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New Prospects for Stem Cell Therapy in Alzheimer's Disease

Kun Jiang, Yongqi Zhu and Lei Zhang

Abstract

Alzheimer's disease (AD) is a kind of neurodegenerative disease with insidious onset and progressive progression. The etiology of AD may be related to the loss of neurons, astrocytes, and microglial in the nervous system. Exogenous stem cell transplantation has brought hope to the treatment of AD. Stem cell transplantation can reduce amyloid β-protein (Aβ) deposition and Tau phosphorylation, and provide secretory factor support to improve learning and memory deficits. The purpose of this review is to provide an overview of the relationship between different stem cell species and the treatment of AD, and also summarize current experimental stem cell therapy strategies and their potential clinical applications in the future.

Keywords: Stem cells, Therapy, Alzheimer's disease (AD)

1. Introduction

According to the World Alzheimer Report 2019, more than 50 million people worldwide suffer from dementia. It is expected to grow to 152 million by 2050. The current cost of treating dementia is $1 trillion a year, and that cost is expected to double by 2030. There are more than 200 subtypes of dementia, of which 50 to 60 percent are caused by Alzheimer's disease (AD). The concept of the disease was proposed by Alois Alzheimer in 1907. It was later recognized as the most common neurodegenerative disease. Although decades have passed since the discovery of the pathological mechanism of Alzheimer's disease, we still do not know what causes the disease. It is well known that Alzheimer's disease is a sporadic, age-related disease, with only a small proportion caused by genetic factors. The disease is characterized by a progressive decline in cognitive function. Clinically, these patients present with short-term memory impairments that interfere with activities of daily living, followed by impairments in other cognitive areas such as language, logical understanding, orientation, executive function, judgment, behavior, and finally motor impairments [1]. The pathological features of AD include: Senile Plaques (SP) formed by the deposition of amyloid β-protein (Aβ) outside neurocyte; The abnormal phosphorylation of intracellular Tau protein results in the neurofibrillary tangles (NFTs); Synaptic loss, neuroinflammation, neurocyte apoptosis in the neocortex and hippocampus of the brain. The pathological manifestations were brain atrophy [2–5]. In this review, we believe that the most effective strategies should target the biological feature which is most associated with symptoms, the loss of synapses, to treat the disease. Specifically, we focus on recent advances in cell-based therapies that aim at repopulation or regeneration of degenerating neuronal networks in AD [6].

2. Alzheimer's Disease's neuropathology

As mentioned in the background, we group the pathological changes of Alzheimer's disease into two types, which provide evidence of the disease's occurrence and progression: (1) Positive lesions. The main findings include SP caused by Aβ deposition and NFTs caused by abnormal phosphorylation of intracellular Tau protein. Otherwise, dystrophic neurites, neuropil threads and various other sediments found in the brains of patients with AD also falls into this category. (2) Negative lesions, which can also called loss type lesions. The main clinical manifestation is brain atrophy due to loss of synapses. At the same time, other factors, including neuroinflammation, oxidative stress, and damage to cholinergic neurons, are all important factors leading to the occurrence of neurodegenerative diseases.

2.1 Senile plaques (SP)

The SP are extracellular deposits of Aβ with different morphological forms, including neuritic, diffuse, dense-cored, or classic and compact type plaques [5].

The formation of Aβ is from the amyloidogenic cleavage of human amyloid precursor protein (APP) [7]. The anomalous processing of APP by β-secretases and γ-secretases leads to production of $Aβ_{40}$ and $Aβ_{42}$ monomers, which further oligomerize and aggregate into SP [8, 9]. Although soluble $Aβ_{40}$ is much more abundant than soluble $Aβ_{42}$, $Aβ_{42}$ exhibits a higher propensity for aggregation, due to hydrophobicity within its two terminal residues. Indeed, $Aβ_{42}$ is the main component of amyloid plaques and is shown to be neurotoxic [10]. Recent neuroimaging and neuropathology researches reveal that Aβ sedimentation is mainly related to cognitive disorder of the old, and it is not very relevant with other clinical features [11].

