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Mesenchymal Stem Cells As A Promised Therapy For Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is a chronic neurodegenerative condition and has been classified as the most prevalent classification of dementia in the present day. It manifests itself in the form of an abnormal build-up of protein in the medial entorhinal cortex and the hippocampus, leading to cognitive malfunction. In the present day, there are no known cures for AD; instead, the condition is treated with prescription drugs to help relieve the symptoms. However, recent studies on mesenchymal stem cell transplantations have found that promising results such as improvement of spatial memory, decreased levels of pro-inflammatory cytokines, and reduction in amyloid-protein plaques as well as phosphorylated Tau protein. This article aims to introduce AD and its etiological hallmarks, to illustrate an overview of recent developments on mesenchymal stem cell research specific to AD, and to discuss the future prospects and potential of MSC-based therapies.

Keywords: Alzheimer's Disease, Mesenchymal stem cells, Stem cells

Introduction

Alzheimer's Disease (AD) is a cumulative neurodegenerative disease; classified as the most prevalent classification of dementia (Bondi, Edmonds, & Salmon, 2017). This neurodegenerative disease is caused by the progressive build-up of protein which leads to neuronal death and their connections in the regions of the brain concerned with cognitive function (Weller & Budson, 2018). Tau proteins are natively unfolded microtubule-associated proteins whose function depends on their phosphorylation state (Chong, Ng, Koh, & Chye, 2018; Nam, Lee, Moon, & Chang, 2020; Nu et al., 2018). Aggregated phosphorylation causes the accumulation of the tau protein in the somatodendritic neuron compartment which consequently forms Neurofibrillary tangles (NFTs) leading to neurons becoming unable to maintain their cytoskeleton (Gant et al., 2018; Pascoal et al., 2018; Pascoal et al., 2020). Amyloid plaques (also known as senile plaques) are a pathological hallmark in the progression of AD (Ji et al., 2018; Zhan, Stamova, & Sharp, 2018). Accumulation of amyloid-beta (Aβ) has been implicated in the etiology of AD and is believed to be a characteristic factor in the neural damage in the regions of the hippocampus and cortex (Bayer & Wirths, 2010; Jiang et al., 2018; Martins et al., 2019; Song & Choi, 2013).

As of this time, there are no curative treatments for AD. However, acetylcholinesterase (AChE) inhibitors such as donepezil, galantamine, and rivastigmine are standard prescriptions to inhibit the breakdown of ACh by the enzyme cholinesterase; this helps to temporarily alleviate some symptoms of AD (Long & Holtzman, 2019; Mathew et al., 2019; Murray, Faraoni, Castro, Alza, & Cavallaro, 2013). Even so, these standard treatments cease to reach the desired clinical outcome, therefore leading to a surge of innovation for new treatments to improve therapeutic results for AD. Of many clinical trials and

treatments for a range of diseases, stem cell therapy has risen as an alternative regimen (Connors, Ames, Woodward, & Brodaty, 2018; Hanfelt, Peng, Goldstein, & Lah, 2018; Magalhães, Alves, Fortuna, Llerena, & Falcão, 2020). Recent studies, adipose-derived mesenchymal stem cells (MSCs) have proved to activate microglia, causing a reduction in the level of Aβ. This shows substantial promise in MSC-based treatments for AD (Chang, Kim, Joo, Ha, & Suh, 2014; Deng et al., 2019; Ma et al., 2013; Shigematsu, Takeda, Komori, Tahara, & Yamagishi, 2021; Yan et al., 2014). This paper aims to gather the molecular mechanism of MSC-based treatment of AD and the clinical outcomes in the use of MSC-based remedies for AD in clinical trials in order to broaden ideas of future treatment and to strengthen their potential for success.

