged pro-inflammatory activation to exacerbate the neuronal inflammation and neuronal damage. The current research focus is to restore the normal function of ApoE4 by regulating its conformation. Lifestyle changes also have potential for delaying the AD pathological progression. But further investigation of specific mechanisms of ApoE4 is required to develop safe and effective early intervention strategies,providing more theoretical references for the future.

***Keywords:*** Alzheimer's disease, ApoE4, Mechanism.

## 1. Introduction

Alzheimer's disease (AD) is a common neurodegenerative disease which causes dementia in the old. Approximately 60%-80% of dementia cases are AD. Clinically, there are two kinds of AD, the early-onset AD(EOAD) and the late-onset AD(LOAD). EOAD occurs before 65 years old, accounting about 1% of all patients and usually exhibiting a hereditary. LOAD occurs after 65 years-old, accounting over 95%, which is the major focus of AD research [1]. With the increasing of global population age, AD become a great public health challenge and lead to a heavy burden on the socioeconomic.

Extracellular β-amyloid(Aβ) plaque deposition and the hyperphosphorylated tau protein caused intracellular neurofibrillary tangles (NFTs) are two primary pathological features of AD [1]. These abnormal deposits lead to synaptic damage, neuronal dysfunction, and cognitive decline. However, therapeutic efficacy targeting these features has been limited over years, gradually prompt researchers shift their focus toward the pathogenic factors. From genetic perspective, apolipoprotein E(ApoE) gene is considered as one of the most important risk factors for LOAD, which significantly influences many pathogenic pathways of AD [2]. Due to the special structure, ApoE ε4 allele

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(ApoE4) act as an important role in AD's process, which has as the hotspot in current research. However, the relationship between ApoE4 and the major AD pathological features remains lacking sufficient systematic conclusion and analysis. Therefore, this paper aims to explore how ApoE4 influences AD through various mechanisms and review the theoretical reference for AD treatment.

## 2. ApoE4

ApoE is a glycoprotein with 34kDa molecular weight which is composed of 299 amino acids. It primarily synthesized by astrocytes within blood-brain barrier, serves as a lipid transport protein in central nervous system to transport cholesterol and phospholipid. The N-terminal domain of ApoE4 contains a receptor-binding region and the C-terminal domain contains lipid-binding region are separated by a protease-sensitive hinge region [1]. Three subtypes of ApoE are differ by their amino acid substitution, where ApoE4 has special Arg112 and Arg158 [3].

The Arg112 residue in ApoE4 promotes abnormal interactions between the N-terminal Arg61 and C-terminal Glu255 to form a salt bridge. This bridge brings N- and C-terminal domains closer together and exposes the ApoE4 hinge region to proteolytic cleavage, leading the conformation of ApoE4 more unstable and easier cleavage to generate toxic fragments. This feature increases the risk of dementia in ApoE4 carriers [3]. So ApoE4 is the major factor for LOAD.

## 3. Association of ApoE4 with key pathological features of AD

### 3.1. Effects of ApoE4 on Aβ metabolic processes

β- and γ-secretases cleave membrane bounded β-amyloid precursor protein through proteolytic cleavage to generate Aβ, which is a peptide fragment composed of 38 to 43 amino acid residues [4]. ApoE and Aβ deposit in amyloid plaques together, their interaction is considered as the major mechanism that how ApoE influences AD.

ApoE is important in Aβ fibrillation and amyloid deposition. Compared with other subtypes, ApoE4 carriers have earlier, more extensive, and more severe Aβ deposition exhibit in both preclinical and clinical studies. Research on ApoE-mediated Aβ kinetics indicates that ApoE4 could stabilizes cytotoxic soluble Aβ oligomers and accelerates their aggregation into fibrillar structure. During early Aβ plaque development, ApoE4 significantly increases Aβ forming and prolong its half-life to promote the pathological spread. ApoE4 could increase the proportion of Aβ oligomer in the brain and decrease Aβ levels in cerebrospinal fluid and plasma, make more Aβ trapped within brain tissue to form deposits [4,5].

Under normal conditions, ApoE4 clears Aβ via LRP1 receptor-mediated uptake of Aβ/ApoE complexes or proteolytic degradation. However, the abnormal conformation of ApoE4 leads the instability of ApoE4/Aβ complex, which reducing the efficiency of receptor-mediated uptake, inhibiting Aβ clearance by competing for receptor binding sites. The abnormal conformation of ApoE4 also impairs the lipid transport efficiency, preventing the activation of LXR/ABCA1 pathway to promote the activity of Aβ-degrading enzymes. This reduces the clearance capacity of Aβ-degrading enzymes, making more Aβ aggregate into oligomers and plaques [4,5].

ApoE4 act as an important factor in early AD pathological progression through the dual mechanism of promoting Aβ aggregation and hindering Aβ clearance. It accelerates amyloid pathology formation, exacerbates neuronal damage and ultimately leads to more severe dementia symptoms.