2.2 Neurofibrillary tangles (NFTs)

Tau protein is mainly distributed in neurons. Repeated Pro-Gly-Gly-Gly fragments help it bind to tubulin and maintain the structural stability of microtubules. The presence of Tau protein contributes to the maintenance of cytoskeleton and the integrity of axon transport [12]. NFTs are filamentous structures filled in the cytoplasm of neurons -- paired helical fibers (PHF). The reason of Tau hyperphosphorylation is the increased protein kinase activity. Protein kinase activity such as glycogen synthase kinase 3β (GSK-3β) activity can be decreased to reduce phosphorylation. Meanwhile, decreased phosphatase activity is also the reason of hyperphosphorylation. In addition, the lack of glucose in the brain can make Tau hyperphosphorylated by mediating the signal pathway of p38 mitogen-activated protein kinase (MAPK). Increasing the level of glucose in the brain may provide a new idea for treating AD, by using a pharmacological model of glucose deprivation and investigated its effect on Tau phosphorylation, synaptic function and cognition in a relevant transgenic mouse model of tauopathy, the h-Tau mouse [13]. It has been shown that phosphorylation of Tau protein at the early stage of AD inhibits Aβ toxicity, being that Tau phosphorylation-mediated by p38 MAPK can antagonize the postsynaptic excitation toxicity caused by Aβ [14, 15].

2.3 Synaptic loss

Soluble Aβ collaborate with pTau to induce synapse loss and cognitive impairment in AD [16]. Metabolism of Aβ and Tau proteins is crucially influenced by autophagy. Autophagy is a lysosome-dependent, homeostatic process, in which organelles and proteins are degraded and recycled into energy [17]. Neuroplasticity

is an ongoing process that responds to the activity, injury, and death of neurons, including the regulation of the structure and function of axons, dendrites and synapses [18]. Overdeposition of Aβ and abnormal phosphorylation of Tau both lead to decreased neuroplasticity, which is manifested in a series of clinical symptoms caused by synaptic loss in AD [12, 19]. Aβ and Tau both trigger mitochondrial alterations. Some evidence suggests that mitochondrial perturbation acts as a key factor that is involved in synaptic failure and degeneration in AD [20]. Synaptic plasticity and long-term potentiation (LTP) are all about N-methyl-D-aspartate receptor (NMDAR). Aβ oligomer facilitates astrocytes (AS) to release glutamate by a7nAChR and activates NMDAR, making extracellular regulated protein kinases (ERK) signaling pathway to be suppressed and finally suppressing LTP, therefore the synaptic damages caused by NMDAR hyperactivation are the possible mechanisms of AD occurring [21].

2.4 Neuroinflammation

The AD pathophysiology entails chronic inflammation involving innate immune cells including microglia, astrocytes, and other peripheral blood cells. Inflammatory mediators such as cytokines and complements are also linked to AD pathogenesis [22, 23]. Activation of microglia can induce the production of inflammasomes, which in turn increase inflammatory cytokines, and may eventually result in Aβ deposition [24, 25]. Studies have shown that after being activated, astrocytes will release the corresponding cytokines, which can lead to the enhancement of neuronal toxicity, as well as a decreased outgrowth of neuronal processes and an overall decreased activity rate [26]. Recent studies have shown that there is a direct interaction between microglia and astrocytes. In the form that once microglia are activated, they can lead to activation of astrocytes, thus forming feed-forward loops that are harmful to the surrounding environment [26]. The mechanism showed that when being activated, microglia release IL-1α, TNFα and C1q and astrocytes become activated. Microglia and astrocytes are major modulators of inflammation in the brain, and they are also the major sources of apolipoprotein E (ApoE) in the brain. ApoE is a multifunctional protein with central roles in lipid metabolism. It transports lipids, including cholesterol, through the cerebrospinal fluid (CSF) and plasma [27, 28]. Earlier studies have shown that the presence of ApoE helps to inhibit glial activation of lipopolysaccharides in glial cell culture experiments, suggesting that ApoE may exert a protective anti-inflammatory effect [29, 30]. Moreover, the exacerbated proinflammatory state that occurs during this period of AD can trigger the hyperphosphorylation of Tau. Several of the kinases responsible for Tau phosphorylation are activated by proinflammatory mediators and have been shown to worsen Tau pathology [31].

