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Review article

Prospects for the application of mesenchymal stem cells in Alzheimer's disease treatment

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ABSTRACT

Alzheimer's disease (AD) as a dementia and neurodegenerative disease, is mostly prevalent among people more than 65 years. AD is mostly manifested in the form of degraded mental function, such as losing memory and impaired cognitive function. Due to inefficiency of traditional pharmacological therapeutic approaches with no long-term cure, cell therapy can be considered as a capable approach in AD management. Therapies based on mesenchymal stem cells (MSCs) have provided hopeful results in experimental models regarding several disorders. MSCs enhance the levels of functional recoveries in pathologic experimental models of central nervous system (CNS) and are being investigated in clinical trials in neurological disorders. However, there is limited knowledge on the protective capabilities of MSCs in AD management. Almost, several experiments have suggested positive effects of MSCs and helped to better understand of AD-related dementia mechanism. MSCs have the potential to be used in AD treatment through amyloid-β peptide (AB), Tau protein and cholinergic system. This review aimed to clarify the promising perspective of MSCs in the context of AD.

1. Introduction

As a highly prevalent neurodegenerative disease and the sixth leading cause of mortality in the United States, Alzheimer's disease (AD) has been defined to have characteristics, such as progressive memory loss, disorientation, lingual deterioration, problem-solving, mood swings, along with the lack in motivation and other cognitive functions limiting daily life activities and Quality of Life (QoL) [110]. The global number of AD is 36 million at the present which this number will be tripled by the year 2050 [86]. The progressive and neurodegenerative problem of AD are manifested by gradual deterioration of memory, degrading cognitive abilities, loss of neurons and function in the basal forebrain [9,121]. Firstly, AD was explained by a German neuro-pathologist named Alos Alzheimer. He discovered the Amyloid-beta (Aβ) plaques and neurofibrillary tangles in the brain [56]. Aβ plaques are misfolded proteins accumulated in extracellular space with neurotoxic properties and are able to induce neuronal loss. The Second misfolded protein in AD is Tau, a microtubule-associated protein which accumulates intracellularly and pathological features of this phenomenon shows close association with AD cognitive degradation [34]. However, mutations in Tau encoding gene usually contribute in frontotemporal dementia and not AD [34]. Neurofibrillary tangles are insoluble aggregates of hyperphosphorylated Tau protein. Despite the vagueness of Aβ plaques relationship with Tau neurofibrillary tangles, it has been perceived that their synergistic function result in neuronal and synaptic losses in various cortical regions of the brain, which in turn cause memory loss and cognitive degradation [21,56]. Being an age oriented issue, Early-Onset AD (EOAD) begins before than 65 years old [80]. It has been determined that mutations in three various genes of amyloid beta (A4) amyloid precursor protein (APP), presenilin 1 (PSEN1) and precursor 2 (PSEN2) are responsible for EOAD [86]. Another type of AD is Late-Onset AD (LOAD) (sporadic AD), which is resulted from

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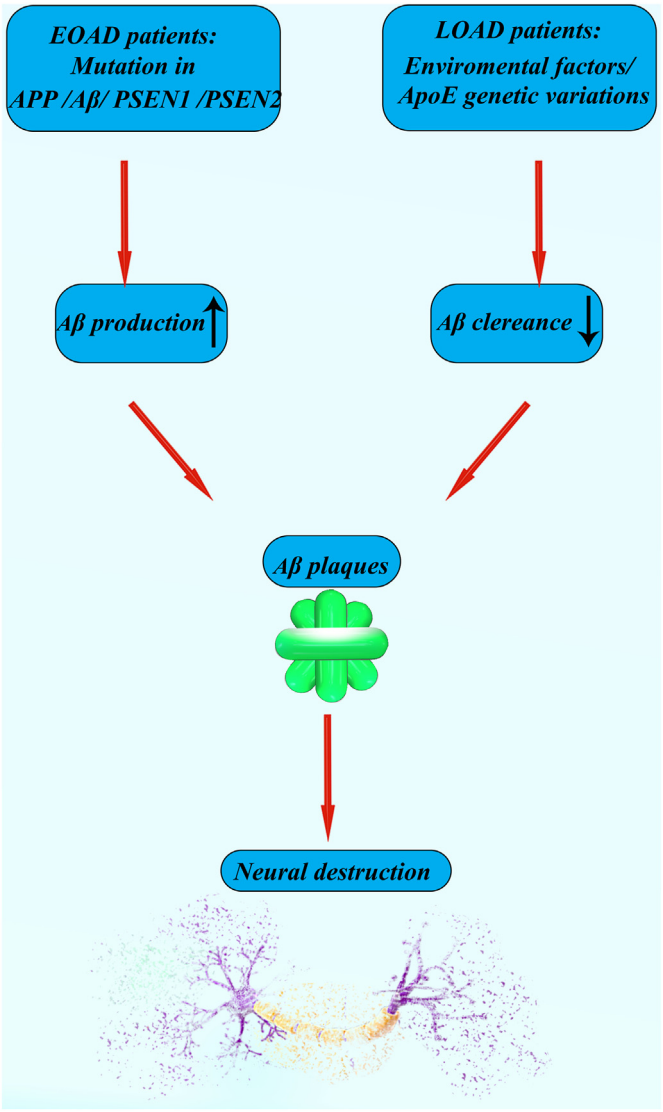

Fig. 1. Types of AD and its molecular pathogenesis mechanism. AD, Alzheimer's disease; EOAD, early-onset AD; APP, amyloid precursor protein; Aβ, amyloid-beta; PSEN1, presenilin 1; PSEN2, precursor 2; LOAD, late-onset AD; ApoE, apolipoprotein.

environmental factors genetic contributions with apolipoprotein E (ApoE) as the most responsible factor (Fig. 1) [86]. Genes encoding apolipoproteins, lipid homeostasis (involved in endocytosis) and membrane spanning 4-domains (MS4) family proteins have been reported to be associated with the risk of LOAD [11,21]. Every person carries two copies of the apoE gene existing in three allelic forms of ε2, ε3 and ε4. These allelic forms are responsible for encoding three corresponding isoforms: ApoE2, ApoE3 and ApoE4, respectively. ApoE4 carriers constitute a 60–75% genetic makeup of AD cases; however, these individuals only and nearly represent 25% of the normal population [103]. Among all populations, the most common ApoE polymorphism is e3 allele (ApoE3) which is risk-neutral, while e2 allele (ApoE2) is less common and it is perceived to be associated with decreased risk of AD [8].

Mutations close to β (*e.g.*, K670N, M671L) and γ (*e.g.*, V717I) secretase cleavage contributing sites forming 42-amino acid Aβ product of APP (Aβ42) (Fig. 2) [89]. In a similar manner, the pathogenic mutations in the most commonly affected genes causing autosomal dominant AD (ADAD), PSEN1, and its homolog presenilin 2 (PSEN2) [53] can increase partial production of Aβ42 [83]. Aβ42 is the most notable component of the extracellular plaques with a high self-binding capability forming β-pleated structures which play an important role in AD [89].

Decreased neurons in the basal forebrain cholinergic nuclei (BFCN) and the decreased levels of choline acetyl transferase, acetylcholine, and acetylcholinesterase (AChE) in the hippocampus and neocortex has made cholinergic hypothesis of AD to be developed [95]. In order to pharmacologically treatment of AD, utilization of acetylcholine esterase inhibitors is necessary, which play an efficient role in cognitive, functional, and behavioral symptoms of the disease, however, their adverse effects in AD are still unclear. Other pharmacological treatments such as the newly confirmed drug memantine (*i.e.* *N*-methyl-D-aspartate (NMDA) channel blocker) are gradually becoming feasible and suggested for advanced AD subjects [93]. For neurodegenerative disorders, stem cell-based therapies aim to hamper the clinical degradation by regeneration and provide a local maintenance for impaired tissue [106].

