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Therapeutic Potential of Mesenchymal Stem Cells in the Treatment of Alzheimer's Disease

[1]Mrs. V. VIJAYA, [2]Mrs. U. NIRMALA, [3]Mr. M. KISHORE, [4]Ms. P. KALYANI
[1, 2, 3, 4]Assoc. Professor, Krishna Chaitanya Degree College, Nellore, AP, India.

***Abstract* — Alzheimer's disease (AD) is a neurodegenerative condition that mostly affects the brain's hippocampus and progresses gradually. It is characterized by both a discernible loss of memory recall and a decline in cognitive function. The impairment of neural genesis, which leads to the depletion of neurons and synaptic connections within the nervous system, is one of the main features of AD. Regretfully, there is now no proven treatment for AD, and no drug can effectively slow the advancement of the neurodegeneration linked to the disease. However, it is important to emphasize that the problematic symptoms of AD have been addressed. Two types of drugs intended to reduce these symptoms have received approval from the Food and Drug Administration. These developments have encouraged the scientific community to look at different treatment possibilities, including stem cell therapy. The potential application of various mesenchymal stem cells as a therapy for AD will be the primary focus of this review.**

***Index Terms* - Alzheimer's disease (AD), mesenchymal stem cells, Aβ plaques, microglia neuroinflammation**

I. INTRODUCTION

Alzheimer's disease (AD) is one of the most common forms of dementia, affecting an estimated 50 million people worldwide. Given that age is a major factor in its prevalence and that the population is aging more quickly, it is estimated that by 2050, 152 million people will suffer from AD. One Dementia is characterized by behavioral disorder, memory loss, disorientation, cognitive decline, and difficulty performing daily duties. Importantly, AD is among the biggest medical, social, and economic issues of our day. Numerous variables, including both genetic and environmental ones, interact to cause sporadic AD. 3. In addition to age, additional known risk factors for AD include cardiovascular illness, depression, low levels of education, and the ApoE4 (apolipoprotein-E4) gene. The majority of AD cases are sporadic and delayed onset. About 5% of cases of familial AD are caused by autosomal mutations in the PSEN1, PSEN2, and occasionally the amyloid precursor protein (APP) genes. Four pathological findings can be used to characterize the various causes and effects of AD. The first is the hyperphosphorylation of a tau protein, which is linked to intracellular microtubules in neurons that are necessary for axonal and structural support. The microtubule collapse and aberrant tau protein buildup within neurons are caused by the hyperphosphorylation. The second occurs when APP, a transmembranal protein present in neurons, is enzymatically cleaved by β- and γ-secretases, resulting in the formation of amyloid β (Aβ) plaques in the brain. A pharmaceutical strategy to remove the amyloid buildup has been to reduce synthesis by blocking secretase or by immunizing. The activation of microglia, which are specialized immune cells found in the central nervous system (CNS), is the third characteristic of AD. Although they are visible from the onset of AD, as the condition worsens, their percentage in the brain declines. Neuroinflammation is caused by cytokines released by activated microglia, including nitric oxide, interleukin (IL)-1β, and tumor necrosis factor (TNF)-α. A widespread weakening of neurons and synapses is the fourth pathogenic feature of AD. The development of AD involves several neurotransmitters. Cholinergic neurons deteriorate, amyloid plaque and neurofibrillary tangles form, and the cholinergic system—which is essential for cognition—is disrupted in AD. The pathogenesis of AD also involves other neurotransmitter systems, specifically some noradrenergic, serotonergic, and glutamatergic systems. Patients with AD may experience synaptic injury as a result of GABAergic neurons losing their inhibitory control. In general, maintaining cognitive function depends on the interaction of many neurotransmitters, and AD may worsen if any of these systems are out of balance.

II. LITERATURE SURVEY

Current Therapies in Treating AD and Challenges

The Food and Drug Administration has only approved two classes of drugs to treat AD, cholinesterase inhibitors and N-methyl D-aspartate antagonists, despite the disease's severity. 5 There are three categories of acetylcholinesterase (AChE) inhibitors: reversible, irreversible, and pseudo-reversible. They work by preventing cholinesterase enzymes that break down acetylcholine (ACh), such as AChE and butyrylcholinesterase, from functioning. These inhibitors thus increase the amount of ACh present in the synaptic cleft. Particularly in the early stages of AD, this elevated ACh level benefits brain and cognitive function. These cholinesterase inhibitors include galantamine (a dual-action tertiary isoquinoline alkaloid, which acts as a competitive inhibitor of AChE by binding allosterically to nicotinic acetylcholine receptors and activating them), rivastigmine (a pseudo-irreversible inhibitor that inhibits AChE and butyrylcholinesterase, which breaks down acetylcholine in the brain), and donepezil (it increases the level of AChE by binding to AChE reversibly, thereby inhibiting the hydrolysis of acetylcholine). The Nmethyl D-aspartate receptor (NMDAR) plays a major role in the pathophysiology of AD because its stimulation results in Ca2+ influx, which initiates signal transduction and gene transcription required for long-term potential formation, which is essential for memory

