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Alzheimer's Disease: Pathological Mechanism and Treatment

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Abstract. Alzheimer's disease (AD) is a neurodegenerative condition marked by progressive cognitive decline, impacting the elderly globally. Pathologically, the disease is defined by the accumulation of amyloid beta (Aβ) plaques, neurofibrillary tangles (NFTs), mitochondrial dysfunction, abnormal synaptic activity, and immune dysregulation, leading to extensive neuronal death. Current clinical treatments, such as acetylcholinesterase inhibitors and NMDA receptor antagonists, primarily alleviate symptoms but do not halt disease progression. Research on targeted therapies for Aβ and Tau proteins has garnered considerable attention, although clinical trials present challenges. Emerging therapies, including immunization, gene therapy, and stem cell therapy, offer promising prospects. Monoclonal antibodies have shown potential in clearing Aβ plaques, while gamma wave stimulation may reduce amyloid levels. Stem cell therapy aims to enhance neural function through neuronal replacement or regeneration. This review examines the primary pathological mechanisms of AD and recent therapeutic advancements, highlighting the potential for substantial breakthroughs as our understanding of the disease deepens and new treatment strategies are developed. By addressing the underlying pathological processes rather than merely alleviating symptoms, these advancements hold promise for more effective AD interventions.

Keywords: Alzheimer's disease, Amyloid beta, Tau protein, Autophagy

1. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that predominantly affecting the elderly population and is the leading cause of dementia worldwide. First described by Alois Alzheimer in 1906 [1], AD has since become a major global public health concern, with its prevalence increasing rapidly, particularly as populations age. According to the World Health Organization (WHO), approximately 50 million people worldwide are living with dementia, with 60-70% of these cases attributed to AD. This figure is projected to reach 152 million by 2050 [2].

AD is characterized by both structural and functional damage to the central nervous system (CNS), involving aberrant protein aggregation and neurodegenerative processes. Two primary lesions associated with AD have been identified: neurofibrillary tangles (NFTs), which result from hyperphosphorylated tau protein accumulation within neurons [3], and amyloid plaques, which form from the extracellular aggregation of Aβ peptides [4]. These pathological changes lead to a progressive decline in cognitive function, memory impairment, behavioral alterations, and eventually, a loss of functional capacity. Additionally, recent studies have highlighted neuroinflammatory syndrome and autophagy impairment as further primary pathologies of AD [1]. Although the pathological mechanisms

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underlying AD have been extensively explored, the precise processes driving these pathological features remain poorly understood.

Traditional treatments of AD focus on symptom management. Currently approved pharmacological treatments primarily include acetylcholinesterase inhibitors, such as Donepezil and Galantamine [5], and the N-methyl-D-aspartate (NMDA) receptor antagonist, Memantine [6]. These drugs mainly work by increasing acetylcholine levels in the brain or modulating the glutamate system to mitigate cognitive decline. However, they offer only partial relief from AD symptoms and do not halt or reverse disease progression.

In recent years, advancements in understanding the pathological mechanisms of AD have spurred the development of novel therapeutic strategies, including immunotherapy targeting amyloid-beta (Aβ) and Tau proteins, gene therapy, and stem cell therapy [7, 8]. Immunotherapy aims to alleviate neurotoxic effects by clearing or preventing the accumulation of Aβ through active or passive immunization. Gene therapy utilizing gene editing technologies to correct or replace genetic mutations associated with AD, or to regulate gene expression to influence metabolic pathways implicated in the disease. Stem cell therapy seeks to replace damaged neurons or promote neuronal regeneration by transplanting or activating endogenous stem cells.

Although these emerging therapies have demonstrated promise in preclinical studies and early-phase clinical trials, they pose significant challenges. Ensuring their safety and efficacy in clinical settings, alongside optimizing treatment regimens, remain a critical concern. Moreover, due to the complex and multifaceted pathological characteristics of AD, a single therapeutic approach may be inadequate to fully manage disease progression, promoting interest in multi-target combination therapies [9].

This review will examine the pathological mechanisms of AD, assess the efficacy and limitations of traditional therapeutic strategies, and highlight recent advancements in research and clinical trial outcomes of emerging therapies. Additionally, we will discuss the practical challenges facing these innovative therapies and explore potential future directions for managing AD.

