Advances in Stem Cell-based Therapy for Alzheimer's Disease: Monotherapy, Combination Strategies and Stem Cell-derived Extracellular Vesicles (Exosomes)

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***Abstract*—Alzheimer's Disease (AD) is the most common neurodegenerative disorder, accounting for 60%–80% of dementia cases. Its core pathological hallmarks include Aβ plaque deposition, hyperphosphorylation of tau protein, neuronal loss, and progressive cognitive decline. However, existing clinical medications only provide short-term symptomatic relief and are incapable of reversing neuronal damage or halting disease progression. In contrast, stem cell therapy exerts disease-modifying effects through multiple pathways, making it a promising strategy for AD treatment. This paper systematically reviews preclinical and clinical research advances in AD therapy using stem cell monotherapy, stem cells combined with drugs/growth factors, and stem cell-derived extracellular vesicles (exosomes). It focuses on the mechanisms of dental mesenchymal stem cells, bone marrow mesenchymal stem cells, induced pluripotent stem cell-derived microglia, and exosomes in reducing Aβ burden, inhibiting tau hyperphosphorylation, suppressing inflammation, promoting neural regeneration, and improving cognitive function. Studies demonstrate that stem cells and their derivatives exert meaningful therapeutic effects in animal models. Early clinical trials have confirmed their favorable safety profile, as well as their ability to delay brain atrophy, reduce neuroinflammation, and improve cognitive scores. However, several challenges remain. Further efforts are required to standardize therapeutic protocols, expand multi-center clinical trials, and conduct long-term safety monitoring to facilitate its clinical translation and application.**

***Keyword*—Alzheimer's Disease (AD), stem cell-based therapy, stem cell extracellular vesicles, exosomes**

I. Introduction

In 2019, the global number of people living with dementia reached 55 million, and it is projected to triple to 139 million by 2050. The growing prevalence of dementia represents a challenging global health issue [1]. Of its causes, neurodegenerative diseases are the most predominant. These are age-related and progressive neurological disorders characterized by the gradual degeneration and death of central and peripheral neurons, with incidence rates rising alongside population aging [2].

Alzheimer's Disease (AD) is the most common form of neurodegenerative disease, accounting for 60%–80% of all dementia cases. It is classified into early-onset autosomal dominant AD and late-onset sporadic AD. The core pathological features of AD include extracellular Aβ plaques, intracellular tau neurofibrillary tangles, and soluble Aβ oligomers, which appear earlier than plaques and exhibit greater neurotoxicity, as well as synaptic and neuronal loss and gliosis. This leads to progressive decline in cognitive function and memory in affected individuals [3]. Currently approved medications include cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and NMDA receptor antagonists (memantine). However, these drugs only offer partial short-term symptomatic improvement. They cannot completely arrest disease progression and are largely ineffective in the advanced stages [4].

This article reviews preclinical and clinical studies of stem cell therapy for AD over the past five years, covering dental Mesenchymal Stem Cells (MSCs), bone marrow MSCs, iPSC-derived microglia, stem cell-derived extracellular vesicles, and other related approaches. Based on monotherapy, stem cell combination therapy with drugs or growth factors, and stem cell-derived extracellular vesicle therapy. The potential of stem cell-based interventions in the treatment of AD is systematically summarized. This review aims to provide theoretical support and directional guidance for future translational research and clinical application.

II. Mechanisms of Stem Cell-Based Therapy

Conventional drugs only provide symptomatic relief, fail to replace lost neurons, and cannot reverse pathological progression. In contrast, stem cell therapy exerts therapeutic effects through multiple pathways, including cell transplantation can reduce Aβ deposition and tau hyperphosphorylation, promote synaptic

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regeneration, and upregulate the levels of BDNF/NGF. Alternatively, stem cell-derived exosomes can regulate inflammation and enhance autophagy, with additional advantages such as being cell-free, low immunogenicity, non-tumorigenicity, and a high ability to penetrate the Blood-Brain-Barrier (BBB).

A review clarified that astrocytes support neurons and clear toxic proteins; microglia exert therapeutic effects in AD via pathological clearance and immune modulation; endothelial vascular cells/pericytes repair the BBB and improve cerebral perfusion; and neural cells achieve global neural repair through multidirectional differentiation. Meanwhile, the review identified key breakthroughs: single-cell sequencing guides precise cell typing, immune-privileged/hypo-immunogenic cells overcome rejection, and intranasal/local transplantation improves delivery efficiency. Accordingly, stem cell-based therapy is currently regarded as the most promising curative strategy for neurodegenerative diseases [5].

