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Analysis of Factors Influencing Amyloid-beta Deposition in the Context of Alzheimer's Disease

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Abstract. As a neurodegenerative ailment, Alzheimer's disease closely associates with the deposition of beta-amyloid (Aβ) proteins. The abnormal accumulation of Aβ plays a pivotal role in the disease's progression, leading to cognitive impairment and neurological damage. APOE is a key gene that affects the accumulation of Aβ, with its ε2, ε3, and ε4 alleles closely associated with the likelihood and advancement of Alzheimer's disease. APOEε2 variant appears to slow disease progression by reducing Aβ deposition, thereby exerting a protective effect; whereas the APOEε4 allele increases the risk of the disease by promoting Aβ deposition and speeding up its advancement. Besides the APOE gene, variations in the TREM2 and Presenilin-1 (PSEN1) genes are also linked to the development of Alzheimer's disease. TREM2 plays a role in immune responses and inflammatory processes, and mutations in this gene may impair the brain's ability to clear Aβ , resulting in increasing deposition. Presenilin-1, a component of the gamma-secretase complex, plays a key role in producing Aβ, and mutations in this gene are linked to the development of early-onset Alzheimer's disease. This paper examines genetic factors, epigenetics, chemical reactions, and cellular dysfunction from multiple dimensions to explore how they interact to affect the production, deposition, and pathogenic mechanisms of Aβ. Through this multidimensional analysis, this study emphasizes the interplay of various factors in the pathological process of Alzheimer's disease, jointly promoting the abnormal accumulation of Aβ. By unveiling these complex mechanisms, the study provides insights into potential targets for upcoming treatment plans.

Keywords: Alzheimer's disease, beta-amyloid, genetics, epigenetics.

1. Introduction

Alzheimer's disease (AD) is a progressive neurological disorder marked by a gradual decline in memory, cognitive and behavioral impairments, and daily living skills. The etiology of AD is complex and its mechanisms are not fully understood, with no specific treatment or drugs available to reverse the progression of the disease. Patients' conditions progressively worsen, often leading to death due to complications such as pulmonary infections, bedsores, and deep vein thrombosis [1]. Genetic and pathological evidence indicates that Alzheimer's disease is associated with the deposition of beta-amyloid (Aβ). Research on amyloid proteins that have been separated from Alzheimer's disease patients' cerebral vascular amyloid deposits indicates that these proteins might have come from a distinct serum source. Amino acid sequence analysis and computer searches have revealed that this protein has no homology with any sequenced proteins to date, underscoring its unique role in the

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disease. Amyloid proteins play a crucial role in the pathological process of Alzheimer's disease, particularly in relation to amyloid deposition in the brain. These deposits primarily consist of twisted beta-sheet fibrils and are a hallmark of Alzheimer's pathology, including intraneuronal neurofibrillary tangles, extracellular amyloid-containing plaques, and amyloid fibril deposition in cerebral vessels. This paper analyzes the factors leading to beta-amyloid protein formation from genetic, epigenetic, chemical, and cellular functional perspectives. By discussing the causes of beta-amyloid deposition, this paper aims to analyze potential targets that could influence the development of therapeutic drugs for Alzheimer's disease.

2. Genetic Factors

2.1. Impact of the APOE gene on Beta-Amyloid deposition

APOE (Apolipoprotein E) is a glycoprotein primarily produced in the liver and brain, and it plays a crucial role in lipid transport and metabolism. APOE exists in three main allelic forms: ε2, ε3, and ε4, which are genetically distinguished by differences in two amino acid positions, affecting their structure and function, thereby influencing lipid binding and cellular receptor affinity [1].

2.1.1. Impact of ε2 on amyloid deposition

Experiment 1: Studies have revealed that E2FAD mice have greater overall Aβ42 levels in the cortex at six months, but similar Aβ42 levels in the hippocampus at different ages compared to E3FAD mice.

Experiment 2: This experiment involved crossing transgenic PDAPP mice that express human amyloid precursor protein (APP) and thus accumulate amyloid-beta (Aβ) in the brain with APOE targeted replacement (APOE-TR) mice to study the impact of APOEε2 on Aβ deposition. This paper explores how APOEε2, compared to other APOE isoforms, affects Aβ accumulation in the brain, a hallmark of Alzheimer's disease pathology. In this specific study, PDAPP/TRE2 animals carrying the APOEε2 allele showed a lower cortical Aβ load at 18 months of age compared to PDAPP/TRE3 animals carrying the APOEε3 allele, as measured by immunohistochemistry. This discovery implies that in this Alzheimer's disease mouse model, APOEε2 may have a preventive function against cortical Aβ accumulation.