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formation, synaptic neurotransmission, and plasticity. Glutamate, the main excitatory neurotransmitter in the central nervous system, is overstimulated when NMDAR is overactivated. Excitotoxicity, synapse disruption, neuronal cell death, and eventually a reduction in cognitive function are all consequences of this overstimulation. The sole approved medication for treating moderate to severe AD in this category is memantine, a low-affinity noncompetitive NMDAR antagonist. The drawback of these medications is that they primarily target symptom management rather than illness cure. Additionally, some medications have negative side effects. For instance, excessive NMDAR activation results in aberrant calcium signaling and overstimulation of glutamate, a neurotransmitter crucial to brain function. Excitotoxicity, impaired synapse function, nerve cell death, and cognitive impairment are the results of this excessive activity. 5, 7 Creating efficient disease-modifying therapies that can halt or decrease the progression of Alzheimer's is the primary problem. Mesenchymal stem cell (MSC) treatment is one of the many strategies being developed by researchers to overcome this obstacle and give patients greater options in the future. Stem cells that are mesenchymal AD applications MSCs have several potencies, move to the site of injury, have a spindle form, and stick to plastic. They can come from a variety of origins, including but not restricted to Wharton's jelly, adipose tissue, and bone marrow. Recently, there has been a lot of interest in employing them as therapeutic tools because to their neurotrophic effects, immune system modulating properties, and multipotency. 10. Because of their antiapoptotic and antioxidant qualities, MSCs stimulate neural progenitor cells to promote neurogenesis, metabolize glutamate and gamma-aminobutyrate, inhibit neural cell necrosis, and multiply astrocytes when used to treat AD. They also release growth factors, such as brain-derived neurotrophic factor [BDNF], to promote neurogenesis. By avoiding or inhibiting the activation of proinflammatory microglia (M1) and promoting the activation of antiinflammatory microglia (M2), MSCs also modulate the immune system to prevent further tissue damage caused by chronic neuroinflammation. MSCs have been shown to increase autophagy activation, which is probably why Aβ plaques are cleared by lysosomes. In order to enable Aβ, MSCs also accelerate the accumulation of microglia close to Aβ deposits. Twelve AD Autophagy and Apoptosis: The Function of Mesenchymal Stem Cells Derived from Bone Marrow in Transplantation Bone Marrow-Derived Mesenchymal Stem Cells and Autophagy's Impact Autophagy is responsible for the elimination of Aβ peptide and the assembly of tau protein in cerebral tissue. After being sequestered into autophagosomes, the cytoplasmic components undergo autophagic breakdown and recycling. In light of the fact that AD is characterized by the accumulation of aberrant Aβ peptide, AD advances when autophagy is dysregulated since healthy autophagy decreases neuropathology as indicated by the expression of molecular markers such as Beclin-1, atg7, Lamp-1, Lamp-2, and mammalian target of rapamycin (mTOR). 13–15 By controlling the main signaling pathways PI3k/AKt, GSk-3, AMPk, and IGf1, mTOR complex major is associated with the elimination of Aβ proteins. 15,16 Autophagy defects in the development of AD, as demonstrated by aberrant mitophagy and the resulting defective Aβ and tau pathology. Synapse degradation and cognitive deficits are linked to decreased mitophagy in both animal models and individuals with sporadic late-onset AD. 15, 17 Improving autophagy is linked to behavioral and cognitive gains. Reduced levels of aberrant Aβ and hyperphosphorylated tau proteins decrease neuron mortality in AD-like animals following bone marrow-derived MSC (BMMSC) transplantation. Both the BECN1/Beclin 1 secretion, which initiates the clearing of Aβ peptides in AD-like mice, and LC3-II-positive autophagosomes are upregulated in the hippocampus. Additionally, a range of cytokines are released into the local microenvironment following BMMSC transplantation via both autocrine and paracrine signaling pathways. 18 Apoptosis and Mesenchymal Stem Cells Derived from Bone Marrow Transplanting BMMSCs can repair the harm brought on by the apoptotic (programmed cell death) process, which causes neurons to die and memory loss in animal models of AD. The apoptosis signaling cascade can be modulated at several levels, including indirectly regulating signal molecules like stromal cell-derived factor-1 and neurotrophic growth factor, increasing antiapoptotic proteins like B cell lymphoma-2 and survivin, and activating nuclear factors like p53, Foxa2, and C/EBP.

