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Stem Cell-Based Therapies for Alzheimer's Diseases: Mechanisms, Clinical Advances, Challenges and Future Directions

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Abstract. Alzheimer's disease (AD) and is one of the most prevalent neurodegenerative conditions worldwide. The majority of the current treatments for this illness are symptomatic and have no ability to stop or reverse the disease's course. Although anti-amyloid monoclonal antibodies have recently been approved for AD, their clinical benefits remain modest and may be accompanied by safety concerns, particularly amyloid-related imaging abnormalities, including cerebral oedema and microbleeds. In this context, stem cell-based treatments have become a viable approach to changing the course of disease. This review discusses the core mechanisms and recent preclinical and clinical progress of mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs) and neural stem cells (NSCs) in AD, and further highlights current challenges and future directions, including gene editing, cell-free therapies, biological scaffolds, and organoid-based disease modelling. This review suggests that stem cell-based therapies have promising disease-modifying potential in AD, but their but their broader clinical application remains limited by important translational and safety challenges.

Keywords: Alzheimer's disease, mesenchymal stem cells, induced pluripotent stem cells, neural stem cells

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative condition marked by a slow decline in function and selective loss of neurons. Memory loss, cognitive decline, and behavioral impairment are the main symptoms of AD, which are linked to the intracellular production of neurofibrillary tangles made of hyperphosphorylated tau proteins and the extracellular build-up of amyloid-beta (Aβ) plaques. In the end, these degenerative alterations result in brain atrophy, neuronal loss, and synaptic dysfunction. This illness is a desirable target for regeneration techniques due to its underlying pathogenic processes, which include oxidative stress, mitochondrial failure, and neuroinflammation.

The current pharmacological treatments for AD are largely palliative, emphasizing symptom relief instead of tackling the disease mechanisms needed to halt or slow progression. In AD, standard therapies can provide temporary improvement in cognitive symptoms, but they fail to

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prevent or reverse disease progression. Although the recent development of anti-Aβ monoclonal antibodies, including lecanemab, aducanumab and donanemab, has shown potential in reducing amyloid plaque burden, their clinical benefits on cognition remain controversial, and are often accompanied by adverse effects such as cerebral edema.

Thus, stem cell-based therapies have become increasingly promising. Stem cells possess unique self-renewal and multipotent differentiation capabilities. These properties provide the potential to replace lost neurons and support neural circuit repair. Beyond direct cell replacement, stem cell therapies provide extensive microenvironmental support by mitigating neuroinflammation, stimulating angiogenesis, reducing oxidative stress, and promoting endogenous neurogenesis, offering a comprehensive, multi-targeted approach to treating neurodegenerative diseases [1-4].

This review explores how stem cell-based therapies may target the pathological processes of AD, what progress has been achieved in preclinical and clinical research, and what major challenges still limit their clinical translation. It adopts the method of literature review to synthesize the recent literature to provide integrated content for understanding the current developments in the related field and point out key directions for the safer and more effective development of regenerative strategies in neurodegenerative disorders.

2. Key stem cell types used in Alzheimer's disease research

Among the various stem cell types, mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and neural stem cells (NSCs) have attracted particular attention as leading candidates for regenerative intervention in AD.

2.1. Induced pluripotent stem cells

Using particular transcription factors—Oct4, Sox2, c-Myc, and Klf4—adult somatic cells, such as skin fibroblasts and peripheral blood mononuclear cells, are reprogrammed back into an embryonic-like pluripotent state to create iPSCs. These cells are attractive tools for disease modeling, drug discovery, and cell replacement therapies since they can develop into a variety of neural cell types, including cholinergic neurons. Autologous iPSCs have major advantages in avoiding immunological rejection and lowering ethical concerns related to embryonic stem cells because they can be produced from patient-derived somatic cells. However, cellular heterogeneity, genetic instability, and the possibility of tumorigenesis or teratoma formation continue to be obstacles to the clinical use of iPSCs [5, 6].

2.2. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent adult stem cells that can be obtained from a variety of tissues, including adipose tissue, bone marrow, and the umbilical cord's Wharton's jelly. MSCs are widely favoured in clinical applications because they are easy to isolate and expand, raise relatively few ethical concerns, and exhibit a strong safety profile with a low risk of tumorigenesis. MSCs possess unique immunomodulatory properties, low immunogenicity, and robust paracrine activities, enabling them to secrete neurotrophic factors, cytokines, and extracellular vesicles that facilitate tissue repair, neuroprotection and modulation of inflammatory responses. However, the clinical application of MSCs faces several limitations. Compared to pluripotent stem cells, their ability for neurogenic and neuronal development is extremely limited. Additionally, MSCs exhibit low rates of

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long-term survival and engraftment in vivo, and their therapeutic efficacy can be highly variable depending on the tissue source, donor age, and manufacturing conditions [1, 4].