The relationship between APOEε2 and reduced Aβ deposition emphasizes the potential protective role of APOEε2 against Alzheimer's disease, contrasting with the well-known APOEε4 allele that increases disease risk. The differential impact of APOE isoforms on Aβ pathology observed in this experiment supports the hypothesis that APOEε2 might reduce the risk of developing Alzheimer's disease by influencing the process of Aβ accumulation in the brain.

Experiment 3: The experiment involved virally mediated overexpression of human APOEε2 in a mouse model of amyloid pathology expressing mouse APOE to study its impact on Aβ pathology. In PDAPP mice, lentiviral-mediated overexpression of APOEε2 reduced hippocampal Aβ levels more than overexpression of APOEε3 and APOEε4. Likewise, in brain lysates of APP/PS1 mice, soluble and insoluble fractions of Aβ40 and Aβ42 were found to be lower when APOEε2 (as opposed to APOEε3 or APOEε4) was delivered via gene transfer [2].

2.1.2. ε3

Researchers crossed APOE3 and APOE3ch homozygous knock-in (KI) mice with APP/PS1 Aβ model mice, which have Aβ deposits. At 6 months of age, they injected human AD-tau unilaterally into the hippocampus and cortex. After a period, they assessed brain amyloid deformation and neuroinflammatory plaque-related tau pathology (NP-tau). Comparisons revealed that APP/PS1 mice had significantly reduced sizes and numbers of amyloid plaques in the brain, and anti-phosphorylated tau antibody (AT8) tests showed a reduced total amount of NP-tau in both ipsilateral and contralateral hippocampus and cortex [3].

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2.1.3. ε4

Studies reveal that elevated tau protein loads in Alzheimer disease-prone areas are linked to the interaction between APOEε4 and amyloid proteins, not just the simple additive effect of their individual effects.

Specifically, one APOEε4 allele's interaction with amyloid proteins is associated with an increased tau protein load, however, the interaction of two APOEε4 alleles with amyloid proteins is related to a more widespread aggregation pattern of tau protein.

The study included three distinct samples: people with Alzheimer's disease, people without cognitive impairment, and those with mild cognitive impairment. The subjects received structural MRI, tau-PET imaging, amyloid-PET imaging, cerebrospinal fluid investigation, and APOEε4 genotyping.

Different PET imaging agents were used to visualize amyloid and tau proteins, assessing their distribution and accumulation in the brain. These images were processed through multiple steps, including spatial normalization, partial volume correction, and generating standardized uptake value ratios (SUVR).

Independent of age and clinical diagnosis, the interaction effects of APOEε4 and amyloid on tau load were assessed using a voxel-based regression model. The analysis also considered the potential impact of the number of APOEε4 alleles, exploring how the interaction of single and double copy APOEε4 alleles with amyloid affects tau protein load [4].

2.2. TREM2

Research has found that dysfunction or deficiency of TREM2 leads to a reduced ability of microglia to clear amyloid-beta (Aβ), thereby increasing the deposition of Aβ in the brain [5].

2.3. Presenilin-1 (PSEN1)

PSEN1 is identified as a critical pathogenic factor in early-onset Alzheimer's disease (EOAD) [6]. As part of the gamma-secretase complex, PSEN1 influences the cleavage of amyloid precursor protein (APP) and subsequently affects beta-amyloid (Aβ) deposition. Experiments utilized knock-in (KI) mouse models carrying specific mutations in the PSEN1 gene (L435F or C410Y). Phenotypic analysis of these KI mice and their control group (wild-type mice) revealed that mice carrying the PSEN1 mutation exhibited phenotypes associated with familial Alzheimer's disease (FAD), such as undetectable levels of Aβ40 and Aβ42 production and stability in the mutant mice's brains, and a slight increase in the Aβ42/Aβ40 ratio in heterozygous KI mice (KI/+). Additionally, researchers assessed the impact of PSEN1 mutations on gamma-secretase activity, the enzyme responsible for cleaving APP to produce Aβ, using in vitro gamma-secretase activity assays. The results showed that gamma-secretase activity in the brains of mice carrying the L435F and C410Y mutations was inhibited, leading to reduced production of Aβ. Researchers also measured the production of Aβ43 in the mice's brains using enzyme-linked immunosorbent assays. They found that in KI/+ mice carrying the L435F mutation, the production of Aβ43 was reduced compared to the wild-type control group, and in KI/KI mice carrying the C410Y mutation, the production of Aβ43 was undetectable [7].

