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ADVANCEMENTS IN STEM CELL THERAPY FOR ALZHEIMER'S DISEASE

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ABSTRACT

The advancement of stem cell technologies has generated significant interest in their potential application for treating neurodegenerative diseases such as Alzheimer's disease (AD). This review evaluates various stem cell sources and delivery methods, focusing on bone marrow-derived mesenchymal stem cells (BM-MSCs) and human umbilical cord-derived mesenchymal stem cells (hUC-MSCs). BM-MSCs are notable for their ability to modulate microglial activation, secrete neuroprotective factors, and reduce neuronal apoptosis, although challenges persist in precise targeting and potential embolism risks. In contrast, hUC-MSCs exhibit lower immunogenicity and demonstrate enhanced efficacy in increasing neuroprotective proteins and antioxidants, thus supporting neuronal survival and reducing oxidative stress. Innovative delivery methods, including magnetic targeted cellular delivery (MTCD) and intranasal administration, have been developed to enhance the precision of stem cell localization and distribution. These techniques improve the targeting of therapeutic cells to affected brain regions and facilitate the clearance of amyloid-beta plaques. Despite the progress in stem cell-based therapies, further research is needed to address delivery challenges and optimize therapeutic outcomes. The continued exploration of these technologies and methodologies will be crucial in advancing treatment strategies for AD and related neurodegenerative disorders.

KEYWORDS: Stem Cell Therapy, Alzheimer's, BM-MSCs, HUC-MSCs, IPSCs, ESCs, Cognitive Decline, Memory Loss

INTRODUCTION

Alzheimer's disease (AD) leads to a progressive decline in critical functions, including language, mobility, and balance, accompanied by significant mood alterations and behavioral disturbances. As the disease advances, individuals often withdraw from family and social interactions, and death typically follows 3-9 years after diagnosis. AD is responsible for 60-70% of all dementia cases, making it the most common form. Prior to confirming an AD diagnosis, other potential causes of dementia—such as systemic lupus erythematosus, vascular disease, Parkinson's disease, syphilis, HIV, dementia with Lewy bodies, and Creutzfeldt-Jakob disease—should be ruled out. Additionally, potentially reversible causes, including hypothyroidism, vitamin B-12 deficiency, metabolic imbalances, and heavy metal exposure, should be considered. Diagnosis of AD typically involves a comprehensive approach, incorporating medical history, physical exams, cognitive assessments like the Mini-Mental Status Examination (MMSE), and diagnostic imaging. Managing risk factors such as obesity, hypertension, type 2 diabetes, and smoking has been associated with a reduced risk of AD. While the etiology of AD is still not fully understood, several key pathological mechanisms have been identified. These include (a) hyperphosphorylation of tau proteins leading to neurofibrillary tangles; (b) accumulation of beta-amyloid plaques resulting from amyloid precursor protein (APP) cleavage; (c) neuroinflammation triggered by activated microglia producing cytokines such as IL-1β and TNF-α; and (d) progressive neuronal and synaptic loss. While genetics play a significant role, factors such as comorbidities—head trauma, hypertension, and depression—as well as lifestyle choices may also influence disease onset. Despite the availability of five pharmacological treatments for symptom management, no current therapies are proven to modify the underlying progression of AD. This limitation has driven research into novel treatments such as stem cell therapy (SCT). Stem cells, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs), have been explored for their potential to mitigate the effects of AD. ESCs, derived from early-stage embryos, are classified as totipotent or pluripotent based on their differentiation potential. iPSCs, reprogrammed from mature somatic cells, closely resemble ESCs in their ability to differentiate into various cell types. MSCs, sourced from bone marrow and other tissues, have demonstrated the capacity to form mesodermal tissues such as bone and

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cartilage. At the same time, NSCs generate neurons and glial cells.