2.5 Cholinergic neurons' injuries

The Acetylcholine (ACh) receptor (AChR) is a vital membrane protein on which ACh acts as a neurotransmitter. The cholinergic receptors are broadly categorized as muscarinic ACh receptors (mAChR) and nicotinic ACh receptors (nAChR) on the basis of their exogenous agonists [32]. ACh plays an important role in human memory function and is strongly associated with age-related dementia such as AD, in which hippocampal dependent learning dysfunction is prominent. Cholinergic neurons densely dominate the hippocampus and mediate the production of episodic and semantic memory [33]. In patients with AD, the synthesis, release and uptake of ACh in the hippocampus, neocortex and cerebrospinal fluid were decreased, the choline acetyltransferase (AChE) was significantly decreased, and the activity of

acetylcholinesterase was decreased [34]. Clinically, the main method of drug treatment for AD is to improve the function of the brain's cholinergic system. Although inhibitors of acetylcholinesterase is a symptomatic relief treatment with marginal benefits, it is currently the most available clinical treatment which gives desperate AD patients a glimmer of hope [35].

3. Stem cell therapy for AD

There are some theoretical approaches to treat early AD. One is to target upregulation of resident neural stem cells (NSCs) niches within the adult brain. In fact, this regulation is to stimulate the development of adult hippocampal nerve, which has reached the purpose of compensating the degenerated nerve. Adult hippocampal neurogenesis may play a key role in learning and memory, so promoting this endogenous process may help improve amnesia in patients with early AD. Another approach is to up-regulate growth factors that are known to modulate neurogenesis integrally, either through drug therapy or gene therapy or, as we describe in this paper, through stem cell therapy. This type of growth factor includes brain-derived neurotrophic factor (BDNF) [36, 37], insulin growth factor-1 (IGF-1) [38], nerve growth factor (NGF) [39–42], vascular endothelial growth factor (VEGF) [43, 44] and so on. Stem cell therapy aims to rescue cognitive function by introducing exogenous stem cells to restore degenerated neural networks. These stem cells can be used as cell delivery systems through the natural or induced production of neuroprotective growth factors utilizing the paracrine "bystander" mechanism. Alternatively, therapeutic recovery may occur through the differentiation and involvement of stem cells in refilling degenerated neuronal circuits. It's a finely balanced, complex, multi-step process.

Some of stem cells are now in clinical use, such as embryonic stem cells (ESCs) derived from the inner cell mass of preimplantation embryos and induced pluripotent stem cells (iPSCs) derived from the epiblast layer of implanted embryos [45, 46]. Mesenchymal stem cells (MSCs) can promote tissue repair through the secretion of extracellular vesicles that carry a variety of cytokines, growth factors and microRNAs (miRNAs) [47]. Adipose tissue-derived stem cells (ADSCs) are a replacement therapy for MSCs, with the similar mechanism which secretion extracellular vesicles (EVs) to multiple proteins possessing neuroprotective and neurogenesis activities [48]. NSCs participate extensively in mammalian brain homeostasis and repair and exhibit pleiotropic intrinsic properties which makes them a good method for the treatment of AD [49].

3.1 ESCs

ESCs are cells isolated from early embryos or primitive gonads. It has the characteristics of infinite proliferation, self-renewal and multidirectional differentiation *in vitro* culture. Both *in vitro* and *in vivo*, ESCs can be induced to differentiate into almost all cell types in the body, so they can be used to improve the recovery of neurodegenerative diseases (such as AD). Therefore ESCs have a broad application prospect in autologous stem cell therapy [50, 51]. Thymic epithelial progenitor cells derived from mouse ESCs with deleted amyloid precursor protein gene have been proved to have the ability to alleviate AD symptoms [52]. Early human embryonic stem cells (hESCs)-derived neural populations consist of various embryonic neural progenitors (ENPs) with broad neural developmental propensity. The hESC-ENP-enriched neural transcription factors (TFs) can directly transform human cells into ENP phenotypes. Induced ENPs (IENPs) and their derivatives summarize the

signature pathological characteristics of AD and hold promise for future strategies for disease modeling and clinical intervention [53].

