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The Inner Link between Apolipoprotein E and the risk of Alzheimer's disease

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Abstract:

Alzheimer's disease (AD) is a common neurodegenerative disorder that severely affects the quality of life of the elderly. The APOE gene and its encoded apolipoprotein E (ApoE) play a significant role in the pathogenesis of AD, particularly the APOEε4 allele, which is significantly associated with an increased risk of AD. Current research indicates that different alleles of the APOE gene affect brain development, lipid metabolism, and synaptic function, with ApoE4 being associated with cognitive decline and an increased risk of AD. Moreover, therapeutic strategies targeting the APOE gene, such as gene editing techniques and the development of small molecule drugs, are actively being researched to provide new possibilities for the treatment of AD. Nevertheless, many unknowns remain regarding the specific mechanisms of action of the APOE gene in AD and how to effectively utilize this knowledge to develop treatment methods. This article analyzes the structure and function of the APOE gene and its role in AD, discusses the main drugs and strategies currently used in AD treatment, and proposes the potential for future treatments based on the APOE gene. However, further research and exploration are needed to understand the complex relationship between the APOE gene and AD, as well as the long-term effects and safety of treatment methods. With the advancement of technology, there is hope for the development of more effective and safer AD treatment plans in the future, to improve the quality of life of patients and reduce the societal burden.

Keywords: ApoE; Alzheimer's disease; risk of disease.

1. Introduction

Alzheimer's disease (AD), also known as senile dementia, is a common neurodegenerative disease in the elderly, characterized by slow onset and gradual deterioration of the condition. This disease mainly affects the elderly and has a serious impact on their quality of life. AD has a huge impact on society. Presently, an approximate count of 6.5 million Americans aged 65 and above are afflicted with AD. The prevalence of AD in the United States will rise annually due to the ongoing growth of the population aged over 65 years [1].

In previous studies, there is no particularly clear pathogenesis for AD. However, previous studies have shown that AD is related to various factors such as abnormal deposition of amyloid β-protein (Aβ), excessive phosphorylation of tau protein, destruction of synaptic plasticity, oxidative stress, abnormal metabolism of lipids and glucose, mitochondrial dysfunction, inflammatory response, destruction of vascular integrity, and impaired insulin signaling pathway [2]. The APOE gene, also known as ApoE gene located on autosomes, consists of three main alleles, namely ε2, ε3, and ε4, and ε3/ε3 is the most common genotype associated with the average risk of AD and cardiovascular disease. Previous studies have revealed that the frequency of APOEε4 alleles in AD patients is significantly higher than that in the normal population [3]. ApoE is coded from the APOE gene. ApoE is a significant lipid transporter that controls several crucial signaling pathways and is essential for the growth, upkeep, and repair of the central nervous system [3]. Therefore, The APOE gene and its encoded proteins play a crucial role in brain development and AD. By manipulating the APOE gene and ApoE, targeted therapy for AD has become possible. In addition, recent studies have shown that immunotherapy using APOE genes may have the potential to be widely applied in the pharmaceutical field. By utilizing an anti-APOE antibody to target APOE, amyloid pathology is lessened while maintaining the integrity and function of the cerebrovascular system [4].

This article aims to summarize the research progress on the relationship between APOE genes and the pathogenesis of AD, as well as the treatment plans related to AD, and propose new possible treatment plans for the future.

This will contribute to the future treatment of AD, aid Alzheimer's patients in managing discomfort.

2. The Role of APOE Gene in AD

2.1 The Relationship between APOE Gene and Brain Development

2.1.1 The structure, expression, and regulation of APOE genes

The APOE gene is a gene encoding ApoE, which plays a crucial role in lipid metabolism. The APOE gene is located on human chromosome 19 and contains four exons and three introns. There are three main APOE genotypes in humans, namely APOEε2, APOEε3, and APOEε4. These genotypes are defined by differences in individual amino acids: APOEε2 (Cys112, Cys158) contains cysteine at sites 112 and 158; APOEε3 (Cys112, Arg158) contains cysteine at site 112 and arginine at site 158; APOEε4 (Arg112, Arg158) contains arginine at both positions 112 and 158 (Figure 1).