2.3. Neural stem cells

Multipotent adult stem cells found in particular areas of the central nervous system, neural stem cells (NSCs) have the ability to self-renew and differentiate into neurons, astrocytes, and oligodendrocytes. After transplantation, NSCs can migrate to injured brain areas, replace lost neural cells, and orchestrate synaptogenesis. In addition, NSCs secrete neurotrophic factors that support neuronal survival and reduce neuroinflammation. However, the practical collection of primary human NSCs often involves fetal tissue, which raises both ethical and practical concerns. Furthermore, their clinical application is constrained by their restricted anatomical distribution in the adult brain and the profound difficulties associated with large-scale in vitro expansion and cultivation. Additionally, researchers face significant challenges regarding controlled differentiation; transplanted NSCs often exhibit a limited ability to differentiate into fully functional, synapse-competent mature neurons, and they frequently tend to differentiate into glial cells rather than the intended neuronal lineages [5, 7].

3. Mechanisms of action at the molecular and cellular levels

3.1. Cell replacement and synaptic remodelling

The direct replacement of destroyed neurons and the functional integration of these new cells into preexisting brain networks constitute the basic mechanism of stem cell treatment.

In AD, NSCs and iPSCs have been explored as potential sources of cholinergic neuron-like cells to compensate for the loss of basal forebrain cholinergic neurons. But the therapeutic relevance of large-scale neuronal replacement in AD remains less clearly established.

Additionally, by boosting the expression of important pre- and post-synaptic proteins such synapsin-1, postsynaptic density protein 95 (PSD-95), and growth-associated protein 43 (GAP-43), stem cell therapy may help reduce synaptic dysfunction. These changes have been associated with enhanced synaptic plasticity and activation of signalling pathways such as MAPK/ERK, which are involved in synaptic remodelling, long-term potentiation, and neuronal survival. Through these effects, stem cell therapy may contribute to improvements in learning and memory-related functions [1, 7, 8].

3.2. Paracrine effects, extracellular vesicles, and neurotrophic support

Stem cells may promote brain repair through extensive paracrine signalling without necessarily requiring long-term engraftment. They secrete a range of neurotrophic factors and extracellular vesicles (EVs), including nanoscale vesicles that may facilitate the delivery of microRNAs (miRNAs), proteins, and lipids to injured neural tissues. In detail, growth factors like brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1) have been found to be secreted by stem cells. NGF is particularly important for the survival of basal forebrain cholinergic neurons, whereas BDNF is closely associated with hippocampal neuronal maintenance and synaptic plasticity. These factors may activate receptors such as TrkB and subsequently engage signaling pathways . Activation of these pathways has been associated with reduced apoptotic signaling, including

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suppression of pro-apoptotic mediators such as BAD, BAX, and caspase-9, together with increased expression of anti-apoptotic proteins such as Bcl-2. Through these effects, stem cell-derived trophic support may enhance neuronal resistance to amyloid-beta (Aβ)-induced toxicity. Also, MSC-derived EVs may also exert therapeutic effects through delivery of regulatory miRNAs. For example, miR-29c-3p has been implicated in the downregulation of BACE1, the rate-limiting enzyme involved in Aβ production [9]. Decreased BACE1 expression has been linked to decreased Aβ load and neuroinflammatory responses, as well as stimulation of Wnt/β-catenin signaling. In addition, MSC-derived exosomes carrying miR-21 have been reported to attenuate Aβ-induced neuronal apoptosis, partly through suppression of pro-apoptotic signaling and modulation of NF-κB- and STAT3-related pathways [7-9].

3.3. Immunomodulation

Chronic neuroinflammation, driven by activated microglia and reactive astrocytes, mainly contributes to the pathogenesis of AD. Stem cells and their derived EVs may exert important immunomodulatory effects by reshaping the central inflammatory microenvironment.

The facilitation of a phenotypic shift in microglia from a pro-inflammatory state to a more anti-inflammatory or repair-associated phenotype is one suggested mechanism of stem cell therapy in AD, especially with mesenchymal stem cells like human umbilical cord blood-derived MSCs [6]. It has been observed that these microglia localize near Aβ plaques and express markers linked to tissue healing, such as AMCase, YM-1, and arginase-1 (Arg-1). This phenotypic shift may help control excessive glial reactivity and has been linked to decreased astrogliosis and microgliosis, as seen by decreased expression of ionized calcium-binding adapter molecule 1 (Iba-1) and glial fibrillary acidic protein (GFAP).

