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ApoE Proteins and the Pathogenesis of Alzheimer‘s Disease and Its Early Diagnosis Progress

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Abstract:

With the quick pace of the society, changing of the majority part of the population age distribution, and the aggravation of the population aging results in the gradual growth of Alzheimer disease (AD) patients' percentage. Nowadays, researchers are still not totally clear about the etiology and pathogenesis of AD; nonetheless, two hypotheses have emerged: AB amyloid protein and ApoE4 apolipoprotein hypothesis. This paper aims to go through the introduction of ApoE4, then elaborate on the pathogenic mechanism of the ApoE4 hypothesis in AD disease, and finally analyze the new detection method of AD disease. Last but not least, determining whether people suffer from AD and the degree of AD disease through whether tau181 site phosphorylation. This paper provides minimal help for researchers to conduct deeper detection and research in the future. In the future, studying the exact pathogenesis of AD, more perfect AD detection protocols, and ways to treat different levels of AD will still be some of the main challenges that researchers will face when conducting more in-depth research in the field of AD.

Keywords: ApoE; Alzheimer's Disease; early diagnosis.

1. Introduction

With the quick enhancement of human mass health consciousness, Alzheimer‘s Disease (AD) has aggrandized its prevalence during people‘s communication. AD, the most commonly degenerative brain disorder in the world caused by environmental factors or inheritance, results in cerebral atrophy, dysfunction of neurons, and also cell apoptosis. This disease was detected to be extracellular plaques formed by aggregation of amyloid beta protein and intracytoplasmic neurofibrillary tangles (NFTs) caused by hyperphosphorylation of tau protein impede synaptic transmission, activate inflammatory responses, and disrupt neuronal metabolism of amyloid plaques. Blocking synaptic transmission, activating inflammatory responses, disrupting neuronal metabolism, blockage of ion channels, disturbance of calcium homeostasis, mitochondrial oxidative stress, impaired energy metabolism, abnormal glucose regulation, altered synaptic function, and causing cell apoptosis are the results of accumulation of the Aβ amyloid protein [1]. The second hypothesis about AD is related to the ApoE apolipoprotein. Apolipoprotein E can be classified into several types, and the ε4 allele of Apolipoprotein E (ApoE4 for short) was thought to be the culprit leading to the AD. It is a polymorphic protein detected on chromosome 19 that binds to triglycerides in the human body, forming lipoproteins, which are mainly detected in the brain and liver [2]. It is also the genetic risk factor for late-onset AD cases, with homozygous APOE4 carriers being approximately 15 times more likely to develop the disease [3].

Playing an integral role in AD disease and associated with multiple substances, cells' complexion and the limitation of current technology bring about no specific drug targeting medicine made by any company yet. A great deal of countries are confronted with the obstacles posed by the aging population, as well as the rapid progress of our society, including a significant number of Alzheimer‘s disease patients. Hence, A major hurdle remains in understanding how AD works and how it interacts with other substances in different brain regions. It is worth it for experts to do further research. Understanding this allele plays a crucial role in the pathogenesis and pathology of AD because up to 25% of people carry APOE4 in their genes. Although the exact reason why the epsilon 4 allele increases the risk of developing AD is not clear, the process caused by APOE suggests potential therapeutic directions for researchers. This passage explores how ApoE4 affects AD disease and gives some advice for future exploration and experiments.

2. The Intrinsic Connection between APOE4 and AD Pathology

ApoE4, as described above, has a high probability of causing AD. To understand its pathogenesis, researchers must first understand this type of apolipoprotein. Apo is the protein part of plasma lipoprotein, mainly containing A, B, C, D, and E, these five varieties. Moreover, as shown in figure1, the density of Apo E contained in the human body‘s blood vessels is positively correlated with triglyceride content; it is also closely related to lipoprotein metabolism.

ApoE is composed of three kinds of isoforms, E2, E3, and E4, resulting in six phenotypes expressed in the human body. ApoE2 protein is commonly considered the protective gene released in the gene sequence. In other words, people who get ApoE2 in their chromatin may have a relatively lower percentage of AD disease; nevertheless, people who contained ApoE4 allele expressed in their chromatin became the higher risk group for AD disease. Although how ApoE4 became the etiological factor causing AD has still not been excavation and identified yet, some scientists have set the research orientation for the relationship between ApoE and amyloid-beta peptide accumulation and debriding. Strittmatter and his group found that ApoE and AD are closely related, and the report was published in 1993 [4].