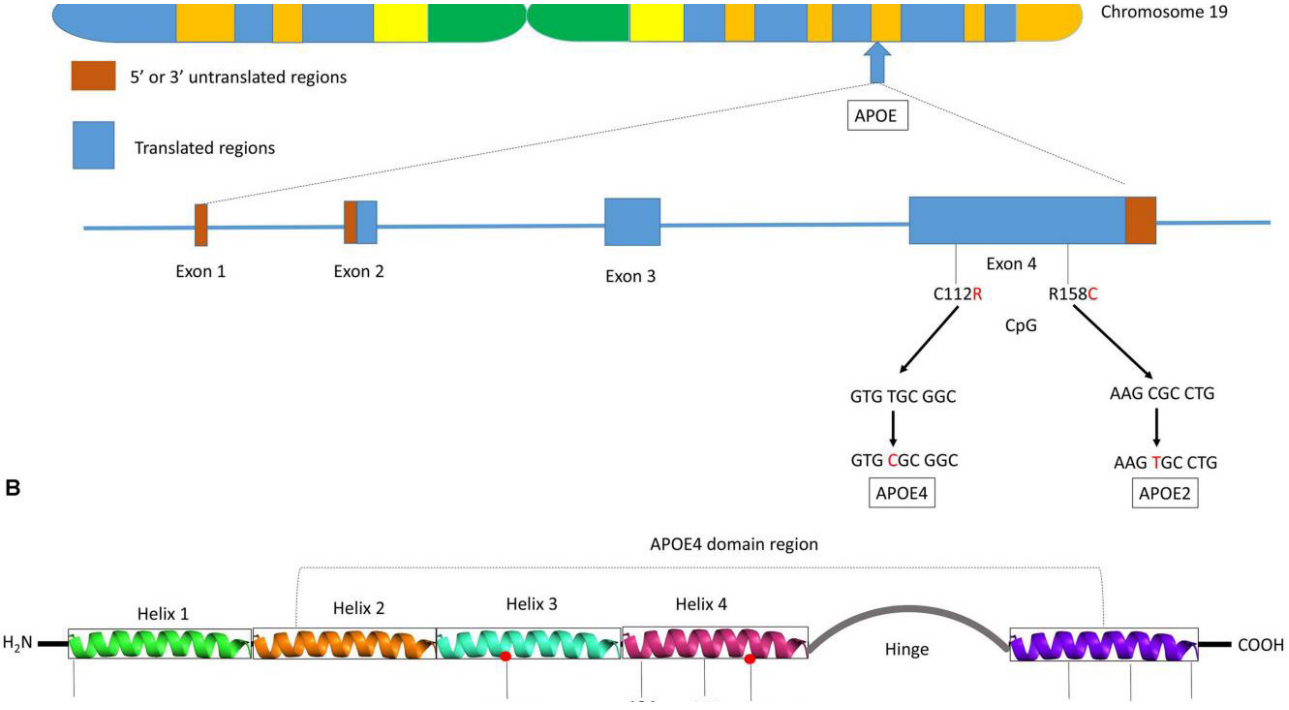

Fig. 1 Location and structure of APOE gene at q13.32 on chromosome 19 [3].

The differences in APOE genotypes not only affect the binding of LDLR, but also affect the interaction between ApoE and lipids. For example, ApoE4 has a stronger binding ability to lipids than ApoE3, which may affect its metabolism and function in the body. The amino acid differences between ApoE2 and ApoE4 lead to differences in their processing and metabolism in vivo, and ApoE4 is associated with higher cardiovascular disease risk and AD risk.

