Types of Stem Cell for Alzheimer's Disease Therapy

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Alzheimer's disease (AD) has been a major causal factor for mortality among elders around the world. Stem cell therapy, compared to drug therapies and many other therapeutic options, has many advantages and is very promising in the future. Currently (up till 2023), there are four major types of stem cells used in AD therapy: neural stem cells, mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells. Of course, there are many other types of stem cells at the stage of experimentation for potential usage in treating AD, but most research centered on the four major types of stem cells that are discussed in detail below.

Keywords: Alzheimer's disease ; stem cell therapy ; dementia

1. Neural Stem Cell (NSC)

Up until now, the regeneration of cognitive decline and loss of brain tissue in AD patients have been non-curable. Thus, the majority of effective AD therapies focus on targeting AD pathology in the early stage to preserve cerebrovascular function. Because NSCs contribute considerably to brain homeostasis and repair, they reveal pleiotropic fundamental properties for the treatment of AD in the early stages [1].

In order to develop treatments for AD, it is vital to develop experimental models which represent a specific cellular phase of AD and laborious analysis of the cellular pathological mechanisms [2]. In 2018, McGinley et al. [3] discovered that transplantation of human NSC enhanced cognition of AD in a murine model APP/PS1 (amyloid precursor protein and presenilin 1 mutated mice). The transplantation was targeted to the fimbria fornix, and it significantly improved cognition in the hippocampal-dependent memory tasks at 4 and 16 weeks after transplantation. Furthermore, in 2020, Hayashi et al. [4] modeled human-derived NCS (hNSC) and murine-derived NSC (mNSC) transplantation. Both hNSC and mNSC gave positive results in treating AD.

More recent research has dived into the cellular mechanisms of NSC, and its therapeutic pathology for AD. In 2021, Apodaca et al. [5] discovered that hNSC-derived extracellular vesicles can mitigate the hallmarks of AD. They gave 2-/6-month old 5 × AD mice injections of hNSC-derived extracellular vesicles (EV). NSC treatment significantly decreased dense core amyloid-β plaque accumulation in both age groups, which showed neuroprotective effects for the redress of AD neuropathologies. In 2022, Reveulta et al. [6] studied microglia-mediated inflammation and NSC differentiation in AD, and the possible therapeutic effect of K(V)1.3 channel blockade. They concluded that K(V)1.3 blockers hinder microglia-mediated neurotoxicity in culture, reducing the manifestation and construction of the pro-inflammatory cytokines through NF-kB and p38MAPK pathways.

In general, NSC therapy has developed more advanced and detailed pathology mechanisms, with greater effectiveness in treating AD in the early stage.

2. Mesenchymal Stem Cell (MSC)

MSC is the most studied type of stem cell in stem cell therapies for AD, due to its excellent accessibility and wide range of differentiating potential. It can be administered intravenously to perform blood–brain barrier penetration with low immune response. In particular, MSC-derived exosomes (MSC-exos) are able to have donor-derived properties with minimal immunogenicity. MSC-exos also have little risk of forming tumors post-therapy, which make them a promising treatment for AD [7].

Several pre-clinical research studies have received significant results in recent years. In 2019, Zaldivar et al. [8] discovered that MSC-exos could increase neural plasticity and enhance cognitive impairment. They injected amyloid-β 1–42 aggregates into the dentate gyrus of murine models bilaterally, and performed novel object recognition tests on days 14 and 28. Results indicated that MSC-exos stimulated neurogenesis in the subventricular zone. In 2020, Nakano et al. [9]

discovered that bone marrow-derived MSC (BM-MSC) could enhance cognitive impairment in an AD model by enhancing the expression of microRNA-146a in the hippocampus. BM-MSC were injected intracerebroventricularly into the choroid plexus in the lateral ventricle, and secreted exosomes in the cerebrospinal fluid. In vitro experiments illustrated that exosomal miR-146a from BM-MSC was absorbed in astrocytes, and the level of miR-146a was increased. As the key to forming synapses, astrocytes restore cognitive function and mitigate AD. In the same year, Wei et al. [10] also investigated whether MSC-derived exosomal miR-223 regulates apoptosis of neuronal cells. MSC-derived exosomal miR-223 targeted PTEN, thus activating the PI3K/Akt pathway to inhibit neuron apoptosis, and hence become a potential treatment for AD.