Recent advancements suggest that adult-derived telomerase-positive stem cells, including totipotent stem cells (TSCs), pluripotent stem cells (PSCs), and mesodermal stem cells (MesoSCs), may offer a promising alternative to conventional SCT approaches. In preclinical studies, these cells have shown the ability to differentiate into neuronal cell types, repair damaged brain tissues, and potentially restore cognitive function. MesoSCs, in particular, have exhibited reparative properties in various conditions, including cardiovascular and pulmonary disorders, as well as autoimmune diseases. Given these findings, telomerase-positive stem cells may represent a viable therapeutic avenue for reversing the cognitive decline observed in AD patients, potentially evidenced by improvements in MMSE scores. While SCT remains in the early stages of clinical development, its potential to target the underlying mechanisms of AD is noteworthy. Ongoing research continues to refine stem cell-based approaches, aiming to develop therapies that may offer meaningful improvements in patient outcomes. Though challenges remain, SCT represents a forward-looking strategy for addressing the unmet needs of Alzheimer's disease treatment.

LITERATURE REVIEW

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss, with hallmark features including amyloid plaques and neurofibrillary tangles. The disease progresses through preclinical stages, mild cognitive impairment (MCI), and eventually advanced AD, which significantly impacts daily functioning and behavioral health [1]. As of 2019, AD affected 55 million people globally, with projections indicating a rise to 139 million by 2050. Many cases remain undiagnosed, particularly in low- and middle-income regions. AD represents 75-80% of dementia cases, primarily affecting individuals over 65 and imposing a substantial socio-economic burden. Early detection and effective treatment are critical. The cognitive decline in AD is linked to amyloid-beta (Aβ) plaque accumulation and tau protein hyperphosphorylation, leading to neuroinflammation and neuronal damage. Aβ is produced through the cleavage of amyloid precursor protein (APP) and promotes tau protein hyperphosphorylation, forming neurofibrillary tangles [2]. Diagnostic methods include CT, MRI, and PET scans, with brain biopsy being definitive. AD treatment strategies include managing cognitive symptoms and behavioral issues. Cholinesterase inhibitors like rivastigmine and galantamine enhance acetylcholine levels, while memantine, an NMDA receptor antagonist, mitigates excitotoxicity. Novel therapies target amyloid-beta and tau pathology through BACE-1 inhibitors, γ-secretase inhibitors, and immunotherapeutic agents. NSAIDs and other agents addressing neuroinflammation and cardiovascular risk show mixed results Stem cell therapy, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs), is emerging as a promising approach. Stem cells can regenerate damaged neurons and target multiple disease mechanisms. Advances in stem cell therapy, such as enhanced delivery methods and genetic modifications, offer the potential for significant therapeutic benefits. In summary, while conventional pharmacological treatments remain integral to Alzheimer's disease management, emerging therapeutic approaches, including advanced stem cell therapies and novel delivery systems, offer significant potential for improved outcomes [3]. The integration of these innovative strategies may enhance our capacity to manage AD and advance the field of neurodegenerative disease treatment.

METHODS, MATERIALS AND INVESTIGATIONS

Autologous (TSCs, PSCs, and MesoSCs) or allogeneic (TSCs and PSCs) telomerase-positive stem cells, derived from adult sources, were utilized in an investigation conducted under a rigorously approved IRB protocol, targeting neurodegenerative diseases, with a specific focus on Alzheimer's dementia [4]. Eligible participants were males and females aged 18 to 120 who had received a clinical diagnosis of Alzheimer's disease. The study cohort comprised two female subjects, aged 72 and 92, alongside two male subjects, aged 58 and 75. Cognitive performance was assessed using the Mini-Mental State Examination (MMSE), a 30-point scale that quantifies cognitive impairment. At baseline, participants' MMSE scores ranged from 0 to 25, with neither of the female participants capable of ambulating without assistance. Ambulation for the male participants was not evaluated at the outset. Participants were instructed to adhere to a preparatory protocol involving the daily intake of combinatorial nutraceuticals (CN) (DFRD, Macon, GA) for a minimum of 30 days before the initial harvest of stem cells [5]. This regimen was designed to enhance the endogenous proliferation of telomerase-positive stem cells within the participants' connective tissues, thereby transforming their bodies into a "bioreactor" for the expansion of these regenerative cells. Participants were further advised to maintain optimal hydration for two weeks preceding stem cell extraction, ensuring efficient blood withdrawal during the procedure. Vigorous physical activity was restricted during the two-week window surrounding stem cell collection to maximize tissue repair response. Eighteen hours before the stem cell harvest, participants consumed glacial caps (GC, DFRD) to promote the mobilization of telomerase-positive stem cells into circulation. The 72-year-old female and both male participants received autologous transplants of telomerase-positive stem cells, while the 92-year-old female underwent one autologous transplant in addition to six allogeneic transplants. The allogeneic stem cells, harvested from the 92-year-old participant's identical twin daughters, were carefully screened for blood type (A-positive), gender, and the absence of infectious diseases. Blood collection for telomerase-positive stem cell harvesting was performed via venipuncture, with volumes ranging from 210 to 420cc, depending on the participant's body weight. The stem cells were separated from other blood components using FDA-compliant, minimally manipulative techniques, incorporating zeta potential, gravity sedimentation, and differential gradient centrifugation with sterile saline and serum. The cells were then classified into totipotent stem cells (TSCs), pluripotent stem cells (PSCs), and mesodermal stem cells (MesoSCs), followed by activation [6]. Adherence to the informed consent guidelines specific to telomerase-positive stem cell therapy was mandatory