Although ESCs are good candidates for AD cell therapy, they may bring some ethical and practical problems. Even if we overcome the problem of immune rejection, there have been reports of teratomas resulting from transplanted ESCs [54].

3.2 NSCs

NSCs have the ability to differentiate into neuronal astrocytes and oligodendrocytes, which are self-renewing and sufficient to provide a large number of brain tissue cells [55, 56]. In the past, it was thought that NSCs lost their ability to regenerate during the prenatal period or several months after birth. However, some recent studies have shown that NSCs also exist in adult brain tissues, mainly located in the subventricular zone (SVZ) and hippocampus dentate gyrus (DG) [57–60]. Due to their multidirectional differentiation and self-renewal, NSCs play an important role in maintaining brain homeostasis, promoting normal nerve development and repairing damaged nerves, which provides a possible choice for stem cell therapy for AD [49, 61]. A large number of studies have shown that the gradual accumulation of Aβ leading to the loss of synapses related to cognitive deficits is an important mechanism of AD [62]. In the hippocampus of AD mice after NSCs transplantation, the level of Synaptophysin (SYP), postsynaptic density protein 95 (PSD-95) and microtubule-associated protein (MAP-2) were significantly increased, which are important protein markers related to synaptic plasticity and play an important role in synaptic plasticity and stability, indicating improved learning and memory ability in AD mice [63–65]. Damage of cholinergic neurons in the basal forebrain is another important feature of AD [66]. Reduced cholinergic function due to cholinergic neuron injury may results in learning and memory impairments [67]. Transplantation of NSCs into the basal forebrain will increase the level of choline acetyltransferase (ChAT) protein, restoring the damaged neurons and improving the learning and memory ability [68, 69].

Recent studies have demonstrated the mechanism of NSCs transplantation to improve cognitive function, which is replacing damaged neurons with the differentiation of transplanted NSCs and enhancing synaptic density by releasing neurotrophic factors [61, 70, 71]. Neurotrophic factors have been shown to improve cognitive impairment [72, 73]. Although NSCs transplantation has great potential to be an excellent choice of cell therapy for AD in the future, there are many problems in its application: (1) The attribution that supports the differentiation of NSCs into a specific cell type is not clear. (2) Although NSCs transplantation can salvage synaptic damage and participate in the interaction of endogenous neuronal circuit function, there is no accurate answer to the duration of this effect. (3) The localization of the transplanted area and the viability of the transplanted cells are only the initial challenges of NSCs therapy, and subsequent interactions with cells in the host environment are also important. In some studies, NSCs after transplantation is difficult to trace, and in the cases where NSCs can be traced, the number of activated cells is also difficult to quantify [74]. (4) Many studies have identified transplanted NSCs have potential risk of developing brain tumors, such as glioblastoma [75, 76]. (5) Extrinsic NSCs transplantation also involves ethical issues. Direct isolation of NSCs from the primary tissue is dangerous. Non-patient-specific NSCs are more likely to result in immune rejection [54, 77].

3.3 MSCs

MSCs are pluripotent stem cells, which have all the common features of stem cells, namely self-renewal and multidirectional differentiation. As major stem cells

that have undergone extensive clinical trials, MSCs bring hope for the treatment of a variety of diseases [78]. MSCs come from a wide range of sources. The most common ones are bone marrow mesenchymal stem cells (BMSCs), adipose-derived stem cells (ADSCs), umbilical cord derived mesenchymal stem cells (UC-MSCs), etc. Their biological characteristics are also different [79].