2.4. Presenilin-2 (PS2)

Mutations in the PS2 gene associated with familial Alzheimer's disease (FAD) have been shown to enhance the production of Aβ42, similar to PS1 mutations, thus suggesting a similar amyloidogenic function [8].

2.5. Endoplasmic reticulum retention protein 1

Endoplasmic reticulum retention protein 1 (RER1) is a protein, involved in the intracellular transport of secretases and amyloid precursor protein (APP), thus affecting the production of amyloid-beta (Aβ). RER1 acts as an ER retention/retrieval factor for gamma-secretase and APP, regulating Aβ production by modulating their transport and localization. Researchers observed that RER1 levels directly affect

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the transport and localization of gamma-secretase and APP through over-expression and knockdown experiments. While RER1 knockdown increased the amounts of these molecules in the late secretory pathway, boosting Aβ synthesis, over-expression of RER1 decreased Aβ secretion and gamma-secretase localization at the cell surface. Co-immunoprecipitation experiments confirmed the association of RER1 with the gamma-secretase complex, indicating that RER1 impacts Aβ production by regulating the intracellular localization and transport of gamma-secretase.

These findings indicate that RER1 regulates the transport of gamma-secretase and APP in early secretory pathways. Experimental results also showed that RER1 affects APP maturation and transport, as it reduces levels of mature APP while increasing levels of immature APP, leading to reduced accumulation of APP at the cell surface. Thus, RER1 regulates Aβ production and secretion by affecting the maturation and transport of APP [9].

3. Chemical Factors

3.1. Osteocalcin (OCN)

Osteocalcin, a peptide produced exclusively by osteoblasts, influence various hormonal activities via its active form, ucOCN [10]. Studies have shown that maternal OCN crosses the placental barrier and play a role in fetal hippocampal development, maintaining postnatal neural activity [11]. In a study involving APP/PS1 transgenic AD mice, researcher administered OCN at doses of 1μg/kg or 10μg/kg through daily injections for four weeks. Analysis revealed that OCN alleviated anxiety-like behaviors and improved cognitive dysfunction in these mice. Immunohistochemical analysis of brain tissue sections from the mice showed that OCN significantly reduced Aβ deposition in the hippocampus and cortex of AD mice. Notably, while extensive amyloid plaques were observed in the cortex and hippocampal regions of AD mice, these plaques were absent in wild-type (WT) mice. In the hippocampal and cortical regions of AD mice, the accumulation of amyloid plaque was considerably decreased by both 1μg/kg and 10μg/kg OCN [12].

3.2. Follicle-Stimulating Hormone (FSH)

Daily intraperitoneal injections of FSH (5 IU) were administered to 3-month-old female APP-KI mice for three months. Observations from the experiment showed that FSH treatment increased the expression of C/EBPβ and Asparagine endopeptidase (AEP), promoting APP cleavage and causing the formation of Aβ plaques in the hippocampus and/or cortex, accumulation of Aβ40 and Aβ42 throughout the brain, and cell death in the hippocampus. Mice treated with FSH showed deficits in spatial memory during the Morris water maze test, further demonstrating that FSH impairs cognitive functions by promoting the formation and accumulation of Aβ. Further experiments using a Cebpb+/-3xTg mutant mouse model treated with FSH showed that a single copy deletion of Cebpb reduced baseline events, particularly decreasing AEP activation and APP cleavage. This indicates that FSH induces AD pathology changes through C/EBPβ. FSH activates the C/EBPβ-AEP/δ-secretase pathway, leading to proteolytic cleavage of APP and Tau. Gene knockdown of Cebpb and AEP significantly reduced the FSH-induced cleavage of APP and Tau, proving that C/EBPβ and AEP play key roles in FSH-induced AD pathology [13].