In the nucleus, the APOE gene is transcribed into precursor mRNA by RNA polymerase II, which is then spliced. The splicing of APOE genes usually does not involve variable splicing, so mature mRNA encodes a single ApoE protein. Through ribosomal translation, the primary translation product of ApoE protein is formed. ApoE protein undergoes folding and post-translational modifications in ER, including glycosylation and disulfide bond formation [5]. Glycosylation mainly occurs at the Thr194 site of the C-terminal domain of ApoE, but it may also involve other sites [6]. The modified ApoE protein is packaged into lipoprotein particles and secreted into the extracellular space, forming HDL like lipoprotein particles. In the central nervous system (CNS), astrocytes are the main production and secretion cells of ApoE.

The expression of APOE gene is regulated by various transcription factors, including members of the Hepatonuclear Factor (HNF) family, CCAAT/Enhancer Binding Protein (C/EBP), and Liver X Receptor (LXR). In addition, nutritional and environmental factors: dietary components such as fatty acids and cholesterol, as well as environmental factors such as oxidative stress, can also affect the expression of APOE genes. For example, a high-fat diet can upregulate the expression of APOE, while antioxidants can reduce APOE expression, which may be related to their impact on cholesterol metabolism.

2.1.2 The role of APOE in the normal brain

ApoE is the most abundant apolipoprotein in the brain,

mainly secreted by astrocytes and involved in the transportation and metabolism of cholesterol and other lipids [6]. ApoE participates in clearing cholesterol in the cell membrane by binding to HDL like particles, maintaining the fluidity and function of the cell membrane. In addition, ApoE plays a crucial role in the response after nerve injury, supporting nerve repair by promoting the release of nerve growth factors and axon growth. During development, ApoE supports neuronal survival and synaptic formation, which is crucial for neural development. ApoE affects synaptic plasticity, especially in the hippocampus, which is crucial for learning and memory processes [7]. Different subtypes of ApoE (ApoE2, ApoE3, ApoE4) may affect cognitive function through different mechanisms, among which ApoE4 is associated with the risk of cognitive decline [8]. The APOE genotype also affects individual behavioral performance, including spatial learning ability, memory, and executive function [9]. APOEε4 carriers may exhibit poorer performance in specific cognitive tasks, while APOEε2 carriers may exhibit better cognitive function. The structural differences of ApoE proteins, especially the amino acid differences between ApoE4, ApoE3, and ApoE2, affect their binding and function with lipids. The structural variation of ApoE also affects its interaction with receptors, thereby affecting lipid transport and cellular signaling.

In summary, the APOE gene plays multiple roles in brain health and diseases, and its research provides new avenues for understanding and treating neurodegenerative diseases, cardiovascular diseases, and more. The in-depth understanding of APOE gene will help to develop new treatments, thus improving the quality of life and reducing the incidence rate of related diseases.

2.2 The Influence of APOE Gene Phenotype and Apoe Structure on AD

2.2.1 The association between APOE phenotype and AD incidence

The APOEε4 allele is considered one of the most important genetic risk factors for Alzheimer‘s disease. The frequency of the APOEε4 allele is higher in AD patients than in healthy controls, indicating that individuals carrying the APOEε4 allele are more likely to develop Alzheimer‘s disease. There is a significant association between the APOEε4 allele and the risk of Alzheimer‘s disease. The dose-response of APOEε4 increases the risk of individuals carrying one APOEε4 allele by approximately three times, while the risk of individuals carrying two APOEε4 alleles increases by approximately 12 times [10].