Mesenchymal stem cells (MSCs) are a group of pluripotent stem cells that acquire plasticity characteristics, enabling them to differentiate into non-mesenchymal lineages [22]. Several procedures have been acclaimed *in vitro* for MSCs differentiation into neurons, but there are still major concerns over its efficiency and *in vivo* conditions of such differentiation. Therefore, despite the fact that their neurogenic differentiation properties are still controversial, they are recommended as effective options in neurological diseases including Stroke, Parkinson's diseases (PD), Multiple Sclerosis (MS), and AD treatment [104]. The potential capability of MSCs to be differentiated into neural cells suggests that they can be considered as a therapeutic approach for neurodegenerative diseases in AD. In AD, stem cell-based treatment has tried to replace damaged or lost neurons. Neurons derived from stem cells have the potentiality to be integrated into the neural networks of the hosting brain [58]. The therapeutic effectiveness of MSCs has been attributed to their ability to immigrate and engraft to the target sites. Therapies based on MSCs not only regenerate impaired neuronal tissue, but also inhibit the disease progression. In this review, we have tried to discuss the effect of MSC treatment on AD therapy. Among all types of stem cells, MSCs (the most concentrated type) has provided a great potential for the disease treatments.

2. General treatments of AD

AD is a complicated brain network-degrading disorder generating a challenging issue for development of effective drugs [126]. Aβ deposits are pathological signs of AD and it suggests the notion that Aβ depletion can be considered as a suitable therapy for AD. As known, vitamin E is an antioxidant that prevents lipid peroxidation, and vitamin C is a water-soluble antioxidant which is a pre-requisite for the vitamin E reactivation. In clinical applications, both vitamins have been extensively used to prevent AD [63]. Extracellular Cathepsin B is accompanied by amyloid plaques and is able to be co-localized with Aβ for regulation of secretory vesicles in chromaffin cells [32]. Cathepsin B decreases the partial influence of Aβ *via* limited proteolysis as well as cysteine protease. Therefore, the activation of Cathepsin B can be considered as a novel therapeutic strategy for AD [70]. Neprilysin is another major extracellular Aβ degrading enzyme which clears Aβ from the brain. It has been reported that human neprilysin injection decreases the amyloid plaques levels in the transgenic mouse [64]. Hypoxia-Inducible Factor 1 (HIF-1) regulators can also potentially reduce the activation of Aβ-promoted astrocyte, prevent Aβ toxicity, and improve brain glucose metabolism [126]. M30 or 5-[*N*-methyl-*N*-propargylaminomethyl]-8-hydroxyquinoline is a HIF-1 activator which increases and decreases the HIF-1 expression and the accumulation/plaque formation of Aβ in APPswe/PSEN1 mice model of AD, respectively, by HIF-1-dependent neuroprotective genes upregulation [68].

Former investigations have reported that the Kelch like-ECH-associated protein 1 (Keap1)–nuclear factor (erythroid-derived 2)-like 2

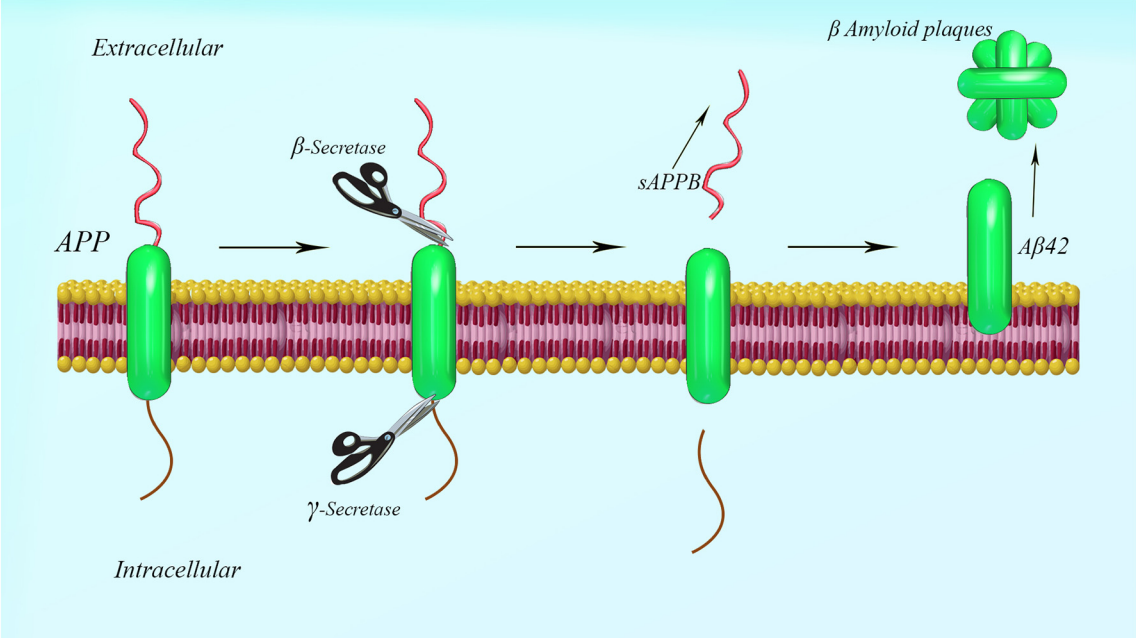

Fig. 2. Cleavage of Amyloid precursor protein (APP). APP is cleaved by β-secretase and γ-secretase, to form the soluble amyloid precursor (sAppβ) and also the 42-amino acid Aβ product of APP (Aβ42). The Aβ42 then is aggregated and form Aβ plaques. AD, Alzheimer's disease; APP, amyloid precursor protein; Aβ, amyloid-beta; sAppβ, soluble amyloid precursor.

(Nrf2); (Keap1–Nrf2) pathway can also regulate different AD-relevant pathogenesis processes, including Aβ deposition, iron homeostasis, oxidative stress (OS), mitochondrial dysfunction, astrocyte activation, and glucose metabolism [99]. As the activators of Nrf2, Tecfidera or Dimethyl Fumarate (DMF), can inhibit the interaction between Keap1–Nrf2 *via* covalent S-alkylation of cysteine thiols of Keap1 and may have therapeutic properties in AD treatment [38]. Recently, researchers have focused on the neurogenesis stimulation *via* brain-permeable molecules. Allopregnanolone has potential anti-AD properties and it can be served as an evidence for therapeutic approaches targeting neural regeneration [14]. This agent is a prototypic neurosteroid displaying an age-associated disease amelioration in the brain as a potential modulating γ-aminobutyric acid (GABA) A receptors agent [14]. However, because of allopregnanolone low solubility and metabolism in the digestive tract and liver, oral use of this agent shows some difficulties [36]. Moreover, the adverse effects of allopregnanolone on cognitive function in human and animal studies have also been reported. Additionally, chronic allopregnanolone use accelerates AD development in impaired episodic memories among healthy female individuals [41].

AChE inhibitors and *N*-methyl-D-aspartate receptor agonist, as other therapeutic agents, have been approved by The US Food and Drug Association (FDA) to be applied in the treatment of mild to moderate AD [5]. However, despite generally well tolerated of the mentioned drugs, these pharmacological interventions have led to palliative results and only delayed disease progression partially [73].

The current AD treatments have only focused on symptoms related to the neurotransmitter systems and they did not target the underlying pathologies. Therefore, more efficient targeted interventions are still required [28]. One such strategy can involve the use of nerve growth factor (NGF). In injury, amyloid overexpression, and aging animal models, NGF has triggered cholinergic function, improved memory and inhibited cholinergic degeneration [112]. NGF also shows a high and low affinity to tropomyosin kinase receptor A (TrkA) and non-selective neurotrophin receptor p75 (P75NTR), respectively [112]. Interactions between TrkA and P75NTR mediate NGF signaling, whereby both pro-survival and apoptotic-regulatory pathways are involved [112]. The balance between these receptors is crucial in AD pathology, so that TrkA (but not P75NTR) decreased levels in basal forebrain cholinergic neurons (BFCN) will result in an increased behavioral symptomology and Aβ pathology [19]. These receptor's interactions develop a time course for AD pathology, in which NGF initially serves as a protective molecule, and then, it is involved in degenerative responses [66]. In an early single-subject study, intraventricular murine recombinant NGF over three months improved verbal episodic memory, and caused significant weight loss in an AD patient [7,15]. Back pain and weight loss were manifested in another similar trial with three AD patients. However, this study was initially ended up because no significant clinical improvement was observed [112]. The painful responses following NGF treatment is due to NGF involvement in the inflammatory response [72]. In a phase I trial of *ex vivo* NGF gene delivery to autologous fibroblasts were implanted into the forebrain of 8 mild-AD patients [105]. After 22 months follow-up, no adverse effects of NGF were observed in 6 subjects. Evaluation of the Mini-Mental Status Examination and Alzheimer's disease Assessment Scale-Cognitive subcomponent showed an improvement in cognitive degradation rate. Moreover, series of positron-emission tomography (PET) scans revealed significant increase of cortical 18-fluorodeoxyglucose levels after treatment. Brain autopsy of a single case also suggested a remarkable growth in response to NGF [105]. An open-labeled phase I trial of *in vivo* NGF gene delivery was also recently conducted on 10 CE patients. The Adeno-Associated Virus serotype 2 (AAV2) vectors were utilized and exhibited high capabilities of long-term gene expression in brain compared to the vectors used in the *ex vivo* NGF trial [84]. This investigation scrutinized the safety, tolerability and preliminary efficacy of three increasing doses of the genetically engineered NGF (AAV2-NGF [CERE-110]). Bilateral AAV2-NGF was received stereotactically into the AD patients meynert nucleus basalis. For two years, AAV2-NGF remained safe and well-tolerated. PET scan and neuro-psychological examinations did not depict any evidence of enhanced degradation. Furthermore, brain tissue autopsy also proved long-term, targeted, gene-mediated NGF expression and bioactivity [84]. This investigation suggested an ongoing multicenter, double-blind, and sham-surgery-controlled trial in future on the same subject matter.