The etiological mechanisms of AD and standard treatment

The first genetic mutations which were found to be linked to early-onset AD were mutations in the amyloid precursor protein (APP). APP is the precursor molecule that is cleaved proteolytically by the cleavage enzymes such as β-secretases and γ-secretases to biosynthesise 37 to 49 amino acid residue peptides, Aβ (Pluta, Furmaga-Jabłońska, Maciejewski, Ułamek-Kozioł, & Jabłoński, 2013; Schauenburg et al., 2018; Wang & Pei, 2018). These amino acids have proven to be the root source to the extracellular senile plaques found in patients with AD. Conventionally, APP is metabolized by two definite pathways: (1) the secretory pathway, and (2) the amyloidogenic pathway. In the secretory pathway (1), APP is cleaved by β-secretase which releases an N-terminal fragment (sAPPβ) along with a C-terminal fragment (C99) which undergoes additional division by γ-secretases, resulting in the yield of monomers; Aβ peptides (Esmieu, Ferrand, Borghesani, & Hureau, 2021; Rana & Sharma, 2019). The monomers, in turn, progressively aggregates to dimmers, trimers, oligomers, protofibrils, and fibrils, leading to protein deposits (amyloid plaques). Soluble Aβ oligomers interact with neuronal and glial cells which cause various cellular dysfunction: induced cell death and neuronal apoptosis, impaired intracellular signalling pathways, and increased Tau protein phosphorylation (Fontana et al., 2020; Y. S. Kim, Jung, & Yoon, 2018; S. Li & Selkoe, 2020). Aβ fibrils form deposits of protein which are the foundation of neuritic plaques in the regions of the cerebral cortex (Fontana et al., 2020; Y. S. Kim et al., 2018; S. Li & Selkoe, 2020). These plaques are deposited in progressive and sequential morphological forms throughout the progressive stages of AD (Fontana et al., 2020; Y. S. Kim et al., 2018; S. Li & Selkoe, 2020). The plaques cause the stimulation of astrocytes and microglia, damage to neuronal cells which cause the loss of synapses, and eventually, cell death (Azevedo et al., 2013; Bessis, Béchade, Bernard, & Roumier, 2007; Fontana et al., 2020; Y. S. Kim et al., 2018; S. Li & Selkoe, 2020).

Tau proteins are microtubule-associated neuronal phosphoproteins that are highly involved in the construction and stabilization of both the neuronal cytoskeleton and its microtubules, as well as the regulation of the axonal transport within neuronal axons. In neuronal axons, the microtubules are uniformly oriented due to the Tau protein (Aanandhi, Niventhi, Rujaswini, Hemalatha, & Praveen, 2018; Baas & Qiang, 2019; Qiang et al., 2018; Samra et al., 2017). During the process of remodeling the cell's cytoskeleton, changes in the state of phosphorylation occur; this makes the regulatory functions and mechanisms of the phosphoprotein essential to increase synaptic plasticity (Alavi Naini & Soussi-Yanicostas, 2015; Feng et al., 2020; Kimura et al., 2014). If the Tau protein were to go under abnormal or aggregated phosphorylation, this would affect its ability to bind to tubulin resulting in an agitated microtubule structure. Hyperphosphorylated Tau protein damages axonal transport and synaptic metabolism which brings about a loss of cell viability, causing the disintegration of microtubular cytoskeleton structures and neurone cell death (Boonen, van Tijn, & Zivkovic, 2009; Narayanan et al., 2020).

The interchange between Tau proteins and tubulin is imperative in the stabilization of the microtubular structure (Bossenmeyer-Pourié et al., 2019). The process consists of the promotion of polymerization by Tau protein which causes the inhibition of the fast depolymerization of tubulin; this is controlled by the balance of phosphorylation and dephosphorylation at the phosphorylation sites of the phosphoepitopes of Tau protein: serine and threonine. Both the phosphorylation and dephosphorylation of epitopes helps to aid the ability of Tau protein to interrelate with α- and β-tubulin (Bhandare, Kumbhar, &

Volume 5, Issue 1; January-February 2022; Page No 1166-1176

Kunwar, 2019; Bossenmeyer-Pourié et al., 2019; Kellogg et al., 2018; Nasu, Furukawa, Suzuki, Takeuchi, & Koriyama, 2020).

Conventionally, a majority of serine and threonine phosphoepitopes in both fetal and Paired Helical Filament Tau (PHF-Tau) is accompanied by proline residues, raising the conclusion that Tau kinases are proline-directed kinases; enzymes that possess the ability to phosphorylate Tau protein. Such enzymes have been discerned in the brains of AD patients and in NFTs (Drepper et al., 2020; Hanger, Betts, Loviny, Blackstock, & Anderton, 1998; Hefti et al., 2019; Morris et al., 2021; Vincent, Zheng, Dickson, Kress, & Davies, 1998). This hyperphosphorylation of Tau protein by the proline-directed kinases causes abnormalities that impair its ability to bind to tubulin; causing an unstable microtubule structure (Hefti et al., 2019). Additionally, the aggregated deposition of such proteins also causes the deterioration of axonal transport, synaptic metabolism, cytoskeleton collapse, and neuronal death (Hefti et al., 2019; Vincent et al., 1998).