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### 3.2. Effects of ApoE4 on tau protein

Abnormal tau protein phosphorylation causes NFTs formation, which is another core pathological feature of AD [6]. As a microtubule-associated protein (MAP), tau protein primarily localized in neuronal cytoplasm and axons, responsible for maintaining the stability of micro-tubule and neuronal structural integrity. Under normal conditions, tau exists in a moderately phosphorylated state, binding to lipid membranes and micro-tubules to support normal neuronal functions or signaling. However, when tau undergoes hyperphosphorylation, the capacity of binding decrease, the stability of cytoskeletal decreased, and the axonal transport impaired. This ultimately results in NFTs formation, then disrupting the neuronal functions and increasing the cognitive impairment [1,6].

Extensive research indicates that ApoE directly influences tau phosphorylation, aggregation, and neurotoxicity. This effect exhibiting marked genotype dependence and ApoE4 is the most relative one [1]. Therefore, ApoE4 is the key genetic factor to promote tau pathology progression and neurodegeneration. Across human studies, animal models and induced pluripotent stem cell models, ApoE4 consistently exhibits features of promoting excessive tau phosphorylation, which accelerating tau aggregation and NFTs formation, exacerbating tau-mediated synaptic loss, neuronal death and neurodegeneration [7].

ApoE4 can activate multiple kinases involved in tau phosphorylation to induce excessive phosphorylation. Simultaneously, ApoE4 also inhibit signaling pathway to indirectly enhance the kinase activity. Excessively phosphorylated tau detaches from microtubules, finally cause the decrease stability of microtubule, damage of axonal transport and the disruption of neuronal structural. ApoE4 exhibits lower affinity for the tau microtubule-binding domain compared to other alleles. It has more phosphorylation sites exposing on tau, so that tau is easier to modify kinase, accelerate the NFTs formation and induce neuronal death. Additionally, ApoE4 enhances glial cell activation and inflammatory cytokine secretion to enlarge the tau-associated neurotoxicity. Studies demonstrate that selectively deleting ApoE4 in astrocytes significantly reduces tau-induced synaptic loss and neurodegeneration, suggesting that ApoE4-driven glial responses serve is the key amplification mechanism for tau pathology.

Tau pathology exhibits prion-like propagation features. ApoE4 disrupts neuronal membrane homeostasis to induce inflammatory and stress responses, thereby promoting the diffusion of pathological tau oligomers between cells. This accelerates the spread and accumulation of tau pathology in brain region [6].

The abnormal of ApoE4-associated tau leads to microtubule disassembly, axonal transport disruption, synaptic loss, neuronal death and sustained amplification of neuroinflammation, ultimately causing cognitive decline and brain region degeneration. In summary, ApoE4 is the key factor of tau pathology. It enlarged tau neurotoxicity through multiple pathways include activating tau phosphorylation signaling, impairing tau binding capacity, intensifying glial inflammatory responses and promoting tau propagation. These mechanisms drive the progression of AD and other tau-related neurodegenerative diseases together.

## 4. Correlation between ApoE4 and other pathological features of AD

### 4.1. ApoE4 and lipid homeostasis

ApoE is the primary lipid and cholesterol transporter in brain, so it is strongly associated with AD risk. Among all subtypes, ApoE4 has the poorest lipid transport capacity. It is inefficient at

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promoting the efflux of cholesterol and phospholipids. These cholesterol and unsaturated fatty acids are accumulated within astrocytes and neurons, which are stored as lipid droplets [8]. Under aging or pathological conditions, similar lipid droplet accumulation occurs in microglia, especially near the areas of Aβ deposits [1].

The abnormal conformation of ApoE4 also reduces receptor binding efficiency, thereby disrupting brain lipid homeostasis. Disrupted lipid metabolism further causes cholesterol accumulation in late endosomal-lysosomal compartments, raises pH levels, impairs endosomal-lysosomal functions, hinders Aβ clearance, and increases the neuronal stress [8,9].

Moreover, ApoE4 disrupts cholesterol and lipid homeostasis in the brain by affecting vascular integrity and microvascular blood flow through its impact on the vascular system. These dysregulated lipid processes not only exacerbate β-amyloid and tau pathology but also provide a critical molecular basis for the AD progression by inducing neuroinflammation, mitochondrial dysfunction, and generating cytotoxic cleaved fragments [1,9].

### 4.2. ApoE4 and neuroinflammation

Many researches indicate that inflammation is also important in neurodegenerative diseases like AD, where ApoE acts as a key regulator in it. ApoE4 promotes continuous pro-inflammatory activation of microglia to cause chronic neuroinflammation [1,8]. This continued inflammation not only inhibits the clearance of abnormal proteins like Aβ and tau, but also aggravates neuronal damage, axonal injury, and synaptic loss through inflammatory mediators secretion, such as tumor necrosis factor-α(TNF-α), interleukin-1β(IL-1β) and interleukin-6 (IL-6) [1,8,10]. Concurrently, ApoE4 reduces the ability of microglia which could trans from M1 to M2 anti-inflammatory and repair phenotype, resulting in an insufficient repair response that further increase the chronic inflammation and neurotoxicity [10].