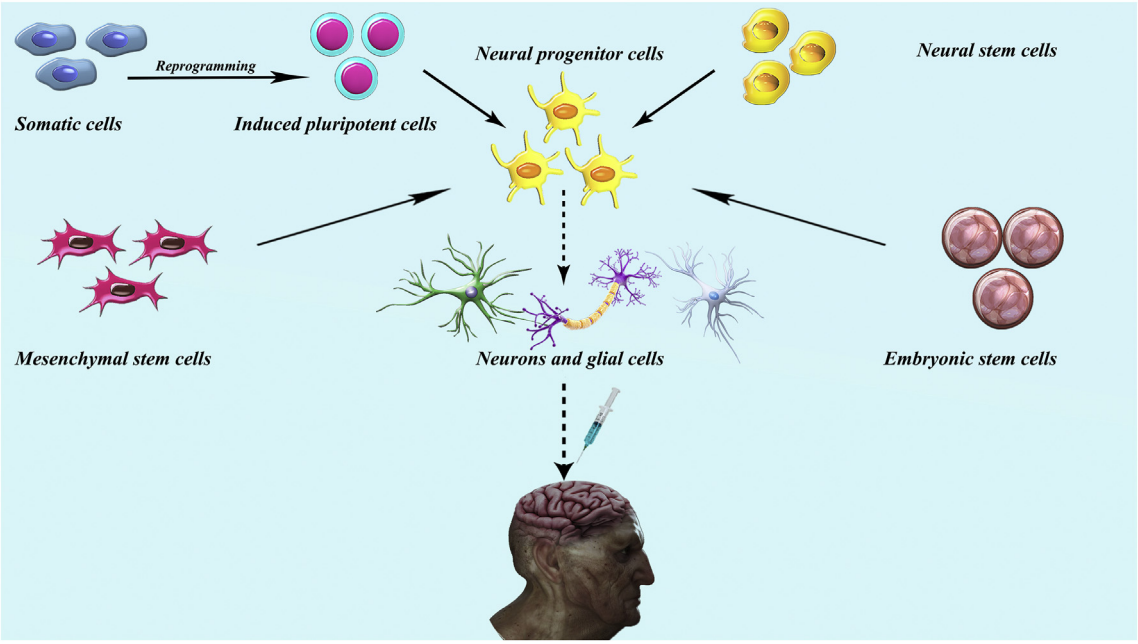

Fig. 3. Schematic diagram of stem cell sources for AD therapy. There are four types of stem cells for treatment of AD: MSC from different sources; iPSCs that reprogrammed from somatic cells; NSC from human brain tissue; ESCs. AD, Alzheimer's disease; iPSCs, induced pluripotent stem cells; MSCs, mesenchymal stem cells; NSCs, neural stem cells; ESCs, embryonic stem cells.

3. Stem cell treatment for AD

The fundamental mechanisms of stem cells therapies for AD treatment are complicated because of AD diverse pathological exhibitions and the complexity of the interactions between engrafted cells and the hosting brain (Fig. 3). Numerous types of stem cells exist in the body. Generally, they can be divided into embryonic and adult (somatic) stem cells [56,100]. However, the special classification of stem cells includes induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), bone marrow (BM) and adipose tissue-derived stem cells (ADSCs) [27].

MSCs are a sub-group of pluripotent stem cells that possess plasticity, allowing them to be differentiated into non-mesenchymal lineages [22]. Stem cell-derived neurons are capable of being integrated with existing neural networks of the hosting brain [57]. Furthermore, stem cells transplantation increases the levels of acetylcholine which improves cognition level and memory in the animal model [77]. Moreover, neurotrophic factors such as brain-derived neurotrophic factor (BDNF) are secreted from stem cells to modulate neuroplasticity and neurogenesis [76]. Some types of stem-cells including MSCs and neural stem cells (NSCs) apparently exert anti-inflammatory effects by decreasing the release of pro-inflammatory cytokines and up-regulation of the anti-inflammatory factors like interleukin (IL)-10 [46]. The engrafted MSCs can also eliminate the Aβ plaques deposits in AD brains through differentiation into microglia cells or activated endogenous microglia cells enrollment [51]. In the following sections the effects of different stem cell therapies on AD treatment will be discussed (Fig. 4). Preclinical studies in the Alzheimer treatment were summarized in Table 1.

3.1. Neural stem cells (NSCs)

NSCs are found in central nervous system (CNS) and are characterized by self-renewal, multilineage differentiation potentiality, and *in vivo* and *in vitro* proliferation [124]. NSCs are ideal donor-cell sources for AD patients cell therapy [47,74]. NSCs reside inside the brain and have the ability to be differentiated into neurons, astrocytes, and oligodendrocytes [102]. Unfortunately, NSCs isolation is a complicated and difficult task. Current studies have used fetal NSCs, however the ethical issues remains debatable in this unregard [25]. NSCs can be supplied from primary tissues such as fetal, and postmortem neonatal or adult brain tissues, as well as ESCs and iPSCs origin [31,122]. NSCs are also utilized as a medium for delivering potential therapeutic agents, including neprilysin, insulin degrading enzyme, plasmin and cathepsin B, leading to decreased Aβ levels in AD mouse models [24]. Reportedly, fibroblast-delivered neprilysin has decreased amyloid plaques in AD mice. Additionally, neprilysin gene delivery by grafted NSCs has also contributed to significant decrease in amyloid plaques among mice [17]. Thus, it is suggested that NSC-based therapies on AD patients must be concentrated on such indirect mechanisms, instead of primary neuronal replacement, during neurotrophic factors delivery [23,65]. In a study, transplantation of NSCs isolated from neonatal rats hippocampus into the brain of an AD rat model by a transected fimbria-fornix (FF), showed a spatial recovery of learning and memory skills and generation of new cholinergic neurons in these rats [115]. Moreover, intra-hippocampal transplantation of murine NSCs (mNSCs) have increased synaptogenesis and promoted cognition level among 3xTg-AD mice and the CaM/Tet-DTA model of hippocampal neuronal loss [12,117]. In other study, it was found that human overexpressing choline acetyltransferase (ChAT) NSCs implementation in an AF64A-cholinotoxin-induced (AF64A is ethylcholine mustard aziridiniumion) AD rat model improves complex learning and memory deficits, and results in enhanced ACh levels in the cerebrospinal fluid (CSF) [75]. Immortalized human NSC lines such as HB1·F3, are also reported to be safe and effective when they were transfected with ChAT and transplanted into the brain of AD models [75]. Furthermore, transplantation of neuron progenitor cells (NPCs) into the cortices of transgenic mice expressing human P301S Tau protein has exerted a neuroprotective effect through stimulating of neurotrophic factors secretion, such as ciliary neurotrophic factor (CNTF), NGF, Glial Cell Line-Derived Neurotrophic Factor (GDNF), and BDNF [30]. In a selective granular neurons loss (induced by Aβ1–40 fragment injection into the upper leaf) animal model, NPCs transplantation into the dentate gyrus (DG), also prompted spatial learning and recovered memory skills. In addition, increased glutamatergic and GABAergic neurons were detected after 8 and 12 weeks of transplantation. Furthermore, donor neurons expressed proteins essential for synaptic transmission, including major subunits of