2. The pathological mechanism of Alzheimer's disease

2.1. Amyloid beta plaque

Amyloid Beta is a short peptide produced by amyloid precursor protein, a transmembrane protein precursor cleaved by β-and γ-secretase enzymes. Aβ has a propensity to aggregate, and when these peptides cluster together, they form insoluble fibers that deposit in brain tissue, creating amyloid plaques. The accumulation of Aβ in central nerve system is a key pathological event in the early stage of AD [10]. Aβ plaques are predominantly present in the cortex and hippocampus, which are closely associated with memory loss and cognitive decline. These plaques can cause neuronal damage through the following mechanisms: (1) Direct toxic effects: Aβ can directly harm neurons by disrupting cell membranes, affecting ion channels, and altering calcium ion homeostasis. (2) Induction of an inflammatory response: The deposition of Aβ can activate microglia and astrocytes, triggering a neuroinflammatory response. This chronic inflammation further exacerbates neuronal damage. (3) Disruption of synaptic function: Aβ can impair synaptic plasticity and inhibit Long-Term Potentiation (LTP), thereby negatively affecting learning and memory.

2.2. Neurofibrillary tangles (NFTs)

The main component of NFTs is the hyperphosphorylated Tau protein. Under normal conditions, Tau in neurons can stabilize microtubules, thereby supporting cellular structure and function. However, in AD, Tau protein become abnormally phosphorylated, causing it to depolymerize and self-aggregate into fibrous tangles. These tangles are mainly found within neurons, especially in the hippocampus and the cerebral cortex.

The pathological mechanisms of Tau protein abnormal aggregation include the following: (1) Microtubule disintegration: Hyperphosphorylated Tau protein loses its ability to stabilize microtubules, leading to microtubule disintegration and subsequent cytoskeletal destruction. (2) Axon transport

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disruption: Following microtubule disintegration, the transport of essential substances within axon is obstructed, impairing signal transmission and nutrient supply between neurons. (3) Induction of apoptosis: Aggregated Tau proteins may directly or indirectly trigger neuronal apoptosis.

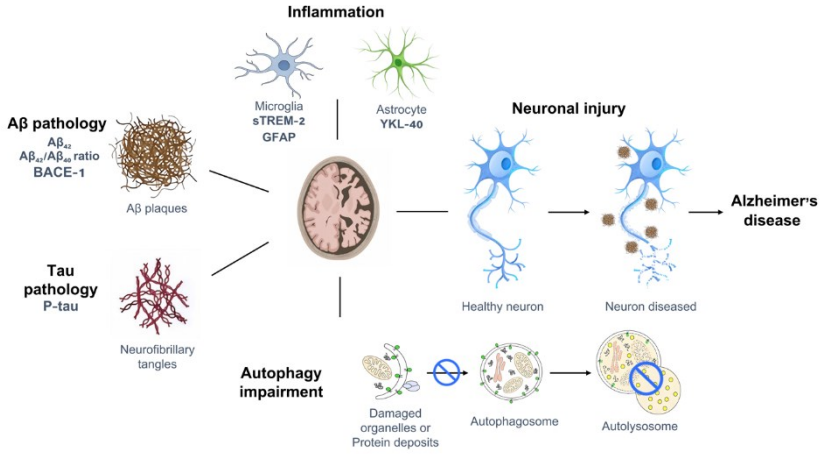

Figure 1. The pathological mechanism of Alzheimer's disease.

Figure 1 shows the main pathological features of Alzheimer's disease and how they lead to neuronal damage that ultimately leads to neurodegeneration. BACE-1, Beta-Site Amyloid Precursor Protein Cleaving Enzyme 1; sTREM-2, soluble triggering receptor expressed on myeloid cells-2; GFAP, glial fibrillary acidic protein; YKL-40, chitinase-3-like protein 1.