Despite extensive pre-clinical research, research on the clinical level has also made remarkable progress recently. In 2021, Kim et al. [11] performed an intracerebroventricular injection of human umbilical cord blood MSC (hUCB-MSC) in AD patients in a phase I clinical trial. They recruited nine mild-to-moderate AD patients and injected low and high doses of hUCB-MSC, respectively. All adverse events subsided within 36 h, and their symptoms of AD were mitigated.

Overall, MSC therapy reduces neuroinflammation by eliminating amyloid-β, tangles in neuro fibers, and abnormal degradation of proteins. MSC therapy promotes blood–brain barrier and autophagy-related recoveries, regulates acetylcholine levels, and improves cognition of the brain [12].

3. Embryonic Stem Cell (ESC)

Because there are still ethical and immunogenic limitations to using ESC for treating AD [12], clinical implementation of ESC-based therapy may not be applicable in the short-term. However, there have been a few pre-clinical studies that have shown progress in using ESC to model AD pathology.

On the genetic and cellular level, ESC modeling has made much progress. In 2019, Ubina et al. [13] modeled human ESC on Aβ-dependent neurodegeneration. An allele of APP locus was modified to express $A\beta_{40}/A\beta_{42}$ secretory so that the edited allele expression could pass the amyloidogenic APP processing pathway. After neural differentiation, pathway analysis indicated downregulation of the extracellular matrix and over-expression in cilia functions. In 2021, Fan et al. [14] discovered that SIRT1 controls sphingolipid metabolism and neural differentiation of ESC through c-Myc-SMPDL3B. They focused on sphingolipids because they are vital structures of the cell membrane, which regulate cell differentiation and apoptosis. In AD patients, there is a deficit in creating enzymes to remove excess levels of sphingolipids, which eventually leads to neurodegeneration. In particular, SIRT1, an NAD(+)-dependent protein deacetylase, regulates the degradation of sphingolipids by increasing the production of the enzyme SMPDL3B. Therefore, targeting SIRT1 may offer innovative strategies to treat AD. Notably, SIRT1 is sensitive to high-fat diets; therefore, maternal obesity could be a cause of AD as infants develop into adulthood.

In addition, there are also studies with animal models on ESCs. In 2020, Kim et al. [15] investigated the efficacy and feasibility of intra-arterial administration of ESC in an animal model of AD. MSC significantly inhibited Aβ-induced cell apoptosis in the hippocampus, and increased autophagolysosomal clearance of Aβ. MSC-treated mice performed with higher memory ability than those with only Aβ injection.

4. Induced Pluripotent Stem Cell (iPSC)

iPSC is a technology in which somatic cells are reprogrammed to pluripotent stem cells, creating an optimal physiologically relevant model that maintains the donor’s genetic identity. iPSC can unlimitedly self-renew in vitro, and differentiate into various cell types, which gives hope to model and cure AD [16].

On the genetic and cellular level, there have been multiple studies on iPSC therapy for AD. In 2020, Butler et al. [17] discovered the genetic relevance of human iPSC-derived microglia (iMG) to AD. Microglia are the major immune cell in the brain that imply the pathogenesis of AD. Using gene expression specific to cell type, they showed that iMG cells are genetically relevant to AD. In 2020, Zhang et al. [18] found that human iPSC-derived neural cells from AD patients showed various susceptibilities to oxidative stress. The oxidative stress response of neural cells is a vital mechanism for cognitive dysfunction and aging in AD. Under exposure to H_2O_2, the vitality and neurite length of human iPSC-induced neurons reduced significantly. Due to the oxidative property of neuron cells, there is a potential to treat AD by targeting the de-oxidization of the neurons.

In a mouse model of AD, iPSC-derived neural precursors showed improvement in memory and synaptic abnormalities. Researchers injected mouse iPSC-derived neural precursors (iPSC-NPCs) stereotaxically into the hippocampus of mice.

Mice with iPSC-NPCs transplantation revealed improvement in synaptic plasticity and reduced AD brain pathology, including decreased tangles deposits and amyloid [19].

iPSC can also be used for drug screening and testing for AD. The flexibility of iPSC includes non-invasive harvesting compatibility and sourcing from patients with AD [20]. iPSC is able to reprogram cells without embryo destruction and with negligibly invasive processes [21]. iPSC could create neuronal cells from specific patients, and eradicate the drawback of species-specificity inherent when using animal models. There are also a few novel technologies that can be combined with iPSC models to treat AD, including organoid technology, genome editing, deep learning artificial intelligence, and single-cell RNA sequencing [22].

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