III. Research Advances in Stem Cell-Based Therapy for Alzheimer's Disease

A. Stem Cell Monotherapy

Preclinical studies confirmed that Dental Pulp Stem Cells (DPSCs), Stem cells from Human Exfoliated Deciduous teeth (SHED), and Periodontal Ligament Stem Cells (PDLSCs) all exert effects on neural differentiation, neuroprotection, anti-inflammation, mitochondrial repair, and cognitive improvement. Among them, DPSCs are the most extensively studied, while PDLSCs are the least reported. The core mechanisms of dental stem cells in AD treatment include: DPSCs/PDLSCs can differentiate into neuron-like cells that highly express MAP2, NSE, and β-tubulin III, and activate the Wnt/β-catenin pathway to promote hippocampal neurogenesis. Meanwhile, dental stem cells secrete BDNF, NGF, GDNF, and VEGF to enhance neuronal survival; upregulate Bcl-2 and downregulate Bax to inhibit neuronal apoptosis; and secrete neprilysin to degrade $A\beta_{1-42}$, thereby achieving neuroprotection.

In addition, they promote the phenotypic switch of microglia from M1 to M2, reducing the secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), inhibiting the NF-κB and p38 MAPK pathways, and alleviating oxidative stress. They can also directly transfer healthy mitochondria to injured neurons to restore ATP production, reduce ROS levels, repair axonal transport, and reverse tau hyperphosphorylation. However, no human clinical trials have been conducted to date. There are also no unified standards for cell dosage, administration route, and treatment frequency, and data on long-term safety (tumorigenicity, immunogenicity) remain insufficient [6].

Another clinical trial demonstrated that intravenous infusion of allogeneic bone marrow mesenchymal stem cell therapy with laromestrocel in mild AD patients met the primary safety endpoint. The incidence of severe adverse events was not significantly different from that of the placebo group, with no ARIA observed. Treatment alleviated whole-brain and left hippocampal atrophy, improved cognitive and daily living activity scores, reduced neuroinflammation, and protected the neurovascular unit. Nevertheless, this trial had a small sample size, a single ethnic population, and a short follow-up period, leaving long-term efficacy unknown [7].

Microglia continuously monitor the brain microenvironment, phagocytose apoptotic cells and cellular debris, and regulate synaptic formation, pruning, and plasticity, thereby maintaining the development of neural circuits and brain homeostasis [8]. A study showed that human iPSC-derived microglia engineered via CRISPR gene editing could secrete neprilysin in a plaque-responsive manner under the control of the CD9 promoter, enabling precise degradation of Aβ. This strategy overcomes the challenge of BBB delivery and achieves global delivery of disease-modifying proteins throughout the central nervous system [9].

B. Stem Cell Therapy Combined with Drugs or Growth Factors

Stem cell therapy for Alzheimer's Disease (AD) shows efficacy but may cause adverse reactions, including fever, headache, nausea, and immune-related inflammation. However, combination with drugs such as dexamethasone can rapidly suppress immune responses, greatly alleviate side effects, and improve patient tolerance.

In a Phase IIa randomized controlled trial for AD, human umbilical cord blood mesenchymal stem cells were injected into the lateral ventricles of patients. The results showed that MSC treatment did not produce notable clinical cognitive benefits. However, it substantially reduced the expression of core AD biomarkers in Cerebrospinal Fluid (CSF), including $A\beta_{42}$, p-tau, and t-tau. Meanwhile, obvious immune-related adverse reactions such as fever, headache, nausea, and vomiting occurred, but these could be effectively alleviated by combined dexamethasone administration, accompanied by decreased leukocytes and IL-6 in CSF. This study suggests that larger sample sizes, earlier intervention stages, and longer follow-up periods are needed to verify the clinical value of MSCs in the future [10].

In contrast, the combination of autologous stem cells and growth factors causes almost no severe adverse events and is more suitable for elderly AD patients. In a clinical trial investigating Autologous Blood-derived Stem Cells (ABSCs) combined with growth factors for moderate to severe AD, intravenous infusion of ABSCs combined with BDNF/VEGF/IGF-1 markedly improved cognitive scores, reduced cerebral amyloid plaque burden, enhanced cerebral glucose metabolism, and alleviated hippocampal atrophy. Neuroprotective and anti-inflammatory effects were achieved via activation of the PI3K/Akt and MAPK/Akt signaling pathways, with no severe adverse events. However, the study noted that

the follow-up period was only 6 months, requiring longer observation to determine potential long-term adverse effects. In addition, with all participants likely of Asian ethnicity, individual patient characteristics may have introduced bias to the results [11].

C. Stem Cell-Derived Extracellular Vesicle Therapy

Extracellular Vesicles (EVs) are membranous particles secreted by cells that participate in intercellular communication. They can be classified into three subtypes by size: exosomes (30–150 nm), microvesicles (100–1000 nm), and apoptotic bodies (50–5000 nm). Their core components include proteins (CD9, CD63, CD81, MHC molecules, cytokines), nucleic acids (miRNA, mRNA, IncRNA), and lipids (cholesterol, phosphatidylserine). EVs can induce immune tolerance by inhibiting effector T-cell activation and antibody production, leading to acute rejection, chronic rejection, and Antibody-Mediated Rejection (ABMR) [12].

Human iPSC-Neural Stem Cell-derived Extracellular Vesicles (hiPSC-NSC-EVs) can comprehensively block neurodegeneration, oxidative stress, mitochondrial damage, apoptosis, autophagy inhibition, and tau hyperphosphorylation induced by $A\beta_{42}$ oligomers [13]. After entering the mouse brain and being taken up by microglia and astrocytes, hiPSC-NSC-EVs distinctly inhibit four pro-inflammatory pathways via transcriptional reprogramming: the DAM phenotype, NLRP3 inflammasomes, p38/MAPK, and cGAS-STING-IFN-I pathways, without impairing microglial phagocytosis. They persistently reduce Aβ plaques, soluble $A\beta_{42}$, and p-tau levels for up to two months, ultimately fully restoring cognitive and emotional function [14]. A study verified that MSC-EVs can cross the BBB into the mouse brain, reduce hippocampal Aβ plaque burden, decrease the co-localization of reactive astrocytes with plaques, improve cognitive function, and delay AD progression [15].

Despite the lack of no unified standards for the isolation and purification of stem cell-derived EVs, issues like mixed EV subtypes, low yield, and difficult quality control persist. In contrast, stem cell-derived exosomes are highly regarded for AD therapy due to their advantages including low immunogenicity, high biocompatibility, ability to cross the BBB, scalability for modification, and optimization of targeting and drug loading through gene editing [16, 17].

Intraventricular injection of Bone Marrow Mesenchymal Stem cell exosomes (BMSC-exos) inhibits excessive activation of hippocampal microglia and astrocytes, reduces neuroinflammation (IL-1β, IL-6, TNF-α), decreases $A\beta_{1\text{-}42}$ deposition and tau hyperphosphorylation, upregulates BDNF expression, promotes neurogenesis, and significantly ameliorates cognitive decline in a STZ-induced sporadic AD mouse model. However, tail vein injection showed no considerable therapeutic effect, indicating that central local administration is a critical route for BMSC-exos to exert therapeutic effects in AD [18].

IV. Conclusion

Stem cell therapy overcomes the limitation of conventional drugs that only provide symptomatic relief, targeting the core pathologies of AD through cell replacement, anti-inflammation, neuroprotection, and toxic protein clearance, making it a highly promising disease-modifying therapy. Nevertheless, the studies included in this review are of uneven quality, dominated by preclinical animal experiments, with few high-quality large-sample randomized controlled trials. Insufficient data standardization hinders quantitative cross-study comparisons. Most follow-up periods are less than one year, leading to inadequate data on tumorigenic risk, chronic immunogenicity, and long-term cognitive outcomes. Furthermore, differences in therapeutic efficacy between Asian, European, and American populations cannot be analyzed in existing clinical research, and no assessment of manufacturing costs or clinical accessibility has been conducted.

Future research may focus on developing gene-edited engineered stem cells, optimizing combination therapeutic strategies, and conducting large-scale, multi-center, long-term Phase III clinical trials enrolling multi-ethnic populations with extended follow-up, using cognitive function, brain atrophy, and biomarkers as combined endpoints. An individualized therapeutic system should be established, and long-term benefits as well as cost-effectiveness should be systematically evaluated.

Conflict of Interest

The author declares no conflict of interest.

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