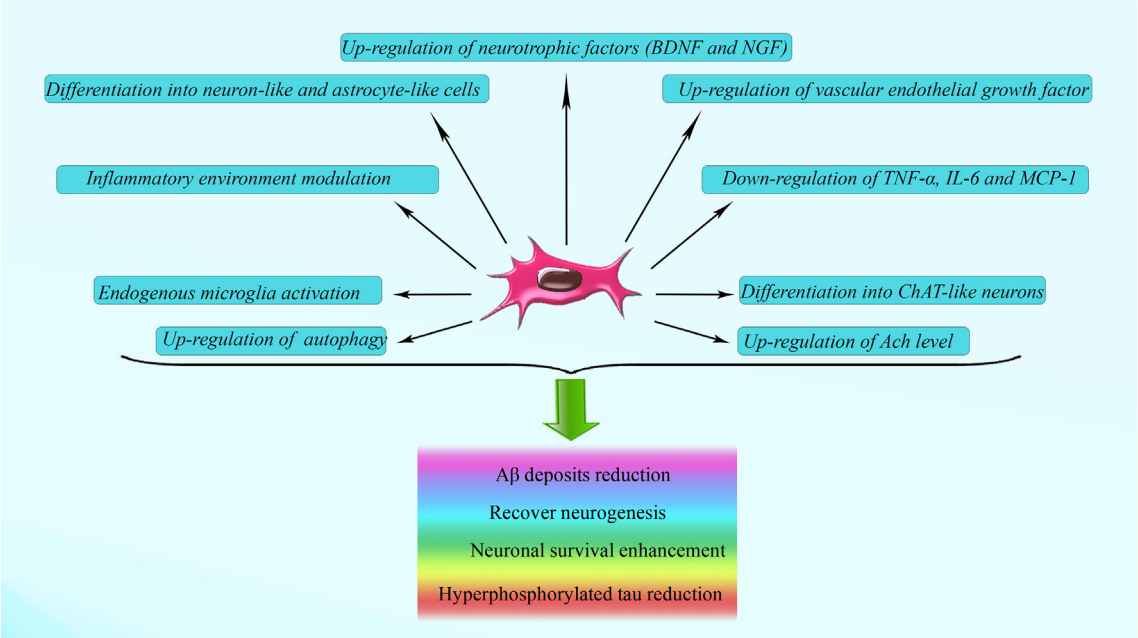

Fig. 4. Mesenchymal stem cells mechanism of action in AD treatment. Aβ, amyloid-beta; AChE, acetylcholinesterase; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor.

ionotropic glutamate and GABA receptors (NR1, GluR1, and GABAA receptor β-chain) [55]. Thus, NPCs transplantation into the DG of the hippocampus, instead of dorsal hippocampus, can be considered as a novel and potential therapeutic approach for AD [55].

Other studies have reported that transplantation of human NGF-overexpressing NSCs into the hippocampus of ibotenic acid induced learning deficits in rats, will be survived, blended with the hosting brain, and promote cognitive performance [49]. Thereupon, it was revealed that cognitive degradation in transgenic mice model of AD can be hampered by NSC therapy with no changes in Aβ or Tau protein

Table 1
Preclinical studies in the Alzheimer treatment.

Cell type	Study design	Outcomes	References
-Murine NSCs	- Intra-hippocampal transfer into 3xTg-AD mice	- Increase synaptogenesis -Promote cognition level	[117]
-Human NSCs	- Transfer of ChAT- overexpressing NSCs into AF64A-cholinotoxin-induced AD rat	- Improve learning and memory deficits -Enhance levels of ACh in CSF	[75]
-Human NPCs	- Inject of the toxic Aβ1–40 fragment into the DG of the hippocampus	- Recover spatial learning and memory skills - Detect abundant glutamatergic and GABAergic neurons	[55]
- Human NSCs	- Transfer of NGF-overexpressing NSCs into Hippocampus of ibotenic acid induced cognitive dysfunction rats	- Promote cognitive performance	[49]
-Human NSCs	- Transplant of cells derived from donated fetal brain tissue into 3xTg-AD model and CaM/Tet-DTA model mice	- Promote cognition level -Enhance endogenous synaptogenesis	[2]
-Human NSCs	- Transplant of cells into the fimbria fornix APP/PS1 murine model of AD	- Reduce amyloid plaque load -Improve memory	[67]
- Mouse ESC-derived NPCs	- Transplant into the Aβ-injured rat model	- Ameliorate memory impairment	[101]
- Mouse ESC-derived NPCs	- Transfer into the unilateral NBM in a rat model of AD	- Improve in memory skills	[69]
-Human MSCs	- Transfer human recombinant activin A in SVZ-derived NSCs into an *in vitro* model of AD.	- Induce neuronal development and neurite outgrowth	[78]
- Mouse MSCs	- Inject 10^6 cells into APP/PS1 mice	- Reduce in the size of Aβ plaques	[71]
-BMMSCs	- Intracerebral transfer MSCs into Aβ-induced AD mice model	- Enhance microglial activation -Rescue cognitive impairment -Reduced the Aβ deposits	[50]
-rBMMSCs	- Infuse cells into the hippocampus	- Improve in learning and memory skills	[10]
-rBMMSCs	-Transfer of $3*10^5$ rBMMSC into APP/PS1 transgenic mice	- Reduce Aβ deposition - Control the redox status under oxidative stress	[120]
-Human UCB-MSCs	- Transfer into APP/PS1 mice	-Enhance spatial learning and memory degradation	[48]
-Human UCB-MSCs	- Transferred into the hippocampi of AβPP/PS1 mice	-Promote level synapsin I level -Recover cognitive function	[118]
-Human UCB- MSCs	-Transplant into the hippocampus of transgenic mouse model of AD	- Reduce Aβ plaques	[45]
Human MenSCs	-Intracerebral transplant into APP/PS1 mice.	-Promote spatial learning and memory among - Ameliorate amyloid plaques -Reduce tau hyperphosphorylation	[125]

AD, Alzheimer's disease; ChAT, Choline Acetyltransferase; CSF, Cerebrospinal Fluid; DG, Dentate Gyrus; ESCs, Embryonic Stem Cell; MenSCs, Menstrual blood-derived Stem Cells; MSCs, Mesenchymal stem cells; NPCs, Neuron Progenitor Cells; NSCs, Neural Stem Cells; RBMMSC, Rat Bone Marrow-Derived MSCs, SVZ, Subventricular Zone; UCB-MSCs, Umbilical Cord Blood MSCs.

levels [13]. A former imaging study also illustrated parallel findings suggesting that plaques and tangles can be accumulated for many years long before the cognitive function would start to decline [42]. Cognitive improvement is positively correlated with neurogenesis as they found an increase in BDNF, which has role in synaptogenesis and neuronal networking [4]. Post-mortem AD immunohistochemical investigations aimed to study the application of NSCs and aggregated proteins co-localization in identification of Aβ, Tau and NSCs interactions [13]. HuCNS-SC transplantation (a population of human NSCs), derived from donated fetal brain tissue, can also improve the decreased cognition in AD models [2]. HuCNS-SC cells have the capability to migrate and differentiate into immature neurons and glia and significantly increase synaptic and growth-associated markers in both 3xTg-AD and CaM/Tet-DT_A mice. However, improvements in aged 3xTg-AD mice cannot be attributed to alter Aβ or Tau pathology. Additionally, transplantation of human NSC promotes cognition level by enhancing endogenous synaptogenesis [2]. In another proof-of-concept investigation carried out pre-clinically on APP/PS1 murine AD model, human neural stem cells were transplanted into the fimbria fornix. It was observed that the cognition level in two hippocampal-dependent memory tasks were significantly meliorated 4 and 16 weeks after the transplantation [67]. Despite unchanged synapse-related proteins and cholinergic neurons levels, amyloid plaque load was significantly reduced in stem cell transplanted mice in association with increased recruitment of activated microglia. These NSCs induced microglial activation and amyloid phagocytosis *in vitro*, suggesting their immunomodulatory capacities [67].