for both recipients and donors [See Figure 1].

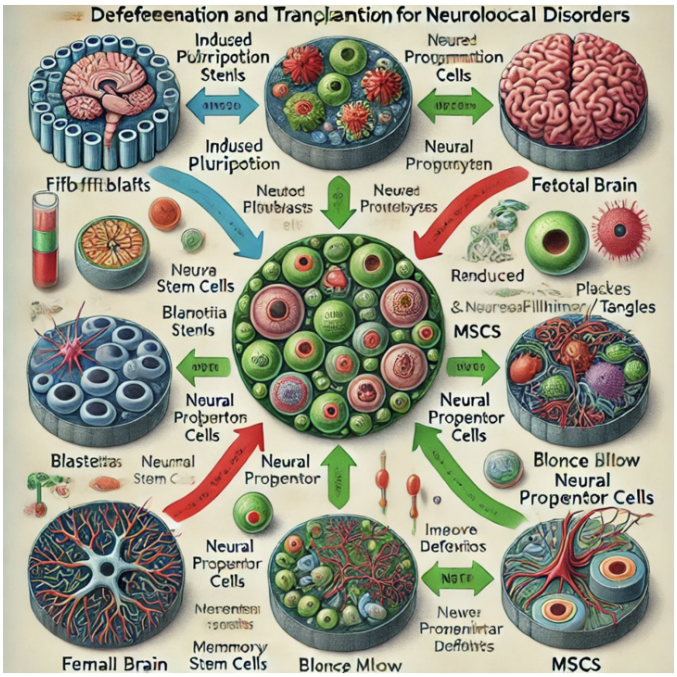

Figure 1: Illustration of the differentiation and transplantation pathways of stem cells for neurological disorders

These guidelines outlined a comprehensive protocol aimed at optimizing the yield and regenerative potential of the harvested cells. Key restrictions included the avoidance of substances such as alcohol, tobacco, recreational drugs, and caffeine, as these may either impair stem cell viability or hinder their differentiation. Corticosteroids were also limited, as they can prematurely drive the commitment of TSCs to specific cell lineages. The entire procedure, from cell collection to administration, spanned approximately 24 hours for male participants and 72 hours for female participants. The administration of telomerase-positive stem cells involved intranasal infusion for neurogenic therapy. Concentrated cell suspensions of 0.5cc were split evenly between the two nostrils, with recipients placed in the reverse Trendelenburg position to facilitate the targeted delivery of cells to the olfactory epithelium. Concurrently, MesoSCs and PSCs were administered intravenously in 250cc of heparinized saline, typically via the median cubital vein. Cognitive function was monitored using the MMSE, a comprehensive assessment tool that evaluates multiple domains of cognition, including attention, memory, orientation, and the ability to follow complex commands [7]. The MMSE scale ranges from 0 to 30, with lower scores reflecting more severe cognitive impairment. Participants were evaluated before, during, and after treatment to determine the degree of cognitive change over time.