As of this time, there are no curative treatments for AD. However, AChE inhibitors such as tacrine, donepezil, galantamine, and rivastigmine were approved for inhibiting the breakdown of ACh by the enzyme cholinesterase. These drugs temporarily help to alleviate some symptoms of AD; though they are not curative treatments (Briggs, Kennelly, & O'Neill, 2016). An alternative to AChE inhibitors for those who do not respond or are allergic to AChE inhibitors is memantine (Murray et al., 2013). Memantine is an N-methyl D-aspartate (NMDA) antagonist which functions by alleviating the effects of exorbitant amounts of glutamate: a chemical found in the brain (Mathew et al., 2019). Furthermore, there was a targeted therapy approved for treating AD is a disease-modifying medication such as aducanumab: an Aβ-directed antibody (Thomas, Wasunna-Smith, & Kuruvilla, 2021). Aducanumab targets the Aβ protein in the brain of AD patients, causing the reduction of amyloid plaques. Currently, there are ongoing studies as to whether this medication is suitable and effective on patients as they progress through the stages of cognitive impairment (Thomas et al., 2021). Therefore, attempts to develop novel strategies for AD treatment such as stem cell therapy are ongoing for finding effective therapies for AD (Thomas et al., 2021).

Stem cell classes based on cell origin

There are four classes of stem cells that are frequently employed in current AD experimentation and studies: (1) embryonic stem cells (ESCs), (2) Mesenchymal stem cells (MSCs), (3) Brain-derived neural stem cells (NSCs), and (4) induced pluripotent stem cells (iPSCs) (S. U. Kim, Lee, & Kim, 2013; Q. Liu et al., 2012; Titomanlio et al., 2011). ESCs are acquired from the inner cells of the blastocyst and are classified as pluripotent stem cells due to their capacity to produce different cell types from the germ layers. iPSCs are commonly obtained from mature adult dermal fibroblasts, in vitro, by laboratory processes (Cho et al., 2010; Hu et al., 2020; Stadtfeld et al., 2010). The genetic alteration of these stem cells provides them with pluripotent capabilities and ESC-like phenotypes and differentiation capacities. MSCs can be derived from a variety of sources, starting with umbilical cord blood (ucb-MSCs), the Wharton jelly, and adult stem cell pupae such as bone marrow and adipose tissue (Zeng et al., 2013). Research done using rodent models of AD and ucb-MSCs have found that the transplantation of ucb-MSCs improved spatial learning and had prevented memory decline in the murine models. The research further proposed additional mechanisms of the transplantation such as the reduction of Aβ plaques, hyperphosphorylation of tau protein, and microglial inflammation, as well as the increase of anti-inflammatory cytokines (Cho et al., 2010; Hei et al., 2017). MSCs have been recorded to have immunomodulatory and anti-inflammatory effects through their ability to upregulate neuroprotection and downregulate pro-inflammatory cytokines (Guo et al., 2020; Prasad, 2017; Zeng et al., 2013).

Mesenchymal stem cell therapeutic strategy in Alzheimer's Disease

MSCs are obtained through bone marrow, adipose tissue, and the tissue of the umbilical cord; its alleged mechanism and perquisites include (1) homing, (2) paracrine neuroprotective agents, and (3) its immunoregulation (Jin et al., 2013; Kern, Eichler, Stoeve, Klüter, & Bieback, 2006; Stanko, Kaiserova, Altanerova, & Altaner, 2014). Though the mechanisms of MSCs are currently still being researched, in light of recent studies, these therapeutic mechanisms proved to have the potential to ameliorate various diseases in innumerable ways

Volume 5, Issue 1; January-February 2022; Page No 1166-1176

(Oh, Son, Choi, Lee, & Byun, 2018). In the present, there has been a limited indication for both the function and neural maturation of MSC-derived neurons in vivo. Additionally, the neuroplacement by MSCs is left in its infancy due to low rates of neuronal differentiation (Donega et al., 2014; Tanna & Sachan, 2014; Wagenaar et al., 2018). Though these aspects cause uncertainty and hesitance in the development of MSC-based therapy, studies of MSCs show potential for the future of neuroregenerative treatments (Donega et al., 2014; Tanna & Sachan, 2014; Wagenaar et al., 2018).