3.2. Embryonic stem cell (ESCs)

ESCs are characterized as totipotent and self-renewing cells which can be differentiated into NPCs *in vitro*. This gives them therapeutic properties when they are transplanted into AD animal models [88]. Usually, direct transplantation of ESCs into AD animal models cause teratoma formation rather than neuron production. Nevertheless, in animal models, the safety level of ESC-derived NPCs and neurons transplantation has been confirmed [88]. Transplantation of ESC-derived NPCs into the Aβ-injured rat model has revealed that the escape latency is significantly increased compared to phosphate buffered saline (PBS)-treated controls two weeks after injection [54,101]. The morris water maze test (MWM) which is usually conducted to measure spatial learning and memory function, also showed a significant decrease in latency escape 16 weeks after transplantation compared to sham controls [101]. Reportedly, ESC-derived NPCs were able to be differentiated into astrocytes and neuron-like cells *in vivo*. These findings implied to the fact that ESC-derived NPCs could ameliorate memory impairment. Although, ESCs may induce teratoma formation, ESC-derived NPCs have the potential to treat neurodegenerative diseases [101].

In vitro culture of mouse ESC (mESC) also suggested that NPCs can be efficiently generated, expanded, and differentiated into neurons and glial cells [114]. Most of the times, conventional protocols on the neural differentiation from ESCs include the formation of embryoid bodies (EBs) and subsequent culture of the attached EBs in selective, serum-free medium to eliminate non-neural cells [113]. Neurospheres derived from ESC are then transferred into the frontal cortex of nucleus basalis of meynert (NBM) mouse model and produce large number ChAT-positive, as well as small number of serotonin-positive neurons in and close to the engrafted cells and elevate memory working [26]. Primed and unprimed transfer of mESCs derived NPCs into the unilateral NBM in a rat model of AD, also has caused great improvements in their learning and memory skills. The mainstream of the engrafted NPCs maintained a neuronal phenotype, however almost 40% of these cells displayed cholinergic cell phenotype [69]. mESCs and human ESCs (hESCs) are different in their properties. Distinct protocols have been designed for human NPCs generation from hESCs. The most typical protocols involve multicellular aggregates, long-term culture, co-culture, and/or genetic manipulation [26]. Despite no reports on the therapeutic potentials of hESCs for AD, evidence has indicated that hESCs can be considered as a novel factor in treatment of different types of neurodegenerative diseases and brain injuries [94]. However, because these cells are derived from preimplantation human embryos, ethical issues must be noted before using hESCs in AD clinical trials. Moreover, the probability of immune rejection in ESC-based cell therapies of AD is still a matter of dispute [94].

3.3. Induced pluripotent stem cells (iPSCs)

iPSCs can be derived from skin cells and are characterized by retroviral expression of octamer-binding transcription factor 4 (OCT4), sex determining region Y-box 2 (SOX2), proto-oncogene proteins c-Myc, and kruppel-like factor 4 (KLF4). These cells can also be differentiated into neural cells [87]. iPSCs are pluripotent cells, having the capability to enhance the number of any cell type of the three germ layers containing mesoderm, ectoderm, and endoderm [18,109]. Unlike ESC-based therapy, which carries immune rejection concerns, iPSCs can be generated from the patient's own somatic cells ending up ethical controversies over the use of human embryos and immunogenic rejection [98]. Regarding the recent progresses in reprogramming technology, iPSCs have acquired great chance to be used in AD treatment. Patients' somatic cells can be reprogrammed to generate iPSCs, which in turn can be directed into the differentiation of neural precursor cells for transplantation [39]. Moreover, iPSCs use can improve modeling of neurodegenerative diseases such as AD, conserving patient's unique genetic phenotype [121]. It creates a model with closest approximation to the sporadic form of the disease to be applied in human for AD treatment [116]. Autologous and genetically modified iPSC-derived neurons can probably make existing cells suitable to be transplanted into Familial AD (FAD) patients [37]. iPSCs also confer an available exceptional platform to identify the early-disease phenotypes during neurogenesis or neurodegeneration as probable underlying AD pathogenic mechanisms [90,98]. Genetically repaired AD-iPSCs can control cells in disease modeling and cells transplantation [98]. Human iPSCs models derived from patients' cells have provided new horizons in improving our understanding of the early molecular stages of these diseases [90].

3.4. Mesenchymal stem cells (MSCs)

This type of stem cells can be isolated from BM, placenta, adipose tissue, lungs, blood, and the umbilical cord. They can be differentiated into diverse cell types [3]. Regarding the barriers against clinical implementation of ESCs and iPSCs, there is an escalating focus on MSCs free from both ethical concerns and teratoma formation [108]. These cells can be considered as the precious sources of cells for therapeutic transplantation as they are capable to be differentiated into therapeutic cells, providing trophic support and modulate immune responses [59,81]. The most common types of MSCs utilized in clinical trials are autologous BM-derived MSCs (BM-MSCs) and Umbilical Cord Blood-derived MSCs (UCB-MSCs) [6,85]. It is still unclear whether a particular subset of MSCs has tendency toward homing to the sites of tissue injury or not. Selecting MSCs, based on their chemokine receptors, is an approach to select the proper population for homing in target tissue [6,119]. Upon homing to the target site, MSCs begin to interact with the existing ligands in the tissue for specific immune responses [6]. When they are located within an inflammatory milieu, they can play as immunosuppressive cells. It has also been revealed that MSCs inflammation-directed homing contains a number of principal cell trafficking-related molecules, such as chemokines, adhesion molecules and matrix metalloproteinases (MMPs) [52]. BM-MSCs are able to be homed in the injured brain and enhance the number of positive cells for choline acetyltransferase. Additionally, they are able annihilate Aβ plaques from the hippocampus and reduce Aβ deposits by activating

endogenous microglia in prompted AD mice model [92]. Further, human MSCs are able to increase autophagy, provoke Aβ clearance and enhance neuronal survival rate in Aβ-treated mice model [20,97]. Shin et al. [97] have particularly focused on amyloid plaque elimination and demonstrated that MSCs can enhance cell autophagy pathway and neuron survival both *in vitro* and *in vivo* MSCs also show long-term survival and replication in culture. In cerebral infarction cases, the transplantation of BM-MSCs is applicable [91]. The intravenously (IV) transplanted MSCs can penetrate into the blood brain barrier (BBB), however the penetrated cells rarely survive and act as neurons in the brain [40,91]. MSCs can expand *ex vivo* in media supplemented with growth factors. Growth factors can induce MSCs differentiation toward a specific lineage [1]. When MSCs are exogenous and systemically administered on humans and animals, they specifically migrate to the damaged tissue sites [33,61]. In one investigation, hMSCs co-culture with Subventricular Zone (SVZ) derived NSCs from 4-month-old 5XFAD mice caused neuronal development and neurite outgrowth [78]. The cytokine array also revealed that hMSCs increasingly began to release activin A. Additionally, mRNA levels of activin A and activin receptor in SVZ of 5XFAD mice were significantly lower than that of the normal mice. Treatment of human recombinant activin A in SVZ-derived NSCs from 5XFAD mice induced neuronal development and neurite outgrowth. It proposes that, in future studies of cortical regeneration, the use of hMSCs and activin A can be considered as a suitable strategy to recover neurogenesis for AD treatment [78]. In another study, researchers injected 10^6 MSCs into APP/PS1 mice through tail vein carried out histological analysis for microglia and amyloid (pE3-Aβ) plaque numbers, glial distribution, and pE3-Aβ plaque size [71]. After 28 days, a significant reduction in microglial numbers and size in animals' cortex was observed. Furthermore, tumor necrosis factor (TNF-α), IL-6, Monocyte chemoattractant protein-1 (MCP-1), and NGF expressions were downregulated in MSC recipients. Despite no transplantation-dependent changes in pE3-Aβ plaque numbers, a reduction in the size of pE3-Aβ plaques was noticed in the recipients' hippocampus [71].