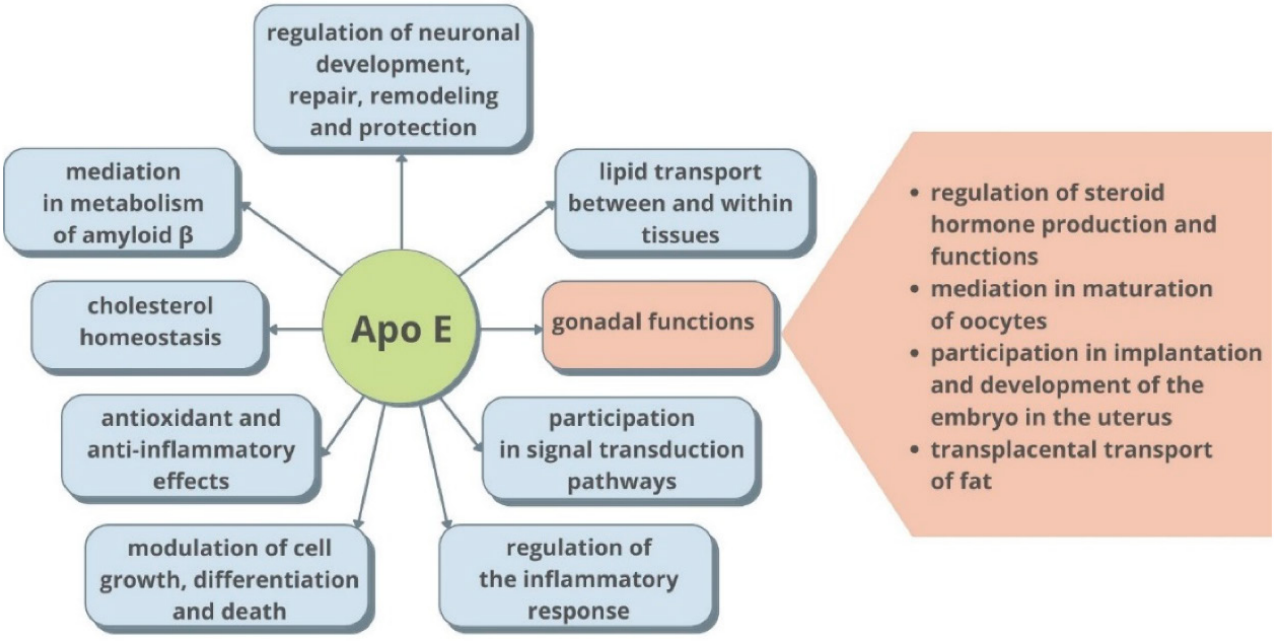

Fig. 1 Biological functions of ApoE proteins [4].

3. The Influence of APOE4 on Lipid Metabolism in Astrocytes

APOE4 serves as an assistant for the management of cholesterol and other lipid types in human blood vessels, so studying how ApoE4 affects lipid metabolism in brain cells plays an essential role in promoting further research in the field of AD. Dr. HuiCai Li and Dr. Susan Lindquist, an MIT doctor, have conducted in-depth research in this field. Furthermore, they published their research output in the periodical Science Translational Medicine in 2021. The researchers used ApoE3 and ApoE4 collected from human body cells, crisper the gene inside these cells, which reform them into astrocytes, a kind of star-shaped cells that produce the most APOE in the brain, as the experimental object. Next, the researchers combined lipidomics with unbiased genome-wide screens in yeast with functional and genetic characterization to demonstrate that human APOE4 induced altered lipid homeostasis. This change resulted in astrocytes, which contained APOE4, changed the way lipids were handled. ApoE4-astrocyte accumulated a large amount of triglyceride droplets of fat, which contained far more unsaturated fatty acid chain levels than normal fat should contain.

The fat accumulated in ApoE4 astrocytes also results in a larger proportion compared to ApoE3 astrocytes. When astrocyte-coaxed ApoE4 cells entered microglia, another crucial cell in people‘s brains, disruptions in lipid metabolism emerged. Moreover, the research team aimed to detect whether yeast cells nourishing the human version of APOE4 would demonstrate an assimilate disruption in lipid metabolism. The results revealed that yeast cells accumulate just like ApoE4cell in the human body. Research-

ers can successfully conclude that boosting phospholipids, which appear inside the cell membrane, may partially revert the precipitation of lipids [5]. According to the results shown by the above research, APOE4 plays an essential role in the pathogenesis of AD by regulating the metabolic capacity of human microglia and the accumulation of triglyceride lipid droplets through APOE4-astrocytes. However, its role in partially alleviating lipid precipitation by increasing phospholipids needs experts to do more further exploration. Therefore, APOE4 has value for further study as a potential target in the treatment of AD.