ApoE4 alters lipid metabolism in microglia, leading to increased lipid accumulation and disrupted cholesterol homeostasis. This induces cellular stress and amplifies pro-inflammatory signaling. ApoE4 also binds weakly to the microglia receptor TREM2, then diminishing its responsiveness to β-amyloid plaques and damaged neurons to trigger abnormal inflammatory signaling pathways. This ApoE4-driven chronic activation of microglia accelerates neuronal death, synaptic loss, and the decline of memory and cognitive function over time [1,8,10].

Remarkably, despite potentially the peripheral serum C-reactive protein level is lower in ApoE4 carriers, the abnormal microglial inflammation within the brain remains a key factor in AD pathogenesis. Both positron emission tomography imaging and cerebrospinal fluid proteomics studies reveal abnormally elevated inflammatory markers in the brains of ApoE4 carriers. This indicates an abnormal immune response to pathological progression [11]. Therefore, restoring M1/M2 balance and neurohomeostasis by targeting the glial inflammatory axis regulated by ApoE4 may represent a critical early intervention strategy for treating AD [8,10].

## 5. Improvement

There are no FDA-approved therapies targeting ApoE for treating AD currently, but the therapeutic strategies target ApoE4 are becoming a new direction for AD intervention. For example, modulating the abnormal conformation of ApoE4 to enhance its function and reduce the pathological promotion effects. Immunotherapy, gene therapy or cell-type-specific modulation strategies can be employed to correct the abnormal of ApoE4 clinically. These strategies aim to “restore or remodel” normal

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ApoE4 function, thereby offering potential benefits in early disease intervention rather than just suppressing Aβ or tau itself.

Lifestyle changes such as physical exercise and dietary interventions may also reduce the pathological progression of AD. Exercise reduces accumulation of Aβ, improving cholesterol levels, alleviating neurological inflammation, and enhancing cognitive function. Meanwhile, physical activity lower the functional connectivity in ApoE4 carriers, maintains normal brain structure and reduces anxiety levels. Although the mechanism remains unclear, it is still an effective strategy to delay the progression of AD symptoms and pathology in ApoE4 carriers. Regarding diet, the ketogenic diet acts as a neural protective agent to decrease AD symptoms by reducing the toxicity of Aβ, neurological inflammation, the reactive oxygen species production, and regulating the mitochondrial homeostasis. Because ApoE is closely linked to glucose and lipid metabolism, the low-carbohydrate and high-fat ketogenic diet can decrease the effects of disordered glucose metabolism in ApoE4 carriers. Providing ketone bodies as an energy source may be helpful for against AD. However, clinical studies generally have small sample sizes, the effects on cognitive improvement are inconsistent and unstable, which is still requiring further exploration.

Additionally, studies confirm that sleep disturbances increase the accumulation of Aβ and tau proteins. ApoE4 carriers may be more likely to develop sleep disturbances or have a higher incidence of such conditions. The presence of the ApoE4 allele can further reduce clearance efficiency. Therefore, clarifying the molecular mechanisms of ApoE4 influence the sleep-wake cycle could also help develop therapeutic strategies to reduce AD-related sleep disturbances [1].

## 6. Challenges and outlook

Although therapeutic strategies targeting ApoE4 have created new avenues for AD treatment, significant challenges remain. ApoE4 participates in multiple pathways such as β-amyloid, tau pathology, lipid metabolism and neuroinflammation. The complexity of these mechanisms and the specificity of associated cell types make single-pathway interventions unlikely to produce lasting effects. Such methods may even pose safety concerns, causing severe side effects. Due to ApoE4's structural instability and easy cleavage, the toxic fragments may accumulate for years before clinical symptoms appear. Therefore, achieving precise intervention in the early or non-symptomatic stages of AD has a major challenge. Furthermore, how to safely regulate the ApoE4 expression or conformation without interfering with normal ApoE transport function is also a priority issue, which needs to be resolved urgently. The lack of sensitive ApoE4-specific biomarkers for real-time disease progression and response monitoring after treatment hindered the development of individualized intervention strategies.

## 7. Conclusion

As the key genetic risk factor for LOAD, ApoE4 speeds up neuronal damage and loss of cognition through various pathways: it influences β-amyloid metabolism, promotes tau protein abnormalities, disrupts lipid homeostasis, drives chronic neuroinflammation. The specific structural of ApoE4 together with its cell-specific functional abnormalities make it involved in nearly every aspect of the core pathology of AD. Although current therapeutic strategies targeting ApoE4 bring hope for early intervention, its complex mechanisms of action still present challenges for safe and effective clinical application.

Future research must study deeper into the functional mechanisms of ApoE4 across different cell types, develop cross-pathway combination therapies and establish clinical biomarkers that reflect

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ApoE4 state in order to promote the clinical applications of ApoE4-targeted treatments.

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