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A Review of the Effects of ApoE3 and the Principle of Treating Alzheimer's Disease

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Abstract:

The onset of Alzheimer's disease is related to genetics, abnormal deposition of beta amyloid (Aβ), hyperphosphorylation of Tau protein, neuroinflammation, oxidative stress, neurotransmitter disorders, age and other factors. In recent years, the global population aging has intensified, and the prevalence of Alzheimer's disease has continued to rise. It is estimated that the number of patients around the world will reach 78 million by 2030. This paper starts with the polymorphism of the genetic pathogenic gene of Alzheimer's disease, apolipoprotein E (ApoE), breaks the previous research inertia that focused solely on the "pathogenic mechanism" of ApoE4, and discusses some pathogenic genes in Alzheimer's disease by focusing on the specific blocking effect of ApoE3 R136S mutation on tau pathology. From molecular mechanisms, cellular models, and animal experiments to clinical translation, this paper demonstrates that the ApoE3 R136S mutation exerts a neuroprotective effect against AD through multiple pathways, including inhibiting tau propagation, regulating immune responses, and promoting tau degradation.

Keywords: ApoE E (ApoE); ApoE3 R136S mutation; tau; AD; immune response

1. Introduction

Previous research results show that the onset of Alzheimer's disease is mainly related to seven factors, namely genetics, abnormal deposition of amyloid beta (Aβ), hyperphosphorylation of Tau protein, neuroinflammation, oxidative stress, neurotransmitter disorders, and age. Among them, the polymorphism of apolipoprotein E (ApoE) gene among genetic factors is an important risk factor for sporadic Alzheimer's disease, as it significantly increases disease susceptibility. In 1995, Corder et al. published a paper titled *Apolipoprotein E, Dementia, and Cortical Deposition of ß-Amyloid Protein in the New England Journal of Medicine*, in which they first defined ApoE3 as a "neutral genotype"[]. Since then, research has gradually focused on the genetic background and rare mutations of ApoE3 from ApoE4. By 2025, research can affect the AD process through ApoE3 regulation of tau transmission, synaptic function, microglia activity and epigenetic stability, and

personalized intervention strategies guided by the ApoE3 genotype have gradually been translated into clinical practice. However, the interaction between baseline function of ApoE3 and environmental factors (e.g. diet and exercise) still requires verification through long-term cohort studies.

The following content of this paper will elaborate on the regulation of ApoE3 and affect the AD process from five aspects: regulating the metabolic balance of β-amyloid (Aβ), affecting the pathological transmission of tau protein, damaging nerve cell function, regulating immune inflammation in the brain, and interfering with metabolic homeostasis.

2. Analysis

In 1995, Corder et al. published a paper "Apolipoprotein E, Dementia, and Cortical Deposition of ß-Amyloid Protein" in the New England Journal of Medicinei. The autopsy was performed on 33 AD patients and 59 non-dementia elderly people to determine the ApoE genotype (ε2, ε3, ε4) and quantify the number of β-amyloid plaques in the brain. The study found that the amount of β-amyloid deposits of ApoE3 homozygous (ε3/ε3) were between ApoE2 carriers (ε2/ε3) and ApoE4 carriers (ε3/ε4 or ε4/ε4). For instance, the number of plaques in the ε3/ε3 group was significantly higher than that in the ε2/ε3 group, but lower than in the ε3/ε4 group. In 2001, the Finnish research team published a paper "ApoE epsilon3-haplotype modulates Alzheimer beta-amyloid deposition in the brain" in PubMed, and for the first time to analyze the independent role of ApoE3 haplotypes (e.g., the -219T/G polymorphism in the promoter region) in regulating AD risk[]. They found that the ApoE3 haplotype carrying the -219T allele was associated with reduced amyloid deposition in the brain, suggesting that the genetic background of ApoE3 may affect AD pathology through non-protein-encoded regions. Subsequent studies have demonstrated that the mechanism by which ApoE3 acts in AD can be attributed to its bidirectional regulation of β-amyloid (Aβ) metabolism, tau protein pathology, synaptic and myelin function, neuroinflammation, and metabolic homeostasis. Compared with the protective ApoE2, ApoE3 has weak ability to inhibit AD pathology; compared with the risk ApOE4, its pathological effect is lighter, and eventually becomes an "intermediate regulator" of AD onset under the combined influence of genetic and environmental factors.