2.3. Autophagy impairment

Autophagy is a cellular process that clears damaged proteins and organelles, playing a key role in maintaining cellular homeostasis. In AD, abnormalities may occur in all aspects of autophagy, particularly in the following aspects: (1) Impairing autophagosome formation: The initiation stage of autophagy involves autophagosome formation. In the brains of AD patients, the accumulation of Aβ and Tau proteins disrupts this process [11]. Specifically, Aβ can inhibit autophagosome formation by interacting with autophagy-associated proteins, such as Beclin-1 [12], thereby hindering the cell's ability to clear damaged proteins. (2) Impairing autophagy lysosome fusion: Once an autophagosome is formed, it must fuse with the lysosome for degradation of its contents. However, this process is often blocked in AD. Studies have shown that in AD brains, the efficiency of autophagosomes-lysosome fusion is significantly reduced, resulting in the accumulation of autophagosomes and the aggregation of undegraded proteins [1]. This may be due to the impaired acidic environment within the lysosome or dysfunction of lysosome-related enzymes. (3) Lysosomal dysfunction: Lysosomal dysfunction is common in AD. Aβ deposits and Tau tangles can directly damage lysosomal membrane integrity, leading to lysosomal enzyme leakage and dysregulation of intracellular degradation system. In addition, inadequate lysosomal acidification is an important contributor to reduced lysosomal function, further exacerbating disruptions in the autophagy pathway.

2.4. Oxidative stress and endoplasmic reticulum stress

Oxidative stress in AD results from an imbalance between the production of reactive oxygen species (ROS) and the cellular antioxidant defenses, leading to neuronal damage. The presence of Aβ and tau protein aggregates exacerbates ROS production, damaging cellular components and contributing to disease progression [13]. Endoplasmic reticulum (ER) stress arises from protein misfolding within the ER, activating the unfolded protein response (UPR) [14]. Activated UPR can protect cells against mild ER stress. However, chronic ER stress can exhaust the capacity of the UPR, leading to cell death [15].

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Oxidative stress and ER stress are interlinked, creating a vicious cycle that promotes neuronal injury and accelerates AD progression.

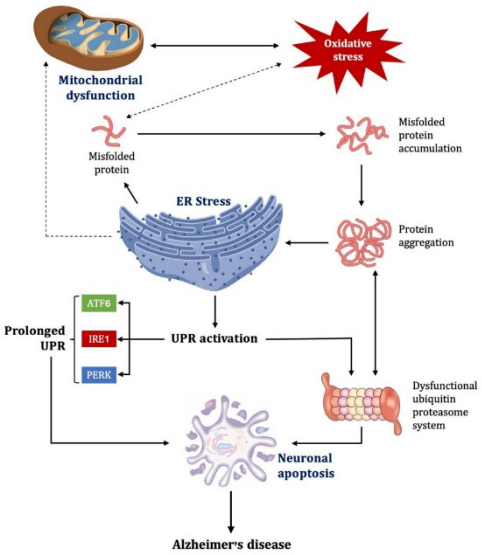

Figure 2. Endoplasmic reticulum stress and oxidative stress.

Figure 2 shows mitochondrial and ER dysfunction, as well as oxidative stress and prolonged UPR activation, leading to neuronal apoptosis. ER, Endoplasmic reticulum; UPR, Unfolded Protein Response; ATF6, Recombinant Activating Transcription Factor 6; IRE1, Inositol-Requiring Enzyme 1; PERK, protein kinase RNA–like endoplasmic reticulum kinase.

3. The symptomatic treatments for Alzheimer's disease

3.1. Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors are a commonly used class of drugs in the treatment of AD and are mainly employed to improve cognitive function in patients. A hallmark of AD is a reduction in of acetylcholine (ACh) levels, which adversely affects memory and learning ability. Acetylcholinesterase inhibitors (AChEIs) reduces the breakdown of acetylcholine through the inhibition of Acetylcholinesterase (AChE), thereby increasing the concentration of acetylcholine in the brain and alleviating cognitive dysfunction [16].

Currently, several acetylcholinesterase inhibitors have been approved for AD treatment, including: (1) Donepezil: For mild to severe Alzheimer's disease, it can improve cognitive function and behavioral symptoms with relatively few adverse effects. (2) Galantamine: In addition to inhibiting acetylcholinesterase, galantamine enhances the activity of nicotine acetylcholine receptor, thereby promoting acetylcholine release. (3) Rivastigmine: Used for mild to moderate Alzheimer's and Parkinson's-related dementias, rivastigmine inhibits both acetylcholinesterase and butyryl cholinesterase, leading to improved efficacy.