2.2.2 The association between ApoE Structure and AD pathogenesis

The structure and function of ApoE are crucial for its association with the pathogenesis of AD. The single amino acid differences between ApoE isomers result in significant structural and functional differences, which in turn affect their binding to lipids, receptor interactions, and pathological proteins such as Aβ. The combination ultimately influenced the development and progress of AD. ApoE is bound to lipids in its physiological state in the body, and its lipid state is crucial for its function. Lipified ApoE may play different roles in AD pathology, such as by interacting with Aβ Competitive receptor binding sites to influence Aβ Clear[11]. Research has shown that ApoE isomers affect Aβ. The pathology of ApoE4 leads to the most Aβ Pathologically, ApoE2 causes the least, while ApoE3 falls between the two. The ApoE molecule is composed of multiple structural domains, including the N-terminal domain, hinge region, and C-terminal domain. These domains are involved in the binding of ApoE to lipids, receptor recognition, and interaction with pathological proteins such as Aβ Plays a crucial role in the interaction between. For example, the N-terminal domain of ApoE is responsible for binding to LDLR, while the C-terminal domain binds to lipids.

2.3 The Association of APOE Gene in the Pathogenesis of AD

2.3.1 Molecular level: APOE gene and Aβ protein and Tau protein

Amyloid proteins are a group of proteins that can deposit in tissues of the body under certain pathological conditions. These protein deposits have certain common characteristics, such as their folding forms are usually complex and intricate β- Folding sheet structure, which is stable and not easily broken down by human enzymes. ApoE has been found to be a core component of amyloid plaques in the brain and blood vessels, similar to Aβ. The combination may have promoted Aβ The formation of plaques. APOEε4 carriers have a higher plaque load and density compared to non carriers. APOEε4 can also promote Aβ. The generation and aggregation of. Research has shown that APOEε4 is associated with Aβ. The tighter combination may lead to A β Reduced clearance of AD increases the risk of AD [11]. In addition, the specific domain of ApoE may directly affect its relationship with Aβ. The interaction between A and B affects Aβ The aggregation and formation of plaques.

Tau is a microtubule associated protein primarily present in the axons of neurons. Its main function is to stabilize microtubule structure and help maintain cell morphology and function. The phosphorylation and dephosphorylation of Tau protein are dynamically balanced in healthy organ-

isms. However, if a specific cause causes an abnormality that results in a higher rate of Tau protein phosphorylation than dephosphorylation, the body will produce more Tau protein and eventually develop the disease. In neurodegenerative diseases such as AD, Tau protein undergoes abnormal phosphorylation, leading to its loss of function. This abnormally phosphorylated Tau protein will detach from microtubules and form abnormal aggregates. The abnormal aggregates of Tau protein can spread in the brain, from one neuron to another, which may be related to the progressive neurodegenerative changes in AD [12].

2.3.2 Cellular level: APOE gene and cellular autophagy and synaptic function

APOEε4 may lead to impaired autophagy and mitochondrial function, which may be due to its influence on intracellular cholesterol metabolism, which may lead to a decrease in autophagy flux and subsequently affect the cell‘s ability to clear pathological protein aggregates [13]. APOEε4 may interfere with the autophagy pathway, leading to reduced clearance of pathological proteins and promoting the pathological process of AD. APOEε4 related autophagy disorders may lead to Aβ Accumulation, because autophagy is the clearance of Aβ One way. In addition, APOEε4 may also affect genes related to autophagy, such as TFEB (transcription factor EB) and mTOR (mammalian rapamycin target protein), which are key factors regulating autophagy [14].

APOEε4 is associated with extensive gene expression changes in all types of cells in the human brain, significantly altering signaling pathways related to cholesterol homeostasis and transport. APOEε4 alters cholesterol homeostasis and localization in oligodendrocytes, leading to abnormal cholesterol deposition, which is associated with endoplasmic reticulum stress and reduced myelin formation. This has an impact on synaptic function, thereby inducing AD [15].

2.3.3 Brain level: The impact of APOE gene on basic brain function

The association mechanism between APOEε4 and impaired blood-brain barrier function includes: damage to endothelial cell function, structural changes in the basement membrane, damage to smooth muscle cells and pericytes, enhanced inflammatory response, abnormal clearance of solutes in the blood, and other factors that ultimately lead to impaired blood-brain barrier function. Meanwhile, neurodegenerative diseases caused by APOE can have a negative impact on the cognitive function of the frontal lobe and other advanced brain functions.