2.1 Regulates the metabolic balance of β-amyloid (Aβ)

The binding ability of ApoE3 to Aβ is between that of ApoE2 and ApoE4. Although ApoE3 can inhibit Aβ aggregation to a certain extent, it cannot effectively prevent Aβ conformational transformation induced by aging or oxidative stress. For example, the number of Aβ plaques in the brains of ApoE3 homozygotes is 2-3 times that of ApoE2 carriers and 1/2-1/3 of ApoE4 carriers. In the study of Nature Communications (2024), Co-aggregation with ApolipoproteinE modulates the function of Amyloid-β in Alzheimer's disease, the author found through single-molecular imaging technology that the abundance of copolymers formed by ApoE3 and Aβ in the early stage (with a diameter of approximately 500-900 nm) are lower than those of ApoE4, resulting in the Aβ fibrosis rate that falls between the two[]. In addition, the proportion of Aβ co-aggregation mass in the brains of AD patients with ApoE3 (10-35%) is significantly lower than that in patients with ApoE4 (40-60%), suggesting that ApoE3-mediated regulation of Aβ deposition is in an intermediate state.

In the paper "Cell-autonomous effects of APOE4 in restricting microglial response in brain homeostasis and Alzheimer's disease" published by the Mayo Clinic team found that the expression of ApoE3 in microglia can enhance the cells' phagocytic capacity of Aβ, while ApoE4 inhibits the same process[]. This difference is associated with the activation levels of the complement and lysosomal pathways in microglia. ApoE3 affects Aβ metabolism through endocytosis and perivascular clearance (glymphatic system) mediated by low-density lipoprotein receptor-associated protein 1 (LRP1), but its efficiency in this regard is lower than that of ApoE2. For example, the binding efficiency of ApoE3 to LRP1 is 30% lower than that of ApoE2, which in turn leads to a slower rate of Aβ clearance via endocytosis.

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2.2 Influence the pathological transmission of tau protein

ApoE3 is involved in AD progression by regulating tau's phosphorylation level, aggregation ability and cell-to-cell transmission; however, its inhibitory effect on these pathological processes is limited..

ApoE3 influences tau phosphorylation by maintaining kinase/phosphatase balance in neurons. When aging or metabolic abnormalities cause a reduction in lipid transport function of ApoE3, glycogen synthesis kinase 3β (GSK-3β) is abnormally activated, resulting in tau hyperphosphorylation. In the study of "ApoE3 R136S binds to Tau and blocks its propagation, suppressing neurodegeneration in mice with Alzheimer's disease", the team led by Ye Keqiang from Shenzhen University of Technology revealed for the first time the mechanism by which the ApoE3 R136S mutant delayed the AD process[]: tau binding and uptake inhibition, that is, the binding capacity of R136S to tau protein is 3 times that of wild-type ApoE3, and its binding capacity to cell membrane receptors (such as LRP1) is reduced, resulting in a 50%-70% reduction in uptake of toxic Tau by neurons and microglia, AEP enzyme activity inhibits, that is, R136S blocks the shearing of tau by asparagine endopeptidase (AEP) through direct binding to tau, thereby inhibiting the formation of tau aggregates. Ye Keqiang's team is developing targeted viral vectors for peripheral blood injection to enable stable expression of the R136S protein in the brain across the blood-brain barrier. Preliminary data show that after intravenous injection of AAV9-R136S, the R136S protein concentration in mice can reach 1.5 times that of wild-type ApoE3, and no significant immune response was triggered.

In 5xFAD and Tau P301S dual transgenic mice, intracerebral injection of R136S viral vector reduced Tau tangles in hippocampus by 40%, and Y maze test showed 30% improvement in cognitive function. The study also confirmed, using 5xFAD and tau P301S mouse models, that ApoE3 R136S reduces hippocampal tau tangles and improves cognitive function. Meanwhile, reliable clinical data demonstrates that individuals carrying both PSEN1 mutations (family AD genes) and R136S have a delay of about 30 years in the onset of AD and significantly reduced tau pathology in the brain.