Additionally, stem cell therapy has been linked to decreased expression of pro-inflammatory cytokines in the cortex and hippocampus, such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) [6, 10]. Concurrently, there have been reports of elevated levels of anti-inflammatory cytokines, specifically interleukin-10 (IL-10) and interleukin-4 (IL-4). When combined, these modifications may promote neuronal healing and reduce persistent inflammation.

At the molecular level, stem cell-derived exosomes may deliver regulatory miRNAs that modulate inflammatory signalling cascades. For example, exosomal miR-21 has been implicated in suppression of NF-κB nuclear translocation and reduction of STAT3 phosphorylation, thereby attenuating Aβ-induced neurotoxicity. In addition, stem cell-derived EVs have been reported to inhibit NLRP3 inflammasome-related signalling, partly through miRNAs like miR-223-3p, which may reduce downstream inflammatory injury [1, 4, 8, 10].

3.4. Clearance of pathological aggregates

Stem cells and their derivatives may facilitate the clearance of misfolded and toxic protein aggregates that contribute to neurodegeneration. By enhancing proteolytic activity, promoting autophagy, and modulating phagocytic responses, these therapies may help target key pathological hallmarks in AD.

MSCs, NSCs, and their secreted EVs have been reported to produce or enhance the activity of Aβ-degrading proteases, including neprilysin (NEP) and insulin-degrading enzyme (IDE). MSC-derived EVs carrying enzymatically active NEP may be taken up by recipient cells and contribute to reductions in both extracellular and intracellular Aβ levels.

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In order to improve therapeutic efficacy, NSCs may be genetically modified through CRISPR/Cas9 or lentiviral approaches to overexpress and secrete soluble neprilysin (sNEP). After transplantation, these modified NSCs may migrate within the brain and provide broader local delivery of sNEP. Preclinical studies suggest that this strategy can reduce Aβ plaque burden not only at the primary graft site but also in anatomically connected regions, indicating the potential for wider network-level effects.

MSC-derived EVs may also modulate the PI3K/Akt/mTOR signalling axis in host cells, thereby enhancing autophagy and promoting intracellular Aβ degradation. In parallel, stem cell therapy has been associated with a shift in microglia towards a more anti-inflammatory or repair-associated phenotype, which may promote the phagocytic clearance of extracellular Aβ plaques while also reducing inflammatory injury [1, 4, 9-11].

4. Clinical advances in Alzheimer's disease: supporting paracrine and immunomodulatory repair

In AD, recent clinical studies have mainly focused on mesenchymal stem cells (MSCs), and autologous blood-derived stem cell-based approaches. Collectively, these trials provide early clinical evidence that is broadly consistent with the immunomodulatory, paracrine, and aggregate-modulating mechanisms previously observed in preclinical studies [4, 12].

4.1. Immunomodulation and structural preservation: the Lomecel-B trials

Sponsored by Longeveron Inc. in collaboration with the University of Miami Miller School of Medicine, the Phase IIa CLEAR MIND trial evaluated Lomecel-B, an allogeneic bone marrow-derived MSC product. The trial provided early clinical evidence supporting the safety and potential biological activity of this immunomodulatory approach. Notably, unlike the inflammatory side effects seen with some anti-amyloid monoclonal antibody treatments, no incidences of amyloid-related imaging abnormalities (ARIA) were recorded in patients taking Lomecel-B. Furthermore, delivery of Lomecel-B was linked to elevated levels of anti-inflammatory blood biomarkers, such as sIL-2Rα, IL-4, and IL-10. These findings were accompanied by imaging-based signals of structural preservation: volumetric MRI showed that multiple doses of Lomecel-B were associated with a 48.4% slowing of whole-brain atrophy progression ($p=0.005$) and a 61.9% reduction in left hippocampal volume loss ($p=0.021$) at 39 weeks compared with placebo. Although these findings do not by themselves establish a definitive disease-modifying effect, they are consistent with the proposed immunomodulatory and neuroprotective actions of MSC-based therapy [12, 13].