MSCs have attested to improving the pathological factors characterizing AD. In a previous study, Aβ was injected into the dentate gyrus of mice, inducing a model of acute AD. Bone marrow-derived mesenchymal stem cells (BM-MSCs) were also intracerebrally transplanted into the affected area causing the activation of microglia near the site. This sprung the diminution of Aβ deposits and enhanced cognitive function, demonstrating the potential of BM-MSCs as a therapeutic agent against AD (Bae, Jin, Lee, Richardson, & Carter, 2013; Neves et al., 2021; Tanna & Sachan, 2014). Human placenta amniotic membrane-derived mesenchymal stem cells (hAMMSCs) were injected intravenously into AD model mice, causing significantly improved spatial learning and function as well as the reduction of amyloid plaques in the brain (Kharat et al., 2019; Neves et al., 2021; Tanna & Sachan, 2014). This was shown through the decreased levels of oxidative stress, indicating a correlation between the improved symptoms of AD and the regulation of oxidative stress (Jiao et al., 2016). Several studies have illustrated the potential of hAMMSCs treatment on the immunology of AD and hippocampal function through oxidative stress (Jiao et al., 2016; Shariati et al., 2020). Intracerebral transplantation of adipose-derived mesenchymal stem cells (ADSCs) poses as a propitious cell genesis for regenerative therapy (Mazini, Rochette, Amine, & Malka, 2019). Results from a research have shown that usage of ADSC transplantation has drastically reduced Aβ peptide deposition along with restoration of cognitive function lost from AD (Jiao et al., 2016; Ma et al., 2013; Mazini et al., 2019; Shariati et al., 2020; Yan et al., 2014). Research done on human adipose tissue-derived mesenchymal stem cells (ADMSCs) being either intravenously or intracerebroventricularly injected into the 18-month-old mice via the brain; this resulted in improved locomotor activity and neurological function in the animals. A study with respect to the transplantation of MSCs into aged rodent models showed that the cells underwent differentiation into various types of neural cells (Jiao et al., 2016; Shariati et al., 2020). With increased levels of neural cells, this resulted in increased concentrations of ACh neurotransmitter, BDNF, and NGF; thus, bringing about improved locomotor and cognitive function in the rodents (Gericke, 2020; Latham, Wang, Patterson, Slikker Jr, & Liu, 2021; Y.-X. Li, Ye, Chen, Jia, & He, 2018; Popova, Kulikov, & Naumenko, 2020).

MSCs can offer therapeutic roles in the design of cell replacement. Chem-Cun Wu et al. report that BM-MSCs -induced by a granulocyte colony-stimulating factor- were able to replace the neural lineage cells (Wu et al., 2017). This discovery exhibits tremendous potential in MSC treatment for the restoration of neurological function in mice models of AD (Wu et al., 2017). Furthering the potential of MSCs in neurodegenerative treatment; experimentation in the topic regarding the role of cytokines and signaling pathways in MSCs has gained substantial attention in the past years. Research conducted by Raheleh Farahzadi et al. have found when BM-MSCs have been co-cultured with Aβ-treated primary cortical and hippocampal neural cells (as an in vitro cell line model for AD), there was observed increase of cytokine secretion and telomere length (Farahzadi, Fathi, & Vietor, 2020). These two factors were regarded as a hallmark of neurodegenerative disorder as well as telomerase activity (Farahzadi et al., 2020).

Stem cell trials in humans

The fact that there have been discrepancies in preclinical research have limited some prospective stem cell therapies from advancing to human clinical trials is a barrier to the success of those therapies (Duncan & Valenzuela, 2017; Klionsky et al., 2021; X.-Y. Liu, Yang, & Zhao, 2020). In contrast, evidence from animal model studies, as well as the simplicity of handling and isolation, has contributed to human clinical trials approving MSC-based therapies (Duncan & Valenzuela, 2017). A recent open-label phase I clinical trial (involving patients who received intravenous injections of human umbilical cord blood-derived mesenchymal stem

Volume 5, Issue 1; January-February 2022; Page No 1166-1176

cells (hUCB-MSCs)) assessed the welfare and tolerability of intracranially injecting allogeneic hUCB-MSCs (Trial identifiers: NCT01297218 and NCT01696591) (Duncan & Valenzuela, 2017). NINDS-ADRA criteria were used to classify nine people with probable AD as participants in the trial (Nicolaou et al., 2001). The following criteria were used to determine who should participate in the study: 10 and 24 score in the Mini-Mental State Examination which indicates mild-moderate AD dementia, along with the Pittsburgh compound B positron emission tomography analysis to verify the presence of amyloid immunology. After receiving an injection of three million cells into the hippocampus and precuneus, participants were separated into a low-dose group (about three million cells) and a high-dose group (approximately six million cells) (Duncan & Valenzuela, 2017). After 3 months and 24 months, none of the patients experienced significant side effects, such as complications from the surgical surgery or MSC treatment (Duncan & Valenzuela, 2017). MSC transplantation, however, failed to impede neurological deterioration throughout the 2-year investigation, as indicated by the Alzheimer's Disease Assessment Scale-cognitive subscale, therefore, it lacked any negative effect on the population. Additional alterations to AD path-ology were found not to have occurred. This means that the immunomodulatory impact of MSCs, commonly described in animal models of AD [30–32], was not apparent (Duncan & Valenzuela, 2017). They believe this may partly be due to dependence on neuroimaging, which is more difficult to interpret in live subjects, instead of more sensitive post-mortem biochemical analysis utilised in animal research (Duncan & Valenzuela, 2017).