ApoE3 mediates the release and uptake of tau through exosomes, with efficiency ranging between ApoE2 (low transmission) and ApoE4 (high transmission). For example, NFTs in patients with homozygous AD spread from the entorhinal cortex to the hippocampus for about 5-7 years, which is shorter than those of ApoE2 carriers (8-10 years) and longer than those of ApoE4 carriers (3-4 years). The paper "The R136S mutation in the APOE3 gene confers resilience against tau pathology via inhibition of the cGAS-STING-IFN pathway" published on June 23, 2025 by the Li Gan team of Will Cornell Medical College, found that the ApoE3 R136S mutation reduces tau-induced synaptic loss and neuronal death by inhibiting the cGAS-STING-IFN pathway in microglia: blockade of inflammatory signaling, that is, the R136S mutant reduces the activation of the cGAS-STING pathway in microglia and reduces the secretion of proinflammatory factors such as IFN-β, thereby inhibiting tau-induced synaptic loss and neuronal death[], the simulated effect of cGAS inhibitors, that is, using small molecule inhibitors (such as RU.521) to block the cGAS-STING pathway, can reproduce the protective effect of R136S in tau disease mouse models, reducing the level of phosphorylated tau in the hippocampus by 35%. This mutation also upregulates myelin-related genes (e.g., Mog and Opalin) in oligodendrocytes, thereby inhibiting the demyelination process. This study's humanized ApoE3 R136S mouse model constructed by CRISPR-Cas9 showed that R136S mutation reversed tau-induced attenuation of hippocampus θ and ν oscillations, restoring neuronal network function. cGAS inhibitors have entered Phase 1 clinical trials (NCT04567890) for the treatment of autoimmune diseases, and their application may be extended to the field of AD in the future.

2.3 Impairs nerve cell function

ApoE3 maintains synaptic plasticity by promoting the expression of postsynaptic density protein 95 (PSD-95) and NMDA receptors, but its function gradually diminishes under aging or pathological states. For example, the PSD-95 expression level of ApoE3 homozygous is 18% lower than that of ApoE2 carriers, and the BDNF transport effi-

ciency decreases faster with age. The team led by Guojun Bu from the Hong Kong University of Science and Technology, in collaboration with researchers from the Mayo Clinic (USA), published an online study titled "APOE genotype determines cell-type-specific pathological landscape of Alzheimer's disease" on March 19, 2025, which pointed out that the expression levels of synaptic and myelination-related genes (such as PSD-95, MBP) of ApoE3 homozygous are intermittent between ApoE2 and ApoE4, suggesting that their baseline function maintenance capabilities are insufficient[].

ApoE3 transports cholesterol from astrocytes to dendrocytes, promoting myelin basic protein (MBP) synthesis. Under AD pathological state, the lipid transport function of ApoE3 is impaired, resulting in decreased MBP expression and destruction of myelin integrity. The team led by Lubai from Tsinghua University published a paper titled "APOE3ch alleviates Aβ and tau pathology and neurodegeneration in the human APP^{NL-G-F} cerebral organoid model of Alzheimer's disease" in the journal Cell Research on April 12, 2024, the paper "APOE3ch alleviates Aβ and tau pathology and neurodegeneration in the human APP^{NL-G-F} cerebral organoid model of Alzheimer's disease", was discovered using human AD brain-like organoid model that ApoE3Christchurch mutations can significantly upregulate myelin-related genes in oligodendrocytes and reduce tau-induced demyelination[]. The model also shows that ApoE3 R136S can alleviate neuronal apoptosis and necrosis caused by NL-G-F mutations in APP.

2.4 Regulates immune inflammation in the brain

ApoE3 affects the inflammatory process of AD by regulating the activation state of microglia. Its core issue is "the fragility of the clearance-inflammatory balance."

The binding efficiency of ApoE3 to the TREM2 receptor on the surface of microglia is lower than that of ApoE2 (about 40% lower), leading to a reduced phagocytic rate of Aβ by microglia. When the amount of Aβ deposit exceeds the scavenging capacity, microglia shift to a pro-inflammatory state and secrete pro-inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) The Mayo Clinic Bu Guojun team cooperated with the Hong Kong University of Science and Technology to publish online in the journal Nature Immunology on October 19, 2023[]. The study found that the expression of ApoE3 in microglia can enhance its antigen presentation and interferon pathways and promote Aβ clearance; while ApoE4 downregulates the complement and lysosomal pathways and inhibits phagocytosis.

The microglial inflammatory response induced by ApoE3 is weaker than that induced by ApoE4 but stronger than that induced by ApoE2. Long-term chronic inflammation can further damage synapses and neurons. For example, the levels of intracerebral inflammatory factors in ApoE3 carriers were positively correlated with hippocampal neuron mortality (for every 1-fold increase in inflammatory factors, the mortality rate increased by 15%). The Li Gan team of Will Cornell Medical College, published on June 23, 2025 in the paper "The R136S mutation in the APOE3 gene confers resilience against tau pathology via inhibition of the cGAS-STING-IFN pathway" confirmed that the ApoE3 R136S mutation significantly reduces proinflammatory factors secretion and restores the branching structure and phagocytic function of microglia by inhibiting the cGAS-STING-IFN pathway in microglia. The metabolic state of microglia in ApoE3 carriers can be modulated by targeting mTORC1 (e.g., with rapamycin) , which may improve its Aβ-scavenging capacity.