The effects of BMMSCs transplantation on apoptosis can be direct or indirect

Direct effects include elevated expression of survivin and seladin-1 and antiapoptotic Bcl-2, which inhibits caspases, a family of proteins implicated in the programmed cell death pathway 1.15,18,19 Additionally, BMMSCs have the ability to increase the synthesis of antiapoptotic proteins like XIAP that are members of the inhibitor of apoptosis proteins (IAPs) family. This increase has neuroprotective benefits by efficiently preventing neuronal death. The removal of Aβ peptides, which build up in AD and cause apoptosis through regulators like stress-activated protein kinases and p53 activation, is one of the indirect effects of BMMSC transplantation. By promoting the natural antioxidant system and inducing mitophagy, which gets rid of oxidized materials and aberrant proteins, BMMSCs can help lower apoptosis. The generation of cytokines and neurotrophic factors that support angiogenesis and neurogenesis is one of the additional outcomes of BMMSC transplantation. Beneficial Effects of Adipose Tissue-Derived MSCs on Microglia for the Treatment of AD The adipose tissue (belly fat, buccal fat pad, and infrapatellar fat pad) is the source of adipose tissue-derived MSCs (AD-MSCs), which adhere to plastic, have surface markers (such as CD29, CD44, and CD105), and lack some surface markers (such as CD14, CD19, and CD45). 21 Studies have shown that AD-MSCs can reduce oxidative stress, relieve mental impairment in APP/PS1 mice, and stimulate endogenous neuron development in the subgranular and subventricular zones. By controlling inflammatory

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mediators, microglia proliferation, polarization, and phagocytic activity, AD-MSCs also alleviate AD symptoms in animal models. 22 Microglia in a healthy brain keep the central nervous system (CNS) in a state of equilibrium. By releasing neurotrophic factors and removing cellular debris in response to changes in the brain, microglia assist the central nervous system. Excessive inflammation produced by microglia can damage the brain in response to chronic triggers or brain injuries. Since the goal of the treatment is to keep microglia in a neuroprotective state that supports the central nervous system by influencing their inflammatory condition, the ability of microglia to change from proinflammatory (having a round morphology in vitro) to neuroprotective (elongated shape) makes them an excellent therapeutic focus in neuroinflammatory diseases.

Aβ accumulation (a pathological hallmark of AD) can trigger the proinflammatory state.

The proinflammatory phenotype is initiated by reactive oxygen species, nitric oxide, and certain proinflammatory cytokines like as TNF-α, IL-1β, and IL-6. 21,23 Research demonstrates that IL-4 and MSCs can both create the neuroprotective phenotype. But compared to its proinflammatory cousin, this phenotypic induction has not gotten as much attention. Neuroprotective chemicals elevated in this condition include BDNF, activity-dependent neurotrophic protein (ADNP), and the fractalkine receptor CX3CR1. 21 Primary microglia in vitro will resemble their in vivo spherical form when they are inflamed; when CNS microglia experience pathogenic events, they will take on an amoeboid morphology. The microglia from a primary mouse—a living animal that hasn't been passaged or altered in a lab setting—underwent a significant morphological change to an elongated cell shape when they were cultured with AD-MSCs in vitro. Since direct cell-to-cell contact is hindered by this inclusion, soluble substances must be the cause of the shape change.

The conditioned medium (CM) from AD-MSC also causes this change in morphology.

The morphological shift indicates that the inflammatory phenotype is transformed into a neuroprotective one with in vitro incorporation of AD-MSC or AD-MSC-CM. 21 This change results in a decrease in the release of proinflammatory cytokines and an increase in neuroprotective factors such as fibroblast-growth factor-2, BDNF, ADNP, and arginase-1, a marker that triggers phagocytosis and macrophage activation. This rise is noteworthy as the AD mouse model demonstrates that phagocytosis decreases with increasing Aβ.

Challenges and Perspective

Clinical experiments have demonstrated the safety of MSCs, but their effectiveness has not yet been established. One of the challenges in treating AD is that by the time it is discovered, it has already resulted in neuronal death and the accumulation of abnormal proteins in numerous brain regions. Furthermore, despite requiring multiple stem cell infusions over an extended period of time, patients in the majority of clinical trial protocols only receive a handful. Because the majority of MSCs are retained in other organs and only a tiny fraction can enter the brain, intravenous infusion of these cells has proven futile. The ability of autologous MSCs to regenerate may be hampered by senescence brought on by aging. One Autophagy activation and neuronal survival are related, although the results are not always consistent. Medication related to autophagy might not be enough to halt the progression of advanced AD. 15 BMMSC implantation may produce neurons that are crucial for synaptogenesis and improving cognitive function, but it's unclear how long this equilibrium will hold true. 18 For people with AD, combining many mechanisms—such as immune system modulation, cell death prevention, nerve cell growth stimulation, cellular self-cleaning process augmentation, and blood vessel formation promotion—may provide therapeutic benefits. 15, 18 Furthermore, exosome-mediated immunomodulation and neuroprotection are similar to transplanted stem cell-mediated mechanisms, although more study is required.

III. CONCLUSION

Lastly, through a variety of processes, such as immunoregulation, antiapoptosis, neurogenesis, autophagy activation, and angiogenesis, MSCs and their exosomes have demonstrated enormous therapeutic promise for AD. Improvements in cognitive performance have been associated with the protection of hippocampus neurons, the improvement of synaptic function, and the transfer of miR-133b into astrocytes and neurons by exosomes generated by MSCs. It is still difficult to assess the efficacy of MSCs and find solutions for issues like the limited brain penetration of intravenous exosomes. To completely understand the potential of MSCs and their exosomes in the therapy of AD, further thorough research is needed.

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