2.3.4 ApoE cascade hypothesis

The ApoE cascade hypothesis suggests that different alleles of ApoE (especially ApoE4, a known major genetic risk factor for AD) affect a series of cellular functions and metabolic processes through their unique biochemical and biophysical properties, ultimately leading to the occurrence and development of AD and other neurodegenerative diseases. In the biochemical stage, the biochemical characteristics of ApoE, such as structure, lipidation, protein level, receptor binding, and oligomerization, play a crucial role. These characteristics of ApoE may be influenced by factors such as APOE genotype, rare variations, and epigenetics. At the cellular stage, differences in biochemical characteristics can spread to functional effects on intracellular homeostasis, including cellular stress, endoplasmic reticulum lysosomal transport, and lipid metabolism. These cellular effects may be cellular autonomously (in cells that express abundant ApoE, such as astrocytes and reactive microglia in the brain, as well as peripheral liver cells and macrophages) or noncellular autonomously (such as through ApoE receptors bound to neurons that themselves express very little ApoE). In the phenotypic stage, cellular effects further propagate, leading to a systemic phenotype that is characterized by neuroinflammation, vascular dysfunction, neuropathology, synaptic loss, and neurodegeneration, resulting in age-related cognitive decline and pathological conditions such as AD.

It is not difficult to see that the genotype of APOE has a significant impact on AD and has a certain correlation. Nowadays, for the treatment of AD, more emphasis is placed on the protein level, with a focus on targeted therapy. With the development of molecular biology, the manipulation and editing of APOE genes is expected to become a new therapeutic approach for AD. Of course, in addition to technological development, the manipulation of individual genes and genotypes may raise ethical issues that need to be discussed.

3. The Role of APOE Gene and ApoE in the Treatment of AD

3.1 AD Monoclonal Antibody Therapy

3.1.1 Modern monoclonal antibody drugs mainly used for the treatment of AD

The main monoclonal antibodies used in modern treatment of AD include Aducanumab, Solanezumab, Bapineuzumab, and Crenezumab. Aducanumab is a humanized monoclonal antibody designed to interact with various forms of Aβ Protein binding. Solanezumab is a type of dissolved Aβ Monoclonal antibodies against aggregates. Bapineuzumab is a type of targeting Aβ Monoclonal antibody against peptide N-terminal. Crenezumab is a type of β Monoclonal antibodies against aggregates. These drugs

are usually administered intravenously and can interact with A in the brain β Sediments bind and promote their clearance through the action of the immune system.

3.1.2 The mechanism, function, and efficacy of monoclonal antibody drugs for treating AD

Aducanumab combines Aβ, Including fibrous and dissolved aggregates, promoting phagocytosis of microglia, thereby reducing A in the brain β Sedimentation. Aducanumab has been shown in some clinical trials to reduce amyloid plaques in the brain, but it is also associated with ARIA (amyloid related imaging abnormalities), which may lead to brain edema and microbleeds [16].

Solanezumab combines dissolved Aβ Aggregation, reducing the accumulation of these aggregates in the brain, thereby slowing down the progression of the disease. Solanezumab has shown limited impact on cognitive function in some clinical trials, but the incidence of ARIA is relatively low [17].

Bapineuzumab combines Aβ the N-terminal prevents it from aggregating into toxic fibrous structures, thereby reducing the formation of amyloid plaques. Bapineuzumab has shown some effectiveness in reducing amyloid plaques in clinical trials, but its improvement in cognitive function is not significant [18].

Crenezumab combines Aβ Gather together to promote its clearance and reduce the formation of amyloid plaques in the brain. Crenezumab has shown some effectiveness in reducing amyloid plaques in clinical trials, but the improvement in cognitive function is not significant [19].