On the other hand, BM-MSCs play an important role by endogenous microglia activation in Aβ-injured mice hippocampi. These cells induce the migration of microglia in response to Aβ exposure *in vivo* [50]. In addition to the paracrine effects of released factors, BM-MSCs can be differentiated into ChAT-like neurons when transplanted into the hippocampi of Aβ-injured mice, leading to a significant learning and memory improvement [111]. In the acute Aβ-induced AD mice model, intracerebral transplanted MSCs enhanced microglial activation, rescued cognitive impairment, and substantially reduced the Aβ deposits, suggesting that BM-MSCs could be viable therapeutic agent against AD [50]. Another research team utilized three factors to motivate endogenous hematopoietic progenitor cells (HPC). It was reported that granulocyte-colony stimulating factor (G-CSF), AMD3100, CXCR4 antagonist, and stromal cell-derived factor-1α (SDF-1α) assisted the mobilization and migration of BM-derived hematopoietic progenitor cell (BM-HPCs) into brain [96]. Additionally, memory and hippocampal neurogenesis were developed in this AD mice model after treatment with the three factors, while Aβ-plaques remained unchanged. These factors may act synergistically to contribute in HPC migration to generate therapeutic effects [96].

Babaei *et al* [10], in a study, induced a *nucleus basalis magnocellularis* (NBM) lesion in rats by an excitotoxin to mimic the decreased cognitive model. The rats then received either MSC or a sham infusion into the hippocampus. Compared to the sham infusion group, MSCs injected group showed significant improvements in learning and memory skills. Since, MSCs were derived from rat tibia in this study, it indicated that stem cells could be harvested from adult BM [10]. However, the authors did not conduct any neuropathological investigation to analyze the outcomes of the MSCs differentiation into functional neurons in the hippocampus. Thus, it is suggested that, in future studies, MSCs would be transplanted from human BM to evaluate the MSCs survival and differentiation in neuropathological investigations. In another investigation, 3×10^5 rat BM-derived MSCs (rBM-MSCs) were transplanted into APP/PS1 transgenic mice (7-month-old) through tail vein. Aβ deposition in the rBM-MSC-treated mice brain was reduced compared to the controls [120]. Moreover, mouse brains redox status changes which were evaluated by electron paramagnetic resonance (EPR) imaging, also indicated an apparent reduction by rBMSC-treatment. Therefore, rBM-MSCs transplantation is probably able to prevent the AD pathological progression by redox status control under oxidative stress [120].

Human AD-MSCs transplantation into the brains of elderly mice also has recovered Ach levels, cognitive and locomotor function, and also modulated the microglia activation [60]. Additional to their capability to be differentiated into neurons and glia, transplanted AD-MSCs has modulated microglial activation and raise the levels of neurotrophic factors, such as BDNF and NGF, protecting hosting neurons and repair neuronal integrity [60]. Transplantation of AD-MSCs also permits them to be differentiated into neuron-like and astrocyte-like cells around the hematoma. It is accompanied by the upregulation of vascular endothelial growth factor (VEGF) and improvement in neural function. This fact proposes that AD-MSCs assist neural differentiation and prompt functional progress in the rat [16]. When human AD-MSCs were IV injected into an AD mouse models, they could be traced in the brain for up to 12 days [29]. Similarly, it has been revealed that AD-MSCs transplantation can modulate and alter the inflammatory environment in AD mice model. Particularly, they enhance the activation of microglia promoting the expression of alternative markers and Aβ-degrading enzymes, and decrease the expression of pro-inflammatory factors. Furthermore, transferring of human UCB-MSCs (hUCB-MSCs) into APP/PS1 mice has considerably enhanced their spatial learning and memory degradation and promoted the disease pathophysiology, due to the reversal of disease-associated microglial neuroinflammation through diminished microglia-induced proinflammatory cytokines, raised alternatively activated microglia, and increased anti-inflammatory cytokines [48]. In this regard, the transplanted group showed significant improvement in cognitive function and reduced Aβ deposition and hyperphosphorylated Tau protein in the brain [48]. These findings opened new horizons in treating AD, because MSCs have probable potentials to develop a kind of a novel immunomodulatory treatment for AD. More recently, Yang et al. [118], established that hUCB-MSC derived neuron-like cells activated M2-like microglia when they were transferred into the hippocampi of AβPP/PS1 mice. It decreased Aβ deposition, promoted synapsin I level, and recovered cognitive function. In another study, Wharton's jelly derived hUCMSCs, after being treated with neuronal induction medium (NIM) which is consisted of BDNF and low-serum media, for 14 days, microtubule associated potein 2 (MAP2), a neuronal specific marker, was expressed, and extended neurite-like processes [123]. Additional to NIM treatment, hippocampal cholinergic neurostimulating peptide (HCNP) or rat denervated hippocampal extract (rDHE) supplementation, also induced hUC-MSCs ChAT expression. This action could be even enhanced when cells are cultured with NIM supplemented with the combination of HCNP and rDHE. These findings suggested that hUC-MSCs have the potentiality to be differentiated into functional ChAT-positive cells *in vitro* and provide a new candidate of cells for transplantation in AD treatment [123]. When human UCB-MSCs were transplanted for three different time periods into the hippocampus of a transgenic AD mouse model, it depicted significant improvements in the Morris-water-maze task and reductions in Aβ and Tau aggregation, probably mediated through immunomodulation. Proposed probable mechanism for this UCB-MSCs mediated protection can be the release of soluble intracellular adhesion molecule-1, which increases neprilysin, an Aβ-degrading enzyme, in the microglia. Moreover, hUCB-MSCs and BV2 microglia Co-culture under amyloid-β42 (Aβ42) exposure reduces Aβ42 in the medium and causes the overexpression of the Aβ-degrading enzyme neprilysin (NEP) in the microglia [45]. Cytokine array of co-cultured media also depicted an increased release of soluble intracellular adhesion molecule-1 (sICAM-

1) from hUCB-MSCs. hUCB-MSCs transplantation into the hippocampus of a 10-month-old transgenic AD mouse model for 10, 20, or 40 days showed an increased NEP expression mice brains. Moreover, active migration of hUCB-MSCs toward Aβ deposits decreased Aβ42 plaques in hippocampus and other regions. This fact indicates that hUCB-MSC-derived sICAM-1 reduces Aβ plaques by inducing NEP expression in microglia *via* sICAM-1/LFA-1 signaling pathway [45]. In another study, 1×10^6 hUCB-MSCs were administered through an IV injection in 10-month-old APP/PS1 mice and they were sacrificed 1, 4, and 7 days after the administration. Most of the injected MSCs were found to be pervaded in lung, heart, and liver [79]. Another recent study revealed that paracrine action of hUCB-MSCs protected the hippocampus from synaptic-density loss in *in vitro* and *in vivo* AD models [43]. In this study, secretome of hUCB-MSCs was co-cultured with Aβ42-treated mouse hippocampal neurons. Treating with exogenous recombinant thrombospondin-1 (TSP-1) or co-cultures with hUCB-MSCs significantly caused increase in the synaptic-density markers expression, such as Synaptophysin (SYP) and post-synaptic density protein-95 (PSD-95) in Aβ42-treated mouse hippocampal neurons. The rescue effect of hUCB-MSC-secreted TSP-1 was mediated by neuroligin-1 (NLGN1) or α2δ-1 receptors. Interestingly, NLGN1 and α2δ-1 expressions, which were reduced in Aβ42-treated hippocampal neurons, were increased when they were co-cultured with hUCB-MSCs or exogenous TSP-1. These findings suggest that hUCB-MSCs can attenuate Aβ42-induced synaptic dysfunction by TSP-1 release regulation. This provides a potential alternative therapeutic approach to treat early-stage AD [43].

Human menstrual blood-derived stem cells (MenSCs) are a novel source of MSCs with higher proliferation rate properties and easy-to-obtain without any ethical concern [125]. In a recent research, intracerebral transplantation of MenSCs drastically promoted spatial learning and memory among APP/PS1 mice. In addition, MenSCs significantly ameliorated amyloid plaques and reduced Tau hyperphosphorylation in APP/PS1 mice. Intracerebral transplantation of MenSCs notably enhanced several Aβ degrading enzymes and modulated a set of pro-inflammatory cytokines related to an altered microglial phenotype. This issue depicts an Aβ degrading and anti-inflammatory effect of MenSCs in APP/PS1 mice brains [125].