RESULTS

At baseline, all participants exhibited significant cognitive impairment, with MMSE scores of 0/30 for the 58-year-old male and both female participants, and 25/30 for the 75-year-old male. The two female participants also demonstrated considerable gait instability, requiring assistance to walk [8]. Post-treatment, all participants displayed varying degrees of cognitive improvement, as reflected by their MMSE scores. The 75-year-old male's MMSE score improved to 29/30, while the female participants exhibited a more pronounced response to telomerase-positive stem cell therapy. Both female participants regained the ability to ambulate independently, and their cognitive function, as measured by MMSE scores, showed marked improvement [9]. Notably, the 72-year-old female achieved a score of 30/30, demonstrating full cognitive recovery, while the 92-year-old female also showed significant cognitive restoration. In the months following treatment, however, cognitive deterioration recurred in participants after cessation of therapy, although no adverse events were reported. One participant also experienced enhanced cardiac function during the study [10].

Embryonic Stem Cells (ESCs)

The application of embryonic stem cells (ESCs) in rodent models of brain injury has demonstrated promising results, particularly in the restoration of functional activity. However, their use in human therapies has been limited. When undifferentiated ESCs are transplanted into individuals, they tend to form teratomas, which are tumor-like growths. To mitigate this risk, researchers have developed protocols where ESCs are pre-differentiated in vitro into neural stem cells (NSCs) and subsequently into cholinergic neurons [11]. These cholinergic neurons, when transplanted, have shown improvements in spatial memory in both rodent models of Alzheimer's disease (AD) and in human trials. Despite these promising outcomes, the use of ESCs in human transplantation raises ethical concerns, in addition to the potential complications associated with immunosuppressive treatments and the risk of graft-versus-host disease (GVHD) when using cells from allogeneic donors. ESCs, which are derived from the inner cell mass of blastocysts, exhibit pluripotency, meaning they can differentiate into multiple cell types. Specifically, ESCs can generate cholinergic neurons and γ-aminobutyric acid (GABA) neurons, both of which have been shown to improve memory and spatial learning in AD models. However, direct transplantation of undifferentiated ESCs is generally avoided due to the high risk of teratoma formation. To address this, scientists differentiate ESCs into neural progenitor cells (NPCs), which then produce neurons and glial cells [12]. This strategy significantly reduces the risk of tumor development while still harnessing the regenerative potential of the stem cells. The differentiation of neural stem cells from ESCs into cholinergic neurons is driven by specific factors, including retinoic acid (RA) and Sonic Hedgehog (Shh), as well as leukemia inhibitory factors (LIFs) [13]. This targeted differentiation makes ESC-derived cells suitable candidates for cell replacement therapies in neurodegenerative diseases like AD. ESC-derived neurons integrate into existing neural networks in regions such as the hippocampus and vitreous, contributing to neural repair and memory improvement. To enhance the specificity of ESC differentiation into neuroectodermal cells, researchers employ specialized culture media like N2B7, which is serum-free. Serum-free conditions inhibit bone morphogenetic protein (BMP) signaling, while the presence of fibroblast growth factor (FGF) and Notch signaling promotes the transition of ESCs into NSCs. A more efficient method for generating NSCs involves using a modified N2B7

medium called RHB-A in monolayer cultures of ESCs. The differentiation of ESCs into basal forebrain cholinergic neurons, which are critical for memory and learning, can also be induced by exposing the cells to retinoic acid. In cancer research, ESCs have been generated from reprogrammed cancer cells using miR302, a microRNA that controls the expression of over 445 genes, including those involved in maintaining pluripotency, such as HMG-box, Forkhead box, and LIM-homeobox family genes. This discovery underscores the versatility of ESCs and their potential applications in both regenerative medicine and oncology [14].

Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells (iPSCs) offer a promising avenue for generating autologous, patient-specific pluripotent cells, sidestepping the ethical dilemmas associated with embryonic stem cells (ESCs) and the immune-related complications linked to immunosuppressants and graft-versus-host disease (GvHD) when utilizing allogeneic donor cells. However, similar concerns arise with the risk of teratoma formation and GvHD when allogeneic iPSCs are introduced in their naïve state. Nonetheless, the potential of autologous iPSCs, pre-induced before transplantation, has shown significant promise in producing various tissues both in vitro and in vivo [15]. Neurons derived from iPSCs are structurally and functionally mature, capable of forming active synaptic connections. By utilizing specific inductive agents in culture, these iPSCs can be directed into distinct neuronal subtypes. Yet, neurons derived from iPSCs of Alzheimer's disease (AD) patients display characteristic neuropathologies, including elevated tau phosphorylation, abnormal amyloid-beta accumulation, reduced neurite outgrowth, and altered electrophysiological properties, limiting their application as effective neuronal replacements in AD models [16].

iPSC Reprogramming and Applications

iPSCs, derived from the patient's own somatic cells, offer a novel platform for studying the genetic underpinnings of neurodegenerative diseases. Traditional models, such as transgenic animals, fail to fully recapitulate human disease pathology, thus iPSCs present a more accurate alternative for studying disease mechanisms. Like ESCs, iPSCs possess the ability to self-renew and differentiate into various cell types. Reprogramming somatic cells into iPSCs typically involves the introduction of specific transcription factors or the use of small molecule combinations, which are favored for their non-immunogenic properties. While the efficiency of small molecule methods is lower compared to viral approaches, protein-based strategies are also employed to establish iPSCs [17]. Lentiviral vectors, in particular, have proven more efficient than retroviral systems for gene delivery, as they reduce the likelihood of transgene silencing. Non-viral reprogramming methods, including the delivery of mRNA and proteins directly to somatic cells, have emerged as superior alternatives, offering greater safety and efficiency. Techniques such as piggyback transposons are preferred for avoiding transgene reactivation, a significant issue that can lead to tumor formation. First achieved in 2006, the reprogramming of fibroblasts into iPSCs using the Yamanaka factors (Oct-4, Sox-2, Klf-4, and c-Myc) revolutionized the field. Modifications of microRNA levels have also been explored to enhance reprogramming efficiency beyond that of traditional transcription factor-based methods [18]. Reprogramming occurs across multiple levels: expression of oncogenes such as c-Myc and Klf-4 to generate iPSCs; epigenetic alterations, including DNA methylation and acetylation, that may inadvertently activate retroelements in the genome; poor DNA repair mechanisms, which increase the risk of mutations; and extraction of iPSCs from patient-derived somatic cells. These iPSCs can be used to study disease mechanisms and therapeutic potential across species, as well as in human models.

Genome Editing and Disease Modeling

Advanced genome editing tools, such as CRISPR/Cas9, zinc-finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs), are employed to correct mutations in iPSCs. Proteins isolated from ESCs can also be used to reprogram fibroblasts, showing promising results in improving cognitive function in models of neurodegeneration. For example, protein-based iPSCs have shown the ability to differentiate into glial cells, enhance oligodendrocyte gene expression, and facilitate amyloid-beta clearance in AD models. Alternative methods to c-Myc have been developed due to concerns about its oncogenic potential. Techniques utilizing retinoic acid signaling, for instance, help maintain the pluripotency of iPSCs. Other signaling pathways, such as PI3K/Akt, preserve iPSC identity and reduce the risks associated with uncontrolled cell proliferation. The flexibility of iPSCs, which can be sourced from patient-derived fibroblasts or even renal exfoliated cells in urine, offers a less invasive and economically feasible approach for cell generation [19] [see Figure 2].

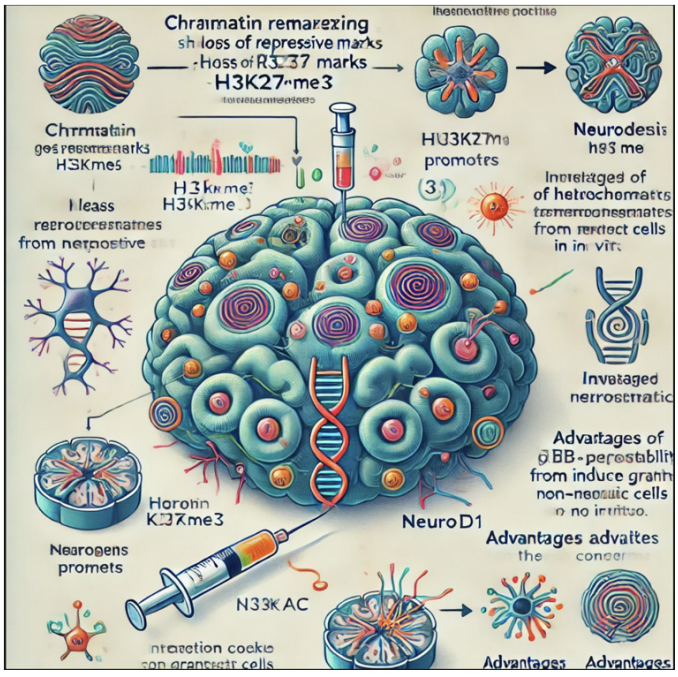

Figure 2: Illustration of the process of neurogenesis induced by the transcription factor NeuroD1

Challenges in Alzheimer's Disease Models

Despite their potential, iPSCs derived from patients with Alzheimer's disease exhibit several disease-specific abnormalities, including increased amyloid-beta accumulation, tau hyperphosphorylation, and oxidative stress. These pathological features, observed in neurons derived from both familial and sporadic AD patients, limit the utility of iPSCs for direct neuronal replacement therapies [20]. Additionally, astrocytes generated from AD patients' iPSCs have been shown to exacerbate neuronal damage, releasing amyloid-beta and inflammatory cytokines that harm healthy neurons. Nonetheless, iPSC-derived models have provided valuable insights into the heterogeneity of AD, revealing that different disease subtypes may require tailored therapeutic approaches [21]. These models serve as powerful tools for drug testing, early disease diagnosis, and precision medicine, offering researchers the ability to dissect the complex molecular underpinnings of Alzheimer's disease and develop more targeted interventions.

Bone Marrow-Derived Mesenchymal Stem Cells

Bone marrow-derived mesenchymal stem cells (BM-MSCs) hold promise for addressing neurodegeneration and cognitive impairments associated with Alzheimer's disease (AD). These cells are capable of replacing damaged neurons and enhancing recovery of cognitive functions. Transplantation of BM-MSCs can modulate microglial activation and improve symptom management. Pre-treatment of BM-MSCs with melatonin has been observed to improve cognitive performance, learning, and memory in AD patients. Additionally, BM-MSCs can migrate to the brain, differentiate into various neuronal subtypes, and secrete growth factors that elevate acetylcholine levels. Recent research is exploring the combined use of BM-MSCs and exosomes to address cellular dysfunction [22]. Exosomes, due to their hydrophobic nature and limited water solubility, can effectively cross the blood-brain barrier (BBB). They carry various proteins and genetic materials that can potentially mitigate AD progression. Exosomes, naturally secreted in bodily fluids such as urine and saliva, avoid lysosomal degradation, fuse with neuronal membranes, and do not provoke atypical immune responses. Exosomes derived from BM-MSCs, which carry miR-29c-3p, have been shown to enhance neuronal expression of this miRNA, typically reduced in AD. This mechanism inhibits BACE-1, stimulates the Wnt/β-catenin signaling pathway, and decreases amyloid-beta (Aβ1–42) levels and inflammatory cytokines, thus offering symptomatic relief in AD. BM-MSC transplantation has also been associated with improved memory and behavioral functions in AD patients. Hematopoietic stem cells from bone marrow can be directed to differentiate into microglia, which then help clear Aβ plaques from the brain [23]. These stem cells, when combined with growth factors, have shown the potential to rectify memory deficits in AD mouse models. Exosomes from microglia are involved in neurite outgrowth, neuronal activity regulation, and immune system activation. Additionally, nanovesicles containing small interfering RNAs (siRNAs) within exosomes are being investigated for their therapeutic potential in AD [24].

Human Umbilical Cord Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) derived from human umbilical cords are readily extracted from cord blood postnatally. These cells secrete soluble ICAM (sICAM), which enhances neprilysin (NEP) activity in microglia, thereby facilitating the clearance of amyloid-beta (Aβ) [25]. In vitro studies indicate that umbilical cord-derived MSCs secrete galectin-3 in response to Aβ-42 exposure, mitigating its neurotoxic effects. Compared to adult stem cells, umbilical cord MSCs exhibit a lower risk of immune rejection due to their less mature state and reduced antigenicity. Human umbilical cord MSCs (hUC-MSCs) have demonstrated notable advantages in the treatment of Alzheimer's disease (AD) by increasing levels of Sirt-1, brain-derived neurotrophic factor (BDNF), and synaptophysin, which contribute to neuronal growth in the hippocampus. These cells also alleviate oxidative stress by enhancing superoxide dismutase (SOD) activity. The transfection of MG53 (Mitsugumin-53) into UC-MSCs augments their therapeutic efficacy by activating the Nrf-2 pathway, which regulates a range of antioxidant proteins. This modification also rejuvenates senescent UC-MSCs, thereby offering enhanced protection against neurodegenerative damage in AD models. Furthermore, encapsulation of UC-MSCs in sodium-alginate and hyaluronic acid scaffolds has been found to improve cell proliferation, survival, and neuronal integration, which positively impacts memory and learning in traumatic brain injury (TBI) mouse models with AD [26]. Clinical trials have reported that thrombospondin in hUC-MSCs protects neuronal synapses from harmful Aβ aggregates. In a phase-1 clinical trial conducted in South Korea, nine patients with probable AD received hUCB-MSC injections into the bilateral hippocampus. Follow-up evaluations over 24 months showed no adverse effects, with participants remaining free from both long-term and acute side effects [27].