MSCs have the ability of immune regulation, neuroprotection and regeneration. The main mechanisms of MSCs in the treatment of AD are as follows [80]: (1) Secrete growth factors: MSCs secrete a variety of pro-cytokines that may play a beneficial role in AD [81]. (2) Secrete exosomes: Exosomes refer to extracellular vesicles, which are biocompatible nanoparticles with lipid membranes. These vesicles can transmit messages across biological barriers. Studies have shown that intercellular exchange of miRNA and proteins through EVs can reduce neuroinflammation, promote neurogenesis and angiogenesis, save learning disabilities and improve functional recovery [82, 83]. (3) Reduce neuroinflammation by regulating autophagy: MSCs can affect the autophagy of immune cells involved in injury-induced inflammation, thereby reducing their survival, proliferation and function, and facilitating the regression of inflammation. In addition, MSCs can affect the autophagy of endogenous adult or progenitor cells, promote their survival, proliferation and differentiation, and support the recovery of functional tissues [84]. In addition, foreign proteins conveyed by MSCs can regulate microglia function and enhance neurogenesis, so as to alleviate early memory deficits in AD [85]. Transplantation of MSCs carrying CX3CL1 (a multifunctional inflammatory chemokine with a single receptor CX3CR1) [86] and Wnt3a (CX3CL1-Wnt3a-MSC) can regulate phosphoinositide 3-kinase/activated protein kinase B (PI3K/AKT) signaling to inhibit the activity of glycogen synthase kinase 3 beta (GSK3β), improving the neurobehavioral function of mice by transplanting microglia with neurotoxicity and promoting hippocampal neurogenesis.

Reports have shown that EVs secreted by adipocytes derived from ADSCs may treat AD by alleviating neuronal damage, promoting neurogenesis and reducing the increase of neuronal apoptosis [48, 87]. EVs secreted by BMSCs can reach astrocytes to promote synaptic development and improve cognitive impairment [88, 89]. Hepatocyte growth factor (HGF), a core functional factor secreted by UC-MSCs, plays a key role in regulating the recovery of damaged nerve cells [90]. MSCs derived from ESCs have a better effect than BMSCs in the treatment of AD [91].

Modified MSCs pretreated with different conditions or reagents can significantly enhance the therapeutic effect of AD and improve cognitive impairment, such as cytokine pretreated MSCs [92], hypoxia preconditioned MSCs (PCMSCs) [93], MSCs modified by lin28B [94], MSCs prepared by cerebrospinal fluid of AD patients [95], ADSCs pretreated by melatonin (MT) [96], UC-MSCs combined with resveratrol [97].

3.4 iPSCs

Using defined reprogramming factors to reprogram fully differentiated somatic cells into iPSCs has become a novel strategy to produce pluripotent cells derived from patients that enable autologous transplantation [98]. The apolipoprotein E4 (ApoE4) variant is the single greatest genetic risk factor for sporadic Alzheimer's disease (sAD) [27–30]. sAD iPSCs convert ApoE4 to ApoE3 in brain cell types. This conversion can reduce many AD-related diseases [99]. The generation of neural precursors from iPSCs has also been extensively studied. In the production of astrocytes, the mutation in presenilin1 (PSEN1) increased Aβ production and oxidative stress. At the same time, it also altered cytokine release and Ca^{2+} homeostasis. These changes reducing neuronal support function in PSEN1 astrocytes [100, 101]. EVs of either

50–200 nm in size (called exosomes) or 200 nm^{-1} μm in size (called micro-vesicles) are membrane-bounded vesicles. They can carry RNAs, proteins, and other metabolites. They are secreted from all cell types and present in biological fluids such as serum and plasma [50, 102]. Human iPSCs can be cultured infinitely under a chemically defined medium. The properties and functions of exosomes and micro-vesicles (called EMVs) from human iPSCs are different with the ones secreted by human MSCs. Purified EVs produced by both stem cell types have similar sizes, but human iPSCs produced 16-fold more EVs than MSCs [103]. Neurons from patients with early-onset familial Alzheimer's disease (fAD) and patients with late-onset sAD showed increased phosphorylation of Tau protein at all investigated phosphorylation sites. Relative to the control neurons, neurons derived from patients with fAD and patients with sAD exhibited higher levels of extracellular amyloid-β 1–40 (Aβ$_{1-40}$) and amyloid-β 1–42 (Aβ$_{1-42}$) [104–106]. Using iPSCs-derived neurons to recapitulate AD pathology *in vitro* has significant applications in the study of pathogenesis and screening for potential therapeutic drugs. They are now the subject of extensive study *in vitro* [107]. Studies have also shown that EVs from iPSCs can play an important role in heart repair [108].