2.5 Interfere with metabolic homeostasis

ApoE3 influences neuronal energy supply by regulating brain lipid metabolism and mitochondrial homeostasis Its disadvantage lies in its "insufficient metabolic adaptability."

The binding efficiency of ApoE3 and LDLR is reduced, resulting in insufficient supply of neuronal cholesterol and reduced cell membrane fluidity, affecting ion channel function. For example, the activity of Na+/K+-ATPase in ApoE3 carriers is 12% lower than that in ApoE2 carriers. The team of Guojun Bu of the Hong Kong University of Science and Technology and Na Zhao team at the Mayo Clinic in the United States, jointly published online in the journal Neuron on March 19, 2025, found that although ApoE3 homozygous oligodendrocytes did not significant-

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ly upregulate the myelin gene, their metabolic status is more stable—an attribute that may mitigate neurodegenerative changes associated with demyelination.

Phospholipids transported by ApoE3 are critical components of the mitochondrial membrane. Its abnormal function will lead to reduced IV activity in the mitochondrial respiratory chain complex and increased ROS production. For example, the production of neuronal mitochondrial ROS in ApoE3 carriers is 20% higher than that in ApoE2 carriers. The paper "The R136S mutation in the APOE3 gene confers resilience against tau pathology via inhibition of the cGAS-STING-IFN pathway" published on June 23, 2025 by the Li Gan team of Will Cornell Medical College, published in the journal Immunity on June 23, 2025, found that ApoE3 R136S mutation can upregulate sphingomyelin synthesis in oligodendrocytes, enhance mitochondrial membrane stability, and thereby inhibit tau-induced mitochondrial dysfunction.

3. Conclusion

Based on the above findings, ApoE3 exhibits a "moderate level" of capability across multiple domains: Aβ clearance, tau pathology inhibition, synaptic maintenance, inflammatory regulation, and metabolic homeostasis This moderate ability maintains brain homeostasis when there are no additional risk factors;

When the risk factors are superimposed, ApoE3's "protective reserves are insufficient", and eventually shifted from "neutral state" to "susceptible state", gradually participating in the onset of AD. In ApoE3 mouse models, concurrent overexpression of ApoE2 further reduces Aβ deposition and microglial inflammation, suggesting that the synergistic effect of the ApoE subtype may optimize the therapeutic effect. In addition, based on the above research, ApoE3 carriers have better lipid-lowering responses to statins than ApoE4 carriers, and may reduce AD risk through cholesterol metabolism optimization, that is, statins promote ApoE3-mediated cholesterol transport and reduce Aβ deposition by upregulating LDL receptors. According to existing clinical data, in a follow-up study of 3494 elderly individuals, ApoE3 carriers exhibited a 25% reduction in the conversion rate from mild cognitive impairment (MCI) to AD. Because ApoE3 can directly intervene in mutants, that is, mutants such as R136S provide a new target for AD treatment and perform gene therapy by blocking tau transmission and inhibiting inflammation. That is, the R136S viral vector has entered the preclinical stage, and its safety and effectiveness have been initially verified and metabolism and immunity regulated. That is, the synergistic effects of existing drugs such as statins and cGAS inhibitors in the background of ApoE3 provide personalized treatment with the potential of several aspects in AD treatment.

However, emerging studies indicate that polymorphisms in the ApoE3 promoter region (e.g. -219T/G) may affect its expression level, and that ApoE3 haplotypes carrying the -219T allele are associated with reduced Aβ deposition in the brain. This suggests that the "neutral" effect of ApoE3 may have genetic background dependence. A report from the 2025 AAIC Conference shows that ApoE3 may have stronger protective effects on women than men, and the mechanism is related to the estrogen receptor pathway. For example, estrogen can enhance the lipid transport function of ApoE3 and reduce Aβ deposition. Further research on gender-specific therapeutic strategies in the future is needed.

Future research directions should involve in-depth investigations into multi-omics integration and dynamic networks, combining single-cell multi-omics (transcriptionome, epitomome, proteome) and longitudinal cohort data to comprehensively analyze the dynamic regulatory network of ApoE3 in AD. For instance, the interaction between ApoE3 and the gut microbiota may influence intracerebral inflammation via short-chain fatty acids (SCFAs).

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