3.2 Small Molecule Drugs for AD Treatment

3.2.1 BACE inhibitor

β- Secretory enzyme (BACE) inhibitors include but are not limited to Verubecestat (MK-893), Azeliragon (TTP488), etc. These drugs reduce amyloidosis by inhibiting the activity of BACE enzyme β. The generation of BACE generates Aβ the key enzyme of peptides, whose inhibition can slow down A β. The accumulation of amyloid and the formation of amyloid plaques. In clinical trials, BACE inhibitors have shown potential to slow cognitive decline and reduce amyloid plaques in the brain, but further research is needed to confirm their safety and efficacy.

3.2.2 γ- Secretory enzyme regulators

γ- Secretory enzyme regulators include but are not limited to Semacastatat (LY450139) and Elenbecestatat (JNJ-40417737). These drugs regulate γ- The activity of secretase affects Aβ The generation and cutting process of. γ-Secretase generates Aβ the key enzyme in the last step of can reduce harmful A by regulating its activity β. The generation of 42. Although some γ- Secretase modulators have been shown to reduce A in early studies β. Their clinical development is challenged due to safety concerns, despite their potential [20].

3.2.3 Chelating agents

Metal ion chelating agents, such as Piracetam and Cladribine, reduce the impact of metal ions on A by chelating metal ions β. The promoting effect of aggregation and oxidative stress. Metal ions such as copper and zinc can catalyze Aβ. The aggregation and oxidation of lead to neurotoxicity. These drugs have shown some neuroprotective effects in clinical trials, but more research is needed to determine their long-term effects in AD treatment.

3.2.4 Antiinflammatory drug

Antiinflammatory drug molecules such as nonsteroidal anti-inflammatory drugs (NSAIDs) reduce neuroinflammation associated with Alzheimer‘s disease by inhibiting inflammatory pathways. Inflammation plays a crucial role in the pathological process of Alzheimer‘s disease, and anti-inflammatory drugs can reduce the production and release of inflammatory mediators. Although some studies have shown that NSAIDs may help slow down the progression of AD, long-term use may be associated with side effects in the gastrointestinal and other systems.

3.3 APOE Gene Research and Potential for Future Treatments

The treatment strategies for APOEε4 are actively being studied, and there are many potential directions at present. For example, the application of APOE gene editing technology, the development of small molecule drugs, and personalized healthcare

With the development of gene editing technology, such as CRISPR-Cas9, there may be a possibility in the future to directly reduce the risk of AD by modifying the APOE gene. By precisely altering the coding sequence of the APOEε4 allele, it may also be possible to reduce or eliminate its contribution to AD risk.

The development of small molecule drugs aims to directly affect the function of ApoE through oral administration. For example, some drugs may slow down the progression of AD by enhancing the protective function of ApoE3 or inhibiting the harmful effects of ApoE4. These drugs may alter the interaction between ApoE and lipids or regulate their function in Aβ Play a role in metabolism.

For personalized issues, in the future, doctors may provide customized prevention and treatment plans for patients based on individual APOE genotypes. For example, for APOEε4 carriers, earlier screening and more proactive intervention measures may be needed, while for APOEε2 carriers, different strategies may be adopted.

4. Conclusion

This article first summarizes the structure and function of the APOE gene, as well as its role in healthy individuals. Secondly, a summary of previous research and results on the impact between APOE and AD. Finally, the modern treatment ideas and plans for AD were summarized, as well as the potential for future treatment of AD. This article provides a relatively comprehensive overview of the relationship between APOE genes and AD, and proposes the potential for future treatments, which will be beneficial for inspiring treatment ideas, medical development, and social progress. Future research can refer to the summary of previous studies in this article and conduct in-depth research on more detailed directions. Of course, this article did not summarize some rare cases in AD, and did not introduce some mechanisms such as cellular pathways. Finally, the diversification and maturation of AD treatment plans is of great significance to society, as it not only provides hope for patients with Alzheimer‘s disease and their families and friends to be cured, but also promotes research and development in other medical fields and neurodegenerative diseases. I hope that with the development of technology, the cost of treating AD will decrease, and it can benefit more and more people.

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