3.2. N-methyl-D-aspartate (NMDA) receptor antagonist

In AD, overactivation of NMDA receptors by elevated glutamate levels results in excessive calcium ion influx and subsequent neuronal death. NMDA receptor antagonists, such as Memantine—the only FDA-approved NMDA receptor antagonist for moderate-to-severe AD—are essential in mitigating this glutamate-induced excitotoxicity.

Memantine acts through non-competitive binding to NMDA receptors, preventing overstimulation and subsequent neurotoxicity, thereby protecting neurons from damage [17]. Clinical studies indicate

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that memantine effectively alleviates cognitive and functional declines while exhibiting minimal side effects, making it a widely utilized therapeutic option [18]. Overall, Memantine's therapeutic mechanism involves the attenuation of glutamate neurotoxicity, reduction of calcium overload, and potential mitigation of beta-amyloid neurotoxicity, offering a partial delay in the neurodegeneration associated with AD [17, 18].

4. The emerging treatments for AD

4.1. Immunization therapy

Immunization therapy has shown great potential in the treatment of AD in recent years, especially in clearing accumulated Aβ and Tau proteins in the brain. Immunization therapy is mainly categorized into passive and active immunization therapies.

Passive immunization therapy targets pathological proteins, such as Aβ and Tau, by delivering exogenous antibodies directly, aiding the body in clearing their abnormal accumulation. Multiple monoclonal antibodies have shown promise in animal models and clinical studies.

4.2. Passive immunization therapy against Aβ.

In recent years, monoclonal antibodies against Aβ have become a prominent area of research in AD, with several antibodies progressing to clinical trial stages. The most notable of these is aducanumab, a monoclonal antibody that targets Aβ and clears deposited Aβ plaques [19]. On June 7, 2021, aducanumab received accelerated approval from the FDA for the treatment of AD, making it the first new drug for AD treatment since 2003 and the first to potentially alter the disease course. This marks a significant advancement in AD treatment through immunization therapy [20]. Additionally, novel antibodies such as lecanemab and donanemab have shown improvements in cognitive function and significant reductions in Aβ deposits in clinical trials [21, 22].

Beyond Aβ, the excessive phosphorylation and aggregation of the Tau protein play an important role in the pathogenesis of AD. Recently, passive immunotherapy against Tau has gained attention, with antibodies such as Gosuranemab and Zagotenemab aiming to inhibit Tau spread within neurons, showing promising neuroprotective effects in clinical trials [23].

4.2.1. Active immunization therapy.

Active immunization therapy involves the use of vaccines to stimulate the body to produce its own antibodies, aiming for long-term clearance of Aβ or Tau proteins. Unlike passive immunization therapy, active immunization therapy has the potential to achieve more lasting effects.

In recent years, several Aβ-targeted vaccines have entered clinical trials. For example, the CAD106 vaccine is designed to reduce Aβ deposits by inducing an antibody response against Aβ. Clinical trials have shown that CAD106 has a favorable safety profile and successfully induces an antibody response [24].

For active immunization therapy targeting Tau, AADvac1 vaccine is one of the more studied options. This vaccine induces the production of anti-Tau antibodies, reducing pathological Tau aggregation. Clinical studies have shown that AADvac1 can reduce Tau protein accumulation and slow cognitive decline in early-stage patients [25].

Despite the promise of immunization therapy for AD, several challenges remain. Firstly, response to immunization therapy vary among patients, with some experiencing side effects such as brain edema or bleeding. Secondly, immunotherapy has limited efficacy in advanced disease stages, highlighting the importance of early intervention. Future studies should focus on optimizing antibody design to enhance therapeutic efficacy while minimizing adverse reactions. In addition, combining immunotherapy with other treatments, such as gene therapy and stem cell therapy, may further improve treatment outcomes for AD.