Treating AD with MSCs is not a directly focused subject matter of clinical trials; though the results of some pre-clinical researches are available. In a phase I clinical trial on nine mild-to-moderate AD participants the safety and dose-limiting toxicity of stereotactic brain injection of hUCB-MSCs was evaluated [44]. The low-dose ($n = 3$) and high-dose ($n = 6$) groups were infused with a total of 3×10^6 cells/60 μL and 6×10^6 cells/60 μL, respectively, into the bilateral hippocampi and right precuneus. No patients showed serious complications such as fever during a 24-month of follow-up. However, during the 12-week follow-up, the most common acute complication was surgically induced wound pain ($n = 9$), followed by headache ($n = 4$), dizziness (n = 3), and postoperative delirium (n = 3). No dose-limiting toxicities also were observed. The administration of hUCB-MSCs into the hippocampus and precuneus by stereotactic injection was a feasible, safe, and well-tolerated method (NCT01297218 and NCT01696591) [44]. In 2015, the FDA also accepted the first phase 2A clinical trial of MCSs for AD treatment. Now similar trials are running or being intended in Europe and Asia [35]. The “Allogeneic Human MSCs for Alzheimer's Disease” study (NCT02833792) is an American phase IIa multicenter, single-blind, randomized, placebo-controlled and crossover study. It is designed to assess the safety, tolerability and initial efficiency of ischemia-tolerant allogeneic human MSCs among patients with mild/moderate AD induced dementia. The “Safety and Exploratory Efficacy Study of NEUROSTEM® Versus Placebo in Patients With Alzheimer's Disease” study (NCT02054208) is a combined phase 1/2a double-blind, single-center clinical trial in Korea and is now in its recruiting stage [107].

MSCs derived from oral cavity have differentiation capacity and immunomodulatory effects. Specially, MSCs and their derivatives, for instance conditioned medium (CM) and extracellular vesicles (EVs), have revealed to be capable to regenerate. Human periodontal-ligament stem cells (hPDLSCs) and CM or EVs or EVs engineered with polyethylenimine (PEI-EVs) in rats with calvarial defect may promote bone regeneration of calvaria defects, correlated with an increased vascularization [82]. Human periodontal-ligament stem cells (hPDLSCs) increase gene expression and the protein levels of VEGF and VEGF receptor 2 (VEGFR2). The positive role of VEGF on regeneration has been confirmed by this time and vascularization is an essential process throughout regeneration [82]. Upregulation of VEGF cause to improve in neural function.

One preclinical study has emphasized the ability of gingival mesenchymal stem cells (GMSCs) to progress long-term functional recovery in Spinal cord injury (SCI). Moringin (MOR) treatment hastens the differentiation procedure in mesenchymal stem cells prompting an initial increase of neural development related genes. Regenerative effects of GMSCs pretreated with nanostructured liposomes enriched with MOR in ICR (CD-1) mice (animal model of SCI) were investigated [62]. Results from this study show that MOR-treated GMSCs exert anti-inflammatory and anti-apoptotic activities. Particularly, MOR-treated GMSCs are capable to decrease the levels of COX-2, and IL-1β and IL-6. Moreover, MOR-treated GMSCs reduce Bax, caspase 3, and caspase 9 expressions [62]. So, future investigations must focus on GMSCs utilization to deliver neurotrophic factors and alter neurogenesis in AD models.

4. Conclusion

As mentioned earlier, loss of neurons in the brain or spinal cord are the main characteristics of neurodegenerative diseases. Absence of any effective therapy for neurological diseases has forced the researchers to find more effective alternatives. Effective ways for AD treatment will result in cognitive and behavior symptoms improvement, save impaired neurons, regenerate new neurons, and even halt or stop neurodegeneration. It has been shown that decreased neurogenesis mainly contributes in dementia among AD patients, rather than protein aggregates accumulation. Hopefully, MSCs can be considered as a suitable way for treatment of neurodegenerative diseases, because of their capability to promote functional recovery in different disease models. Post-transplantation Clinical complications and mortality have plagued previous attempts at intracranial transplantations of therapeutic cells. Therefore, development of safe methods should be considered as a priority to deliver therapeutic MSCs. Further studies are still needed to evaluate various tissue sources, genetic manipulations, administration methods, and clinical challenges facing therapeutic MSCs to facilitate developing new therapies for neurodegenerative diseases.

Declaration of Competing Interest

Authors declare no conflict of interest.

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References

[1] R. Adami, G. Scesa, D. Bottai, Stem cell transplantation in neurological diseases: improving effectiveness in animal models, Stem Cell Treatments 2 (2014) 17.
[2] R.R. Ager, J.L. Davis, A. Agazaryan, F. Benavente, W.W. Poon, F.M. LaFerla, et al., Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss, 25 (2015) 813–826.
[3] Aghebati-Maleki L, Dolati S, Zandi R, Fotouhi A, Ahmadi M, Aghebati A, et al. Prospect of mesenchymal stem cells in therapy of osteoporosis: a review. 2018.

[4] F. Aguado, M.A. Carmona, E. Pozas, A. Aguiló, F.J. Martínez-Guijarro, S. Alcantara, et al., BDNF regulates spontaneous correlated activity at early developmental stages by increasing synaptogenesis and expression of the K+/Cl-co-transporter KCC2, Development 130 (2003) 1267–1280.

[5] P.S. Aisen, J. Cummings, L.S. Schneider, Symptomatic and nonamyloid/tau based pharmacologic treatment for Alzheimer disease, Cold Spring Harbor perspectives in medicine 2 (2012) a006395.

[6] A. Aleynik, K.M. Gernavage, Y.S. Mourad, L.S. Sherman, K. Liu, Y.A. Gubenko, et al., Stem cell delivery of therapies for brain disorders, Clinical and translational medicine 3 (2014) 24.

[7] L. Aloe, M.L. Rocco, P. Bianchi, L. Manni, Nerve growth factor: from the early discoveries to the potential clinical use, J. Transl. Med. 10 (2012) 239.

[8] A. Altmann, L. Tian, V.W. Henderson, M.D. Greicius, Sex modifies the APOE-related risk of developing Alzheimer disease, Ann. Neurol. 75 (2014) 563–573.

[9] D.S. Auld, T.J. Kornecook, S. Bastianetto, R. Quirion, Alzheimer's disease and the basal forebrain cholinergic system: relations to β-amyloid peptides, cognition, and treatment strategies, Prog. Neurobiol. 68 (2002) 209–245.

[10] P. Babaei, B. Soltani Tehrani, A. Alizadeh, Transplanted bone marrow mesenchymal stem cells improve memory in rat models of Alzheimer's disease, Stem Cells Int. 2012 (2012).

[11] L. Bertram, M.B. McQueen, K. Mullin, D. Blacker, R.E. Tanzi, Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database, Nat. Genet. 39 (2007) 17–23.

[12] M. Blurton-Jones, R. Ager, J. Nerhus, A. Agazaryan, S. Huhn, A. Capela, et al., Restoration of Memory in Mouse Models of Alzheimer's Disease and Neuronal Loss: A New Paradigm Using Human Neural Stem Cell Therapy, vol. 8, (2012) (P577-P8).

[13] M. Blurton-Jones, M. Kitazawa, H. Martinez-Coria, N.A. Castello, F.-J. Müller, J.F. Loring, et al., Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease, Proc. Natl. Acad. Sci. 106 (2009) 13594–13599.

[14] Brinton Rdjnre, Neurosteroids as Regenerative Agents in the Brain: Therapeutic Implications, vol. 9, (2013), p. 241.

[15] A. Cattaneo, P. Calissano, Nerve growth factor and Alzheimer's disease: new facts for an old hypothesis, Mol. Neurobiol. 46 (2012) 588–604.

[16] J. Chen, Y.X. Tang, Y.M. Liu, J. Chen, X.Q. Hu, N. Liu, et al., Transplantation of adipose-derived stem cells is associated with neural differentiation and functional improvement in a rat model of intracerebral hemorrhage, CNS Neuroscience & Therapeutics 18 (2012) 847–854.

[17] S.-Q. Chen, Q. Cai, Y.-Y. Shen, P.-J. Wang, G.-J. Teng, M.-H. Li, et al., 1H-MRS evaluation of therapeutic effect of neural stem cell transplantation on Alzheimer's disease in AβPP/PS1 double transgenic mice, J. Alzheimers Dis. 28 (2012) 71–80.