MSCs produced from the umbilical cord blood are still commonly utilised. However, there are notable differences in the number of cells, and the delivery schedule. Two distinct trials are now running and recruiting, each utilising MSC sources that are different from each other. In a study of the welfare and effectiveness of adipose-derived stromal vascular fraction cells collected following liposuction procedures, one trial (Trial identifier: NCT02912169) will use participants who have had such procedures. Ischaemia-tolerant allogeneic human bone marrow-derived MSCs will be the subjects of a new study (Trial identifier: NCT02833792) (Duncan & Valenzuela, 2017). To be more like the physiological milieu of the central nervous system, these MSCs were grown in hypoxic circumstances, which increase the expression of angiogenic growth factors such as VEGF and angiopoietin. As a result, these cells demonstrate improved migratory behaviour (Duncan & Valenzuela, 2017).

Future directions

Preclinical research implies that stem cells can cure AD; nevertheless, the difficulty in translation between animal and human studies holds back the use of stem cells in this area. Several research groups have found numerous approaches to treat AD in transgenic mouse models. Regrettably, all of these techniques have disappointed in human clinical trials (Duncan & Valenzuela, 2017). While genetically engineered models are far from being valuable predictors, they provide little if any predictive utility (Duncan & Valenzuela, 2017). The majority of human AD arises in a markedly heterogeneous population, while genetically engineered models are mainly based on family AD-related assumptions in a genetically homogeneous population (Duncan & Valenzuela, 2017; Klionsky et al., 2021). At this point, the use of rat models and associated theoretical causal hypotheses for human diseases is incompetent for predicting human clinical outcomes. Additionally, the neurons and synapses they use to simulate AD fail to reiterate the loss of neuronal function that is crucial to AD. Because AD cell therapies will be required to illustrate success in animals which mirrors the scientific and neurodegenerative aspects of human AD, they will be required to demonstrate clinical and neurodegenerative AD-like symptoms in additional animals (Yan et al., 2014).

Other critical problems must also be answered, including long-term safety, the best source of cells, and the delivery technology. The pathogenic AD environment must also be evaluated and understood. In the investigations covered below, heterotopic stem cells were employed. Transplantation of allogeneic foetal NSC, genetically modified MSC, and autologous haematopoietic stem cells has led to tumour growth in rodents and humans. It is also clinically relevant since NSC niches remain inaccessible in adults (Duncan & Valenzuela, 2017). While replacing lost neural circuits with neuron reconstruction therapies may not restore lost neural

Volume 5, Issue 1; January-February 2022; Page No 1166-1176

function, it can temporarily augment existing depleted circuits enough to help improve cognitive performance, everyday functioning, and overall quality of life (Farahzadi et al., 2020). Individuals with AD dementia have a lifespan of approximately four to five years, which translates to a functional cure if a near replacement therapy can rescue and protect brain function over this time. Even though many pathophysiological factors contribute to the AD process, an integrated treatment approach could be required, using pharmacological approaches to address pathology, endogenous neurogenesis and synaptogenesis, and the administration of exogenous neuro resources substances (Duncan & Valenzuela, 2017; X.-Y. Liu et al., 2020).

Conclusion

Stem cell therapy for Alzheimer's disease holds significant potential, although it is still in the early stages of development. New investigations continue to discover treatment mechanisms as new preclinical research has substantiated proof-of-concept. Most clinical trials to date, when employing MSC-based therapies, have been relatively consistent. At present, one such trial has failed, but many others are ongoing. It is essential to understand, however, that there is an enormous chasm between rats and humans. However, before this project gets off the ground, we will need to acknowledge the cells and the brains they want to heal and use models that begin to bridge this gap.

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Volume 5, Issue 1; January-February 2022; Page No 1166-1176

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Volume 5, Issue 1; January-February 2022; Page No 1166-1176

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Volume 5, Issue 1; January-February 2022; Page No 1166-1176

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Volume 5, Issue 1; January-February 2022; Page No 1166-1176

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Volume 5, Issue 1; January-February 2022; Page No 1166-1176