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4.3. Gene therapy

The advent of gene-editing tools, such as CRISPR/Cas9, has provided a powerful tool for Alzheimer's research [26]. Researchers have utilized this technology to target the editing of genes associated with AD, including amyloid beta precursor protein (APP), Presenilin-1 (PSEN), and Apolipoprotein E (APOE). Notably, the APOE gene comprises three isomers: apolipoprotein E2 (ApoE2), apolipoprotein E3 (ApoE3), and apolipoprotein E4 (ApoE4), each exhibiting distinct properties that vary through substitution. Emerging studies indicate that editing the APOE gene via CRISPR/Cas9 technology can convert the high-risk APOE4 allele into the lower-risk APOE3 allele, thereby reducing risk factors associated with Alzheimer's disease [27].

Furthermore, gene transfer therapy employs viral vectors to introduce functional genes into the patient's brain cells, thereby restoring or replacing the function of diseased genes. In the context of AD, researchers utilize adeno-associated virus (AAV) vectors to deliver neuroprotection-related genes, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which promote neuronal survival and mitigate cognitive decline [28].

In addition to gene editing, gene silencing technologies constitute another important avenue for Alzheimer's disease treatment, primarily encompassing RNA interference (RNAi) and antisense oligonucleotide (ASO) technologies. These approaches aim to decelerate disease progression by inhibiting the expression of specific genes, consequently reducing the accumulation of pathological proteins. RNA interference is an intrinsic cellular mechanism that utilizes small interfering RNAs (siRNAs) to target specific mRNAs, thereby suppressing gene expression. In Alzheimer's disease, RNAi technology can be directed to diminish the production of Aβ and Tau proteins, which are closely linked to disease progression. For instance, Aβ is generated by APP under the catalytic action of β-site lyase 1 (BACE1); thus, silencing the BACE1 gene effectively curtails Aβ production. Preclinical studies have demonstrated that following BACE1 gene silencing, Aβ levels significantly decrease and amyloid plaques in the brain are reduced, consequently improving cognitive function [29]. These findings suggest that RNAi technology may possess the potential to delay disease progression at early stages.

Antisense oligonucleotide technology silences gene expression by binding to a specific mRNA, preventing its translation or triggering its degradation. Antisense oligonucleotides are highly sequence specific and can target key disease-causing genes in Alzheimer's disease. For example, antisense oligonucleotides can target mRNA of APP or Tau proteins, inhibiting their overexpression and reducing the deposition of toxic proteins [30]. A recent study successfully reduced Tau protein aggregation in animal models by silencing Tau genes with antisense oligonucleotides and significantly delayed the occurrence of neurodegeneration [31].

Finally, the application of gene editing and silencing technology in the treatment of Alzheimer's disease is still in the preclinical and early clinical trial stage. Although these techniques have shown remarkable results in animal models, their efficacy and safety in humans still need to be further validated.

In addition to existing achievements, gene therapy still faces several challenges, such as the efficiency of vector delivery, off-target effects of gene editing, and the long-term safety and efficacy in humans. Nonetheless, with the continuous optimization of gene editing tools and advancements in viral vector technology, gene therapy is anticipated to become an important modality for the treatment of Alzheimer's disease in the future.

4.4. Oxidative stress and endoplasmic reticulum stress treatment model in AD

Epidemiological studies have shown a link between a decline in antioxidant reserves and an increase in the incidence of a variety of diseases, including cancer, heart disease, premature aging, and neurological disorders [32]. Due to continuous exposure to free radicals and mitochondrial damage, many pathophysiological diseases are associated with oxidative stress. It causes neuroinflammation driven by oxidative stress, which is associated with the pathophysiology of AD and other neurodegenerative diseases [33]. Many endogenous antioxidants, such as low molecular weight compounds such as glutathione, which are normally present at levels sufficient to protect against oxidative damage, and enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, all help biological systems

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fight oxidative stress. The following table shows some recent AD treatment models based on oxidative stress and ER stress.

Table 1. Recent AD based on oxidative stress and endoplasmic reticulum stress.