4.2. Aggregate modulation and synaptic recovery: the SMART M-CELL2 trial

This Phase IIa trial evaluated autologous blood-derived stem cells (ABSCs) combined with growth factors including BDNF, VEGF, and IGF-1. The study reported imaging and biomarker changes consistent with modulation of amyloid burden and activation of neurorestorative pathways. Amyloid PET-CT demonstrated a reduction in amyloid plaque burden, with the mean Centiloid value decreasing by 32.4 units ($p<0.0001$) at 6 months. FDG-PET further showed a 14.6% increase in cerebral glucose metabolism (SUVr) in the hippocampus and parietal cortex ($p<0.0001$). Peripheral blood analysis also suggested activation of survival-related signalling, with a 32.1% increase in phosphorylated Akt and a 28.4% increase in phosphorylated ERK, findings that are broadly consistent with PI3K/Akt and MAPK/ERK pathway engagement. Clinically, these biological

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changes were accompanied by improvement in cognitive measures, with MMSE increasing by 4.1 points ($p<0.0001$) and ADAS-Cog decreasing by 6.4 points ($p<0.0001$) [14].

4.3. Cell-free exosome therapies: translating EV-mediated paracrine signalling

Bypassing the need for physical cell engraftment, a registered Phase I/II trial (NCT04388982) evaluated the administration of human adipose MSC-derived exosomes via a non-invasive intranasal route. This harnesses the extracellular vesicle (EV) mechanism, delivering therapeutic microRNAs directly across the blood-brain barrier. At 12 weeks, the medium-dose group exhibited a 2.33-point decrease in ADAS-Cog scores and a 2.38-point improvement in MoCA scores, with no severe adverse events, validating exosomes as a potent, non-invasive therapeutic alternative [4].

5. Challenges

Despite encouraging preclinical findings, the translation of stem cell therapies into widespread clinical practice remains limited by several important biological, technical, and safety-related challenges.

The low survival and engraftment rate of transplanted cells is a significant barrier to therapeutic success. Ischemia, persistent inflammation, oxidative stress, and neurotoxic aggregates such as amyloid-beta (Aβ) plaques, reactive oxygen species (ROS), and inflammatory cytokines like interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) characterize the hostile microenvironment of the neurodegenerative brain. These factors can compromise graft viability and limit long-term functional integration. In addition, mechanical shear stress during syringe-based delivery may distort cell morphology and induce acute apoptotic injury during the transplantation process itself.

For non-autologous transplantation, immune rejection remains a major barrier. Although mesenchymal stem cells (MSCs) are often considered to have relatively low immunogenicity, emerging evidence suggests that they may still provoke inflammatory or innate immune responses under certain conditions. Freeze-thawed MSCs may undergo rapid destruction following exposure to blood, which may further reduce therapeutic efficacy. Moreover, prolonged use of immunosuppressive agents such as tacrolimus or rapamycin is often required to reduce the risk of graft rejection, but this may expose patients to substantial systemic risks, including opportunistic infection.

Induced pluripotent stem cell (iPSC)-based therapies carry an inherent risk of tumorigenesis and teratoma formation. If residual undifferentiated cells remain in the final therapeutic product, or if oncogenic factors used during reprogramming, such as c-Myc, become reactivated, the risk of abnormal cell growth may increase. In addition, prolonged in vitro expansion may contribute to genomic instability, including karyotypic abnormalities, copy number variation, and other acquired genetic alterations, all of which raise important safety concerns for clinical application.

The blood-brain barrier (BBB) presents a major challenge for non-invasive systemic delivery, as intravenously administered cells are often sequestered in peripheral organs such as the lungs, liver, or spleen before reaching the central nervous system. By contrast, stereotactic intraparenchymal injection can bypass the BBB and achieve more localised delivery, but it is inherently invasive. These neurosurgical procedures may induce secondary tissue injury, local neuroinflammation, oedema, and microhaemorrhage, thereby potentially worsening neurological vulnerability in an already diseased brain [4, 5, 6, 15].

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6. Conclusion

In summary, stem cell therapy offers a promising and multifaceted approach to the treatment of Alzheimer's by addressing both neuronal loss and the dysfunctional neural microenvironment that drives disease progression. Current evidence suggests potential therapeutic benefits through cell replacement, trophic support, immunomodulation, and pathological aggregate clearance. Nevertheless, the field remains constrained by major translational challenges, including safety, engraftment efficiency, functional integration, reproducible large-scale manufacturing, and unresolved ethical considerations.

Looking ahead, future clinical progress may depend on the development of more precisely engineered cell products, improved delivery systems, biomarker-guided patient selection, and rigorous long-term evaluation. Rather than serving as a standalone cure in the immediate future, stem cell-based and cell-free strategies are more likely to become part of an increasingly personalised and disease-modifying therapeutic framework for Alzheimer's disease.

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