4. Early Diagnosis and Prevention of AD

According to the current incomplete statistics data, the number of people suffering from AD is extremely high around the world, with more than 50 million patients; thus, providing efficient biomarker and detection means with high efficiency and easy popularization is really a curative event. For technology and finance, CSF and PET examinations can detect the pathology causing AD, which is the Aβpathology and tau pathology [6]. Unfortunately, CSF and PET tests are not well known to most citizens and patients; therefore, these two methods are relatively difficult to widely accept by the public and used in the detection of AD disease in themselves or their relatives. After reaching this conclusion, researchers have devoted themselves to researching new types of AD detection with greater convenience and affection for people since then.

Professor Kaj Blennow‘s research group at Sahlgrenska Academy, Gothenburg University, Sweden, focused on studying and analyzing protein changes associated with pathophysiology, also known as biochemical markers. Scientists in the team studied our results: Phosphorylation of tau in cerebrospinal fluid at threonine 181 (p-tau181), a highly specific pathological marker in AD disease, can not only predict tau and the Aβ pathology mentioned before but also effectively evaluate the development of AD disease in patients in different situation. Phosphorylation of tau181 occurs only in patients with AD disease but not in other types of demented disease [7]. A paper titled Blood phosphorylated tau 181 as a biomarker for Alzheimer‘s disease: a diagnostic performance and predictive modeling study using data from four prospective cohorts was published in The Lancet Neurology, clearly showing that Kaj Blennow ,s research group developed a method for examining AD blood p-tau181 in the research article [7].

With the increasing severity of the disease, the concentration of p-tau181 in the plasma of patients showed an increasing trend:p-tau181’s concentrations varied with three groups of subjects, that is, in young Aβ-negative and cognitively normal older individuals, in Aβ-positive but cognitively normal older individuals & in individuals with mild cognitive impairment (MCI), and in Aβ-positive MCI and AD individuals, there is A gradual and substantial increase was displayed in this article. In addition, it should be emphasized here that the third group of subjects mentioned above had statistically significant differences in P-tau181 concentrations (i.e., $p<0.001$). All blood p-tau181 concentrations were strongly correlated with AD progression. The concentration of p-tau181 in the blood increases as the disease progresses. Second, the p-tau181 blood marker is good for distinguishing neurodegenerative diseases (such as dementia) and AD. Thirdly, the blood p-tau181 marker is greatly related to Aβ pathology (AUC: 76,14-88,09%) and tau pathology (AUC: 83.08-93.11%) detected by PET. In addition, p-tau181 was also highly correlated with cognitive decline ($p=0.0015$) and hippocampal shrinkage ($p=0.015$) in one year. However, the blood p-tau181 marker AD could not be distinguished from MCI (AUC: 55.00%) [8].

To sum up, the blood p-tau181 test method proposed in the above study can be used as a simple, efficient, and widely promoted scheme for clinical screening and diagnosis of AD, which greatly solves the problem of AD disease detection.

5. Conclusion

Based on the various hypotheses mentioned by researchers in different studies on the possible causes of AD, this article found two promising targets, Aβ amyloid, and ApoE4 apolipoprotein. It analyzed the current application status of the two targets. ApoE protein plays an important role in various metabolic pathways in the human body. In addition to being associated with metabolic diseases such as diabetes and hypertension, it is also inseparable from AD.

ApoE4 in human blood vessels may cause the accumulation of phospholipid droplets in the brain and blood vessels, leading to a decline in metabolism and function in multiple parts of the organism. In addition, this protein can be used to analyze whether AD test methods are effective enough or widely distributed; therefore, this study further reviewed the detection methods and found that using p-tau181 in the blood is the most beneficial method because it can detect AD Differentiated from other common high-incidence degenerative diseases, it can also detect the development of AD in the human body. A basic understanding of disease mechanisms, texting methods, etc., may also enhance their interest in further research in this area.

Although this article has analyzed one of the most popu-

lar theories, the ApoE4 hypothesis, there are still several hypotheses mentioned by researchers and published on various academic websites. Such as environmental influences, brain trauma, sleep disorders, etc., are also related to predisposing factors that cause AD. In addition, the testing method using p-tau 181 mentioned in the article also has some imperfections. It shows many limitations that need to be better improved and solved by researchers in the near future. Although these hypotheses and testing methods are not yet mature enough, and scientists do not fully understand the working process and pathogenesis of AD disease, they are still working to penetrate deeper into these fields and provide further, more accurate data.

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