[18] M.H. Chin, M.J. Mason, W. Xie, S. Volinia, M. Singer, C. Peterson, et al., Induced pluripotent stem cells and embryonic stem cells are distinguished by gene expression signatures, Cell Stem Cell 5 (2009) 111–123.

[19] E. Coulson, L. May, A. Sykes, A. Hamlin, The role of the p75 neurotrophin receptor in cholinergic dysfunction in Alzheimer's disease, Neuroscientist 15 (4) (2009) 317–323.

[20] L. da Silva Meirelles, A.I. Caplan, N.B. Nardi, In search of the in vivo identity of mesenchymal stem cells, Stem Cells 26 (2008) 2287–2299.

[21] E. Dantuma, S. Merchant, K. Sugaya, Stem cells for the treatment of neurodegenerative diseases, Stem Cell Res Ther 1 (2010) 37.

[22] Dolati S, Yousefi M, Mahdipour M, Afrasiabi Rad A, Pishgahi A, Nouri M, et al. Mesenchymal stem cell and bone marrow mononuclear cell therapy for cardiomyopathy: from bench to bedside. 2018.

[23] S.B. Dunnett, A.E. Rosser, Challenges for taking primary and stem cells into clinical neurotransplantation trials for neurodegenerative disease, Neurobiol. Dis. 61 (2014) 79–89.

[24] X. Fan, D. Sun, X. Tang, Y. Cai, Z.Q. Yin, H. Xu, Stem-cell challenges in the treatment of Alzheimer's disease: a long way from bench to bedside, Med. Res. Rev. 34 (2014) 957–978.

[25] X. Fan, D. Sun, X. Tang, Y. Cai, Z.Q. Yin, H. Xu, Stem-cell challenges in the treatment of Alzheimer's disease: a long way from bench to bedside, Med. Res. Rev. 34 (5) (2014) 957–978.

[26] X. Fan, Y. Tang, K. Wang, X. Cui, S. Tao, H. Xu, Embryonic Stem Cell in the Therapy of Neurodegenerative Diseases. Embryonic Stem Cells-Recent Advances in Pluripotent Stem Cell-Based Regenerative Medicine, InTech, 2011.

[27] A. Fotouhi, A. Maleki, S. Dolati, A. Aghebati-Maleki, L.J.B. Aghebati-Maleki, Platelet rich plasma, stromal vascular fraction and autologous conditioned serum in treatment of knee osteoarthritis, Pharmacotherapy 104 (2018) 652–660.

[28] P.T. Francis, M.J. Ramírez, M.K. Lai, Neurochemical basis for symptomatic treatment of Alzheimer's disease, Neuropharmacology 59 (2010) 221–229.

[29] S. Ha, S. Ahn, S. Kim, Y. Joo, Y.H. Chong, Y.-H. Suh, et al., In vivo imaging of human adipose-derived stem cells in Alzheimer's disease animal model, J. Biomed. Opt. 19 (2013) 051206.

[30] D.W. Hampton, D.J. Webber, B. Bilican, M. Goedert, M.G. Spillantini, S. Chandran, Cell-mediated neuroprotection in a mouse model of human tauopathy, J. Neurosci. 30 (2010) 9973–9983.

[31] A. Hermann, A. Storch, Induced neural stem cells (iNSCs) in neurodegenerative diseases, J. Neural Transm. 120 (2013) 19–25.

[32] V. Hook, T. Toneff, M. Bogyo, D. Greenbaum, K.F. Medzihradszky, J. Neveu, et al., Inhibition of cathepsin B reduces β-amyloid production in regulated secretory vesicles of neuronal chromaffin cells: evidence for cathepsin B as a candidate β-secretase of Alzheimer's disease, Biol. Chem. 386 (2005) 931–940.

[33] E.M. Horwitz, P.L. Gordon, W.K. Koo, J.C. Marx, M.D. Neel, R.Y. McNall, et al., Isolated allogeneic bone marrow-derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: implications for cell therapy of bone, Proc. Natl. Acad. Sci. 99 (2002) 8932–8937.

[34] Y. Huang, L. Mucke, Alzheimer mechanisms and therapeutic strategies, Cell 148 (2012) 1204–1222.

[35] J.G. Hunsberger, M. Rao, J. Kurtzberg, J.W. Bulte, A. Atala, F.M. LaFerla, et al., Accelerating stem cell trials for Alzheimer's disease, The Lancet Neurology 15 (2016) 219–230.

[36] R.W. Irwin, R.D. Brinton, Allopregnanolone as Regenerative Therapeutic for Alzheimer's Disease: Translational Development and Clinical Promise, 113 (2014), pp. 40–55.

[37] M.A. Israel, S.H. Yuan, C. Bardy, S.M. Reyna, Y. Mu, C. Herrera, et al., Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells, Nature 482 (2012) 216.

[38] Z.-Y. Jiang, M.-C. Lu, L.L. Xu, T.-T. Yang, M.-Y. Xi, X.-L. Xu, et al., Discovery of Potent Keap1–Nrf2 Protein–Protein Interaction Inhibitor Based on Molecular Binding Determinants Analysis, vol. 57, (2014), pp. 2736–2745.

[39] Y.-W. Jung, E. Hysolli, K.-Y. Kim, Y. Tanaka, I.-H. Park, Human induced pluripotent stem cells and neurodegenerative disease: prospects for novel therapies, Curr. Opin. Neurol. 25 (2012) 125.

[40] H. Kanno, Regenerative therapy for neuronal diseases with transplantation of somatic stem cells, World journal of stem cells 5 (2013) 163.

[41] K. Kask, T. Bäckström, L.-G. Nilsson, I.J.P. Sundström-Poromaa, Allopregnanolone impairs episodic memory in healthy women, 199 (2008) 161.

[42] N. Kemppainen, S. Aalto, I. Wilson, K. Någren, S. Helin, A. Brück, et al., PET amyloid ligand [11C] PIB uptake is increased in mild cognitive impairment, Neurology 68 (2007) 1603–1606.

[43] D.H. Kim, H. Lim, D. Lee, S.J. Choi, W. Oh, Y.S. Yang, et al., Thrombospondin-1 secreted by human umbilical cord blood-derived mesenchymal stem cells rescues neurons from synaptic dysfunction in Alzheimer's disease model, 8 (2018) 354.

[44] H.J. Kim, S.W. Seo, J.W. Chang, J.I. Lee, C.H. Kim, J. Chin, et al., Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: a phase 1 clinical trial, 1 (2015) 95–102.

[45] J. Kim, D. Kim, J. Kim, D. Lee, H. Jeon, S. Kwon, et al., Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived mesenchymal stem cell reduces amyloid-β plaques, 19 (2012) 680.

[46] K.-S. Kim, H.S. Kim, J.-M. Park, H.W. Kim, Park M-k, H.-S. Lee, et al., Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model, Neurobiol. Aging 34 (2013) 2408–2420.

[47] S.U. Kim, H.J. Lee, Y.B. Kim, Neural stem cell-based treatment for neurodegenerative diseases, Neuropathology 33 (2013) 491–504.

[48] H.J. Lee, J.K. Lee, H. Lee, J.E. Carter, J.W. Chang, W. Oh, et al., Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation, Neurobiol. Aging 33 (2012) 588–602.

[49] H.J. Lee, I.J. Lim, S.W. Park, Y.B. Kim, Y. Ko, S.U. Kim, Human neural stem cells genetically modified to express human nerve growth factor (NGF) gene restore cognition in the mouse with ibotenic acid-induced cognitive dysfunction, Cell Transplant. 21 (2012) 2487–2496.

[50] J.K. Lee, H.K. Jin, J.-S. Bae, Bone marrow-derived mesenchymal stem cells reduce brain amyloid-β deposition and accelerate the activation of microglia in an acutely induced Alzheimer's disease mouse model, Neurosci. Lett. 450 (2009) 136–141.

[51] J.K. Lee, H.K. Jin, S. Endo, E.H. Schuchman, J.E. Carter, Bae Js, Intracerebral transplantation of bone marrow-derived mesenchymal stem cells reduces amyloid-beta deposition and rescues memