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Stem Cell Therapy as a Target for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder, a form of dementia commonly affecting people aged 40-65. Growing more prevalent in society, approximately 6.2 million Americans aged 65 and older live with AD. AD is a progressive, long-term neurological disorder that worsens cognitive skills, memory, and communication abilities, leading to a performative decline in daily tasks. Characterized by the accumulation of extracellular amyloid beta ($A\beta$) plaque and neurofibrillary tangles (NFTs) of tau in the central nervous system. AD accounts for neuronal death in the brain. Unfortunately, even with its detrimental impacts, clinical trials of therapeutic drugs are still to be tested and not available to the public. Current research on stem cell transplantation has shown to alleviate neuropathology and is explored as a prospective treatment for AD. This literature review assesses the important uses of stem cell therapy for AD patients to provide a new clinical approach for future treatment. Further clinical research should be conducted on the long-term outcomes of stem cell therapy for deeper analysis of its therapeutic effects for AD.

1. Introduction

Alzheimer's Disease (AD) is a form of dementia affecting memory and behavioral capabilities, resulting in the deterioration of cognitive function. As of 2023, this neurodegenerative disease has impacted around 50-75% of the United States population.[1] Symptoms of AD are characterized by impairments in memory, which interfere with daily activities and other cognitive fields—this is linked through a reduction in brain volume of such individuals.[2] The risk of AD increases with age, which doubles about every five years above the age of 65. With increasing age, the hippocampus' cognitive function declines, a common trait of neurodegenerative disorders and AD. Patients with AD tend to live within 5–12 years of the onset of AD symptoms due to declining performance of basic functions and brain incompatibilities.[3] The hippocampus serves as the main part of the brain responsible for memory. The cerebral cortex and hippocampus are closely associated with cognitive function and neurogenesis (neuronal formation) in the brain.[4] Reduction of brain mass is often indicated through neural death and synapse degradation of the hippocampus. It has been commonly noted that hippocampal degeneration is an indication of AD.[2]

Diagnosis of AD is characterized in the brain by an increase in the buildup of proteins between neurons.[5] AD can be examined through chronic neuroinflammation with neuronal loss of the extracellular senile plaques (SPs), amyloid-β peptide (Aβ) deposits, and tau proteins that form neurofibrillary tangles (NFTs), which lead to extensive metabolic dysfunctions. NFTs (abnormal production of tau protein neurons) contribute to neural death, inducing progressive deterioration of memory and cognitive ability.[6] In AD, degeneration occurs with the accumulation of β-amyloid (Aβ) and tau proteins in the brain. Senile plaques of protein fragments beta-amyloid (Aβ) induce the build-up of tau proteins leading to AD patients' nerve cells shrinking and dying, spreading to the entire brain. Neural networks of AD patients are impaired due to a lack of the transmitter acetylcholine, which plays an important role in intercellular signaling.[7,8]

In the gene encoding Aβ precursor protein (APP), mutations of this gene can cause hereditary cerebral hemorrhage, leading to Aβ build-up.[9]

Hereditary cerebral hemorrhage with amyloidosis (Aβ buildup) showed that APP mutations could cause an abnormal amyloid deposition, albeit mainly outside the brain parenchyma.[10] Altered APP processing and Aβ accumulation predate tau. The mechanism for the aggregation of AD is characterized by the "amyloid cascade hypothesis" (Figure 1). According to this hypothesis, the extracellular deposition of Aβ is a critical and central event in the disease's progression, leading to the formation of neurofibrillary tangles, causing neuroinflammation, cell death, and dementia.[11,12] Abnormal processes or mutations of processing APP and Aβ peptides hold significant development for AD. Yet, it is suggested that targeting APP processing to treat AD can result in tumor development.[13] The accumulation of Aβ peptides and tau are caused by disturbances of homeostasis from APP degradation. The clinical manifestations of AD are progressive and clinical trials are still ongoing.

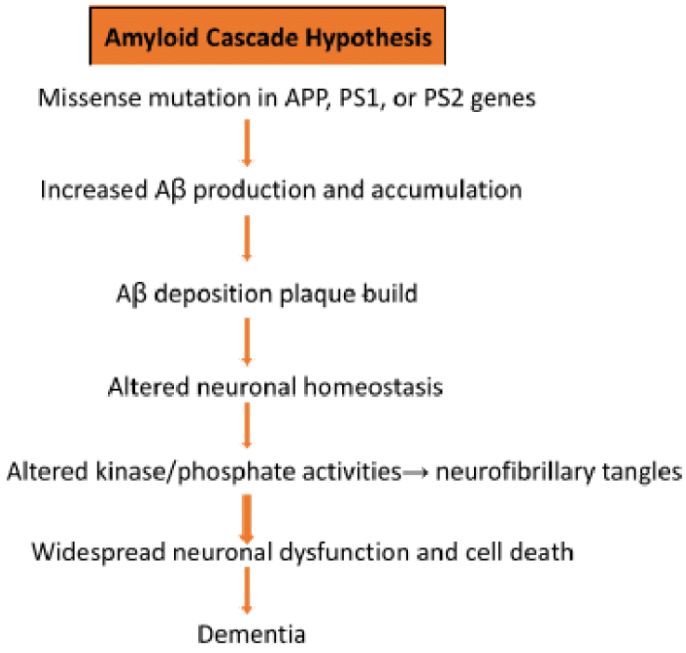

Figure 1: Summary sequence of events of AD development via the amyloid cascade hypothesis, presenting the significance of Aβ plaque buildup in AD symptoms. As previously discussed, APP genes encode amyloid precursor proteins that are the main building block of Aβ plaques. PS1 and PS2 genes express presenilin-1 and presenilin-2 proteins respectively. Mutations in the aforementioned genes lead to exemplified Aβ plaque production, leading to neuronal cell dysfunction and death.

Stem cells are immature cells with self-renewal capabilities and the ability to differentiate into various cell types. Stem cell transplantation can mobilize endogenous stem cells in adult brains and provides a promising form of therapy for other neurodegenerative diseases, such as Parkinson's Disease.[14,15] For cells to be labeled as stem cells, they must have unlimited self-renewal and encompass specialized cell types.[16] Pluripotent stem cells are common regeneration approaches in their abilities to differentiate into all cell types, which naturally don't last before differentiating to a specialized stem cell.[16] They differentiate into cells of all germ layers, making these types of cells effective for stem cell therapies through autologous or allogeneic transplantation.[17, 18] In this instance, stem cells can repair neural damage through cell division, which the most common approach to stem cell therapy.

2. Discussion

AD develops as a process of many factors by high neuropathological diversifications. Therapeutic stem cells can differentiate into other body cells, which brings a promising approach to stimulating neurogenesis circuitry. To develop stem cell therapy, a suitable cell source must be determined. During literature searches, common stem cell types were noted: brain-derived neural stem cells (NSCs), mesenchymal stem cells (MSCs), and embryonic stem cells (ESCs) (Figure 2).

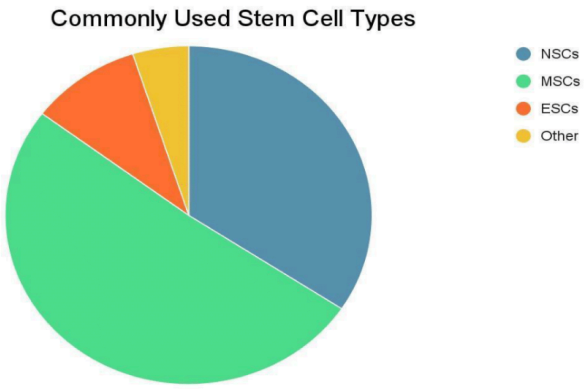

Figure 2: The most common stem cell types are brain-derived neural stem cells (NSCs), mesenchymal stem cells (MSCs), or embryonic stem cells (ESCs). Transplantation of these

cells has been investigated as a prospective therapeutic approach for neurodegenerative disease, including cases with AD.[35]

2.1 Neural Stem Cells

NSCs are multipotent and self-renewing cells capable of differentiating neurons in the brain's hippocampus.[13] AD generates approximately half the rate of neurogenesis compared to normally aging individuals. NSCs can ameliorate AD symptoms by regenerating lost or damaged cells.[6] Mechanisms of improved cognition involving enhanced hippocampal synaptic density are mediated through brain-derived neurotrophic factors (BDNF). Several studies found that the transplantations of NSCs lead to differentiation into neural types, promoting hippocampal neurogenesis and elevating BDNF levels. In mouse models, NSC transplantation rescued cognitive performance in AD mice.[7] Ager, Davis, Agazaryan, Benavente, Poon, La Ferla, and Blurton-Jones found that with human cells and models, human NSCs can improve cognition of AD pathogenesis and hippocampal neural loss.[20] Studies showcased that NSC injections rescued cognitive functions in transgenic mice, exhibiting advanced AD pathology. NSC-derived cells elevated hippocampal BDNF, which led to the increased synaptic density of the hippocampus and restored cognition abilities.[21]

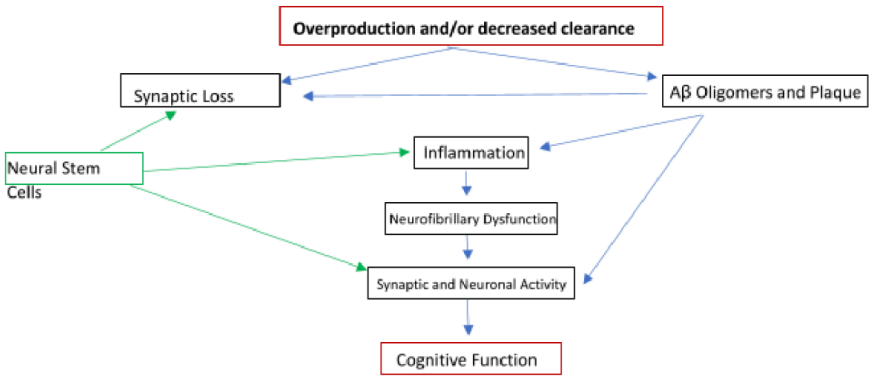

Figure 3: Modified from Chang, Kim, Joo, Ha, and Suh,[3] the amyloid cascade hypothesis illustrates the accumulation of Aβ derived components of AD, including neuronal and synaptic loss, neurofibrillary, and cognitive dysfunction (blue arrows). While drugs target the initial accumulation of Aβ, stem-cell-based therapies intervene at all stages. Stem cell

therapies could treat AD by targeting AD pathogenesis. NSC (green arrows) provides synaptic plasticity and neurotrophic activity.

2.2 Mesenchymal Stem Cells

MSCs can regenerate and differentiate under appropriate conditions, such as standard cultured solutions.[4,23] In particular, MSCs can be isolated from brain regions. A recurring cell in literature reviews was found to be human umbilical cord blood-derived MSCs (hUCB-MCSs) and bone marrow-derived MSCs (BM-MCSs). Hippocampal transplantation of (hUCB-MCSs) showed rescuing of memory deficits and cognitive abilities in AD mice by reducing neuronal apoptosis, which increased brain volume.[24-27] BM-MCSs were transplanted in theAPP mouse model of AD, , resulting in a reduction in microglial numbers without altering amyloid plaques, the baseline of the development of AD.[27] Yet, some studies also show a significant decrease in amyloid plaques after two months of injection.[28] Transplantation of huCB-MSCs and BM-MCSs into the hippocampus through multiple studies has shown to be feasible, safe, and tolerated to improve cognitive function and lower amyloid plaques in the brain.[4,29]

2.3 Embryonic Stem Cells

ESCs from inner masses of blastocysts have shown to be pluripotent and thus capable of cell differentiation and self-renewal into primary germ layers.[2,6] For cell replacement therapies, ESCs provide pluripotency-regulated neural lines. Several reports have explored ESC's roles in mitigating AD in rodent models. Here, ESC progenitor and cultural cells transplanted into the hippocampus of rat models differentiated neuron cells, increased synapse regulation, and improved memory deficits of AD pathologies.[26] Neuron-derived ESCs also differentiated into mature cholinergic neurons and restored the cognitive performance of AD transgenic mice.[16,28] Nevertheless, there are controversial issues with ESCs, such as immune system rejection, ethical concerns, and risks of teratoma (a germ cell tumor) upon transplantation.[6,30] Due to the low number of literature papers on ESCs, more research should be conducted to explore the role and effects of AD as an alleviating factor.

Stem Cell Type	Results from Treatment/Models of AD
NCSs	*Alleviation of AD pathway *Protective effects of Aβ induced cell death *Neural differentiation *Improved spatial memory *Decreased levels of tau, Aβ plaques, Astrogliosis, microgliosis and apoptosis *Increased levels of synaptic proteins in the hippocampus
MSCs	*Promotion of cell survival *Improved spatial memory *Neuronal differentiation in the hippocampus *Reduced number and size of Aβ plaques
ESCs	*Alleviate learning and memory deficits *Maturation of interneurons *Neural regeneration

Table 1: Summary of AD model results of stem cell therapy.

3. Limitations and Future Research

Clinical findings have advanced in recent decades, generating promising results in stem cell technology. Yet, technological challenges remain on stem cell therapy use in AD. Even with the possibility of regenerative medicine, the future of stem cell therapy for regeneration remains unclear. Research concerning stem cell therapy and AD analysis are based on animal models, which may not demonstrate favorable results in humans.[14,36,37] Stem cell therapy results in different cognitive effects based on animal models transfected with AD, proving that it can improve learning and memory deficits.[18,29,32] . The current AD research primarily used transgenic mice models to reveal cellular alterations through disease progression. These findings support the amyloid cascade theory of the accumulation of tau NFTs causing neurodegeneration.[30] Yet, the progressive nature of AD requires longitudinal studies to assess the lasting effects and safety of profile treatments.

Regarding the high aggregate quantities of Aβ plaques and tau in the brain of patients or experimental models with AD, , transplanted cells can typically generate nonneuronal cells or unexpectedly die based on specific environments. This approach does not aid the therapeutic approach, creating a possible discrepancy with the results of experiments.[7,38] A study

by Bae, Jin, Lee, Richardson, and Carter indicated a drastic decrease in Aβ plaques in the brain's hippocampus region after two months.[27] On the other hand, Naaldijk, Jaeger, Fabian, Leovsky, Bluher, Rudolph, and Stolzing found no difference in terms of Aβ plaque concentration but noted improvements in cognitive functions in AD models.[39] Based on recurring inconsistent results, further research on stem cell therapy is necessary to produce a more robust conclusion. Stem cell therapy aims to promote the regeneration of tissues with inhibition of inflammation, reduction of apoptosis, stimulation of angiogenesis (blood vessel formation), and cell differentiation, bringing a considerable amount of attention to stem cell therapy as a feasible way of treating AD patients.[14,27] Additionally, issues with the procedure and basis of stem cell therapy remain unresolved, such as long-term safety of transplantation delivery systems, cell source, and donor cell responsiveness to AD-pathogenic environments.[19,40] Even so, stem cell therapy will become an efficient candidate for AD treatment due to promising results in neuron regeneration.

It is important to note that rather than multiple databases, the literature search used only three: PubMed, Google Scholar, and the National Library of Medicine. This may have limited the information represented in this paper, leading to fewer referenced sources and greater variability in results. Though more current studies were implemented, eliminating those older than 1991 allowed analysis of more recent data and research advances since the beginning of stem cell technology. Further research would be ideal to analyze the effectiveness of stem cell therapy over a longer duration and to ensure the therapeutic does not lead to tumors through excess cell differentiation.

4. Conclusion

While the cause of AD is only partially understood, hereditary genes are thought to play a significant role in determining who contracts it. Hypotheses have tried to explain the cellular events leading to inheritance of AD, with the focus lying on extraneous APP accumulation. However, it has been determined that vaccines removing APP buildup do not reverse AD in patients.[31]

More clinical trials employing stem cell therapy are ongoing for AD, focusing on its capability to differentiate into neuronal and glial cells and alleviate AD symptoms or curation.[2] This paper analyzes the specific stem cells of NSC, MSC, and ESC to foresee possible treatment for AD pathogens (Table 1).

In recent years, stem cells have become a promising alternative to conventional methods for AD research. As a multifactorial disorder, AD creates barriers to alleviating its adverse effects, particularly in the brain's hippocampus. To combat such effects, stem cell therapy uses a multi-targeted approach through cell differentiation upon transplantation. Stem cells have been tested for effective modification in slowing neuronal death and preventing tau accumulation in WAD. Recent data from Quin, Wang, Zhang, Bai; and Shin, Park, Kim, Oh, Bae, Ha, and Lee indicated that transplantation of stem cells alleviated neuropathology and cognitive deficits in several animal models with AD.[32-35] No current drugs demonstrated an improvement in AD symptoms and effects.[16] Research has provided promising results for stem cell transplantation improving memory and learning abilities as a potential treatment for AD.

Therefore, stem cell therapy should be considered a healthy and suitable regeneration of cell function to alleviate cell death and hippocampus damage. Experts convey that stem cell therapy for AD has beneficial outcomes, displaying a clinical efficiency of approximately 82.2%.[41] Hence, treatments that enhance or improve cognition, especially in the presence of aggregate plaque and tangle pathology, are urgently needed. Stem cells are being actively studied for their potential to replace dead or diseased cells.[21,42-44] Regardless of the recent breakthrough of stem cells, advancements in technology confirm the therapeutic as a potential treatment for AD. In the future, a thorough evaluation of implanted cells with AD pathogens should be conducted to confirm their successful therapeutic effects.

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