3.5 Clinical trials and results in humans

Due to the inconsistent results of various preclinical studies, stem cell therapies other than MSCs are still difficult to be applied clinically. Some articles specifically showed us the application of MSCs-based stem cell therapy in human clinical trials [6, 80, 109, 110]. In recent years, more studies have been conducted on rodents. The effects of MSCs on AD pathology and cognitive mouse models may be mediated by the regulation of neuroinflammation [111, 112]. In recent years, clinical trials using mesenchymal stem cells have been conducted around the world. A completed clinical trial in the United States (Trial identifier: NCT03117738) investigated the safety and efficacy of autologous ADSCs. At the same time, a team studied the efficacy of UC-MSCs (Trial identifier: NCT01297218). Compared with cholinergic drugs that only improve symptoms, UC-MSCs are immunologically stable and not-toxic, and have better therapeutic effect on AD. UC-MSCS remain a common cell choice, although there are key differences in cell number, dose quantity, and dose schedule (Trial identifier: NCT03172117). Two separate trials, both currently undergoing recruitment, will utilize alternative MSC sources. One studies human MSCs (Trial identifier: NCT02833792) and evaluates its safety and efficacy. The other utilizes the exosomes derived from allogenic adipose mesenchymal stem cells (MSCs-Exos) (Trial identifier: NCT04388982) to treat patients with mild to moderate dementia due to AD. While many of these trials employ an intravenous infusion administration route, one trial (Trial identifier: NCT03724136) administered BMSCs to the nasal mucosa topically, to investigate whether there was an improvement in efficacy in combination with intravenous injection.

4. Future directions

Numerous preclinical studies have revealed the different mechanisms of various stem cells and demonstrated the great potential of stem cells to treat AD. However, the biggest problem in this area of research is that it is difficult to translate animal studies into human trials. In fact, researchers have used nearly a hundred methods to effectively treat AD in transgenic mouse models. Disappointingly, almost every approach has failed in human clinical trials or has never even been tested in humans. Clearly, rodent models and their pathological assumptions are insufficient

to predict clinical outcomes in humans. Therefore, the establishment of more accurate models is needed for cell therapy of AD. Since the goal of truly simulating the pathological progress of AD in human body has been achieved, more experiments on cell therapy need to be carried out.

At the same time, key questions remain to be addressed, including the safety of treatment, optimal cell source and delivery system. While cell therapies may not be able to fully compensate for the loss of extensive synapses, they can help to temporarily improve existing depleted circuits enough to improve cognitive function, restore basic daily living functions, and improve quality of life. For us, stem cell therapy for AD still has a long way to go.

5. Conclusion

AD is a neurodegenerative disease, which is characterized by excessive deposition of Aβ and abnormal phosphorylation of Tau protein and synaptic loss. Studies and clinical trials in recent years are also based on these basic mechanisms. Although the role of stem cell therapy in AD is not fully understood, many preclinical studies have provided a number of promising results. However, human clinical trials are still in their infancy, and most current research is still centered on animal experiments. But it also shows the broad prospects of stem cell therapy for the AD. A large number of preclinical studies have demonstrated the theoretical basis, and new studies are continuing to reveal the underlying mechanisms. Among many stem cells, MSCs-based therapies are widely accepted and have met certain clinical trial standards. The vast majority of cell therapies for AD have been conducted on rodents, and we must be aware of a wide range of physiological differences between humans and rodents. We need to understand the mechanism of treatment through animal experiments and establish the correct translation model for human application.

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