4. Epigenetic Factors

4.1. DNA methylation

Researchers utilized transgenic mouse models capable of accumulating amyloid-beta (Aβ) in the brain, replicating key characteristics of Alzheimer's disease. They conducted DNA extraction and methylation analysis on brain samples, particularly focusing on the promoter region of the BACE-1 gene. By comparing methylation levels between healthy and AD model mice, researchers observed changes in the methylation of the BACE-1 gene in AD models. S-adenosylmethionine (SAM), a methyl donor, was used in intervention experiments to explore whether increasing methylation levels

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could reduce BACE-1 expression, thereby decreasing the production and deposition of amyloid-beta. Researchers assessed amyloid-beta deposition in the brain using specific staining and protein analysis techniques and evaluated the cognitive impact of SAM intervention on AD model mice through behavioral tests, such as maze tests. These experiments revealed that low methylation of the BACE-1 gene in AD model mice was associated with increased amyloid-beta deposition. By enhancing DNA methylation through SAM intervention, it was possible to reduce BACE-1 expression, and lower amyloid-beta production and deposition, thereby improving cognitive function [14].

4.2. Non-coding mRNA

4.2.1. BACE1

BACE1 is an enzyme that cleaves the beta-amyloid precursor protein (APP), and its increased activity leads to the formation of amyloid-beta, a hallmark of Alzheimer's disease pathology. BACE1-AS upregulates BACE1 expression by increasing the stability of BACE1 mRNA, promoting the production of amyloid-beta. Studies in SH-SY5Y cell models have shown that exogenous Aβ1-42 can induce an increase in BACE1 and BACE1-AS expression. BACE1-AS enhances the stability of BACE1 mRNA by forming RNA dimers. Knockdown of BACE1-AS using siRNA reduces BACE1 activity, decreases APP cleavage and amyloid plaque formation, demonstrating that BACE1-AS plays a crucial role in promoting amyloid-beta production. BACE1-AS also acts as a competitive endogenous RNA (ceRNA), stabilizing BACE1 mRNA expression by inhibiting various microRNAs (miRNAs). After knockdown of BACE1-AS, these miRNAs levels increased, further demonstrating that BACE1-AS regulates BACE1 expression and amyloid-beta production through the miRNA axis [15].

4.2.2. SOX21

AD cell models are constructed with SH-SY5Y and SK-N-SH cells, and treated with different concentrations of amyloid-beta1-42 (Aβ1-42). Quantitative real-time PCR (qRT-PCR) is used to assess the expression of miR-107 and SOX21-AS1. In SH-SY5Y and SK-N-SH cells, treatment with Aβ1-42 upregulates SOX21-AS1 expression while downregulating miR-107. Western blot analysis was performed to measure phosphorylated Tau (p-Tau) protein levels, and cell viability and apoptosis were evaluated using MTT assays and flow cytometry. Results indicated that knocking down SOX21-AS1 mitigated the Aβ1-42-induced elevation in p-Tau, improved cell viability, and decreased apoptosis [16].

5. Potential Future Therapeutic Targets

Long non-coding RNAs (lncRNAs) are known to regulate gene expression, with their dysregulation increasingly associated with human diseases. Thus, the elevated levels of BACE1-AS have been observed, especially in neurodegenerative conditions related to amyloid accumulation, where BACE1 levels remain steady. Both methods show promise for disease diagnosis, and while the inhibition of BACE1 has been extensively studies for its therapeutic potential, BACE1-AS also appears to hold promise. In summary, detecting BACE1-AS or BACE1 offers a straightforward, dependable, and non-invasive diagnostic method [17]. Additionally, Cass4, identified as a genetic risk factor for Alzheimer's, may also become a potential therapeutic target for the disease in the future.

6. Conclusion

This paper summarizes the factors causing beta-amyloid deposition from genetic, chemical, and epigenetic perspectives. At the genetic level, APOEε2 and APOEε3 reduce beta-amyloid deposition, while APOEε4 promotes it. TREM2, PSEN1, and PSEN2 also contribute to beta-amyloid deposition. RER1 causes amyloid deposition by regulating the transport and localization of gamma-secretase and APP. Chemically, OCN decreases beta-amyloid deposition, while FSH promotes APP cleavage and beta-amyloid deposition by enhancing the expression of C/EBPβ and AEP. On the epigenetic level,

SAM methylation intervention on the promoter region of the BACE-1 gene reduces the production and deposition of beta-amyloid, whereas increased BACE1 activity leads to the formation of amyloid-beta. SOX21 also contributes to beta-amyloid deposition. A limitation of this paper is that the summary is not exhaustive. For example, numerous risk factors for Alzheimer's disease have been identified in genome-wide screenings that were not listed here. Future efforts could focus on developing drugs targeting epigenetic factors, reducing amyloid deposition by inhibiting the expression of related genes to treat Alzheimer's disease.

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