Delivery of Stem Cells

The efficacy of neural progenitor cell (NPC) therapies is significantly influenced by the method of their delivery. Various administration routes are employed, including intravenous, intraarterial, intracisternal, intraperitoneal, intraventricular, and intracerebral injections [28]. Intravenous delivery is prevalent, with cells either infused directly into the affected area or distributed systemically. While direct arterial injection facilitates high cell concentrations, it often results in suboptimal targeting accuracy and increased risk of embolism. To improve targeting precision, mesenchymal stem cells (MSCs) can be conjugated with superparamagnetic iron oxide nanoparticles (SPIONs) and green fluorescent proteins (GFP), and subsequently directed using an external magnetic field (EMF) [29]. This technique enhances MSC localization at specific sites. MRI studies reveal that over 80% of umbilical cord-derived MSCs, tagged with SPIONs and GFP and exposed to EMF, achieve precise targeting of damaged tissues, unlike their untagged counterparts Magnetic targeted cellular delivery (MTCD), involving dextran-coated iron SPIONs with MSCs, has shown effectiveness in directing cells to cerebral regions such as the hippocampus. This method has demonstrated the potential to ameliorate memory and cognitive deficits in Alzheimer's disease (AD) patients [30]. Intranasal administration of human neuronal stem cells (hNSCs) represents another advanced strategy. This approach significantly reduces amyloid-beta (Aβ) accumulation in critical brain regions

including the cortex, hippocampus, thalamus, olfactory bulb, and cerebellum. Additionally, it promotes pericyte activity, which aids in Aβ plaque clearance and neuronal regeneration. Scaffolding technologies that replicate the natural extracellular matrix (ECM) are also utilized [31]. These scaffolds stabilize stem cells, facilitate the controlled release of growth factors, and ensure sustained delivery of bioactive molecules, thereby maintaining critical cell-cell and cell-matrix interactions essential for effective AD treatment.

CONCLUSION

The integration of advanced stem cell technologies into therapeutic strategies holds considerable promise for addressing neurodegenerative diseases such as Alzheimer's disease (AD). Both bone marrow-derived mesenchymal stem cells (BM-MSCs) and human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) exhibit unique advantages. BM-MSCs, through mechanisms such as modulating microglial activation and secreting neuroprotective factors, have demonstrated potential in improving cognitive function and reducing neuronal apoptosis. However, the challenge of ensuring precise targeting and mitigating risks associated with their delivery remains. hUC-MSCs, with their lower immunogenicity and ability to enhance levels of neuroprotective proteins and antioxidants, offer a compelling alternative. They are particularly noted for their capacity to reduce oxidative stress and promote neuronal survival. Their delivery can be optimized through innovative methods such as magnetic targeting, which enhances localization accuracy, and intranasal administration, which facilitates distribution to critical brain regions and supports the clearance of amyloid-beta plaques. Technological advancements in delivery methods, including magnetic targeted cellular delivery (MTCD) and scaffold-based approaches, further refine the effectiveness of stem cell therapies. These methods ensure better localization of stem cells, support the sustained release of bioactive factors and improve overall therapeutic outcomes. In conclusion, while significant progress has been made in harnessing stem cell technologies for neurodegenerative diseases, ongoing research is essential to refine these approaches, address delivery challenges, and enhance therapeutic efficacy. The continued exploration of stem cell applications and delivery innovations will be pivotal in advancing treatment options for AD and related conditions.

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This publication is for my grandfather, whose meaningful life touches us all.

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