Compound	Pathway addressed	Reference
Hesperidin	OS	Thenmozi et al. [34]
Gallic acid	OS	Ekundayo et al. [35]
Melatonin	OS, ERS	Promyo et al. [36]
Vardenafil	OS, ERS	Awad et al. [37]
Silymarin	OS	Aboelwafa et al. [38]
Asiatic acid	OS	Ahmad Rather et al. [39]
Taurine	OS, ERS	Liu et al. [40]
Ononin	OS	Chen et al. [41]
Syring acid	OS	Zhao et al. [42]
Spermine	OS	Raj et al. [43]
Ethyl-pyruvate	OS	Chavali et al. [44]
Biotin, Coenzyme Q	OS	Attia et al. [45]
Vanillin	OS	Anand et al. [46]
Fisetin	OS	Prakash et al. [47]

4.5. Stem cell therapy

Stem cell therapy ameliorates the pathological processes of Alzheimer's disease through several mechanisms. Firstly, stem cells can differentiate into neurons and glial cells, thereby replacing degenerated neurons. Secondly, they secrete neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which promote neuronal survival and growth and enhance neuroplasticity. Additionally, stem cells exert anti-inflammatory effects that inhibit the chronic inflammatory response characteristic of Alzheimer's disease, thus reducing neuroinflammation [48].

In current research on Alzheimer's therapy, the primary stem cells utilized include embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs). ESCs possess a strong capacity for differentiation into various neural cell types, such as neurons, astrocytes, and oligodendrocytes. However, their clinical application in Alzheimer's disease is hindered by ethical concerns and potential tumorigenic risks [49]. iPSCs, derived from reprogrammed adult cells, can differentiate into multiple cell types akin to ESCs. They can be sourced autologously from patients, thereby circumventing immune rejection, and have found extensive application in Alzheimer's research. For example, neurons differentiated from patient-derived iPSCs and transplanted into Alzheimer's animal models have demonstrated improvements in neural and cognitive functions [50]. Furthermore, iPSCs facilitate the creation of personalized disease models for drug screening and therapeutic evaluation. MSCs, predominantly derived from bone marrow, adipose tissue, and umbilical cord blood, secrete neurotrophic factors, and exhibit anti-inflammatory and immunoregulatory functions. Research indicates that MSCs not only can differentiate into neuronal cells but also enhance neuron survival and neural network repair through the secretion of exosomes and cytokines [51, 52]. Compared to ESCs and iPSCs, MSCs are more accessible and present fewer ethical concerns, making them a focal point in Alzheimer's stem cell therapy research.

Although most stem cell therapies are still in the preclinical stage, some research has entered early clinical trials. For example, a Phase I clinical trial using autologous MSCs transplantation showed that autologous bone marrow mesenchymal stem cell delivery reduced nerve loss and neuroinflammatory depletion after TBI in adults and children [53, 54], and these results provide preliminary evidence to support further clinical studies.

However, the effectiveness mentioned above, there are drawbacks to stem cell therapy. For example, the efficiency of stem cell transplantation, long-term survival and functional integration in vivo, as well as possible immune response and risk of tumor formation are all issues that need to be overcome. It's believed that future studies should further optimize the delivery methods of stem cells to improve their safety and efficacy. At the same time, with the in-depth understanding of the pathological mechanism of Alzheimer's disease, combined with gene editing and exosomes and other technologies, stem cell therapy is expected to bring breakthroughs in the treatment of Alzheimer's disease in the future.

5. Conclusion

In conclusion, the pathological mechanisms of AD include Aβ deposition, abnormal Tau protein phosphorylation, neuroinflammation, autophagy impairment and oxidative stress. These factors collectively contribute to neuronal damage and cognitive decline. Current symptomatic treatments, such as acetylcholinesterase inhibitors and NMDA receptor antagonists, provide temporary relief but do not address the underlying pathological processes of AD. Recent advances in scientific research have paved the way for promising new treatment strategies, including immunotherapy, gene therapy, and stem cell therapy. Immunotherapy primarily focusing on the clearance of Aβ and tau protein aggregates, thereby reducing the pathological burden. Gene therapy aims to correct genetic abnormalities associated with AD, while stem cell therapy holds potential for neuronal repair and regeneration. These innovative therapeutic approaches represent a paradigm shift from mere symptom management to addressing the fundamental pathological mechanisms of AD. As our understanding of AD deepens and these emerging therapies advance, there is hope for developing more effective interventions that may slow, halt, or even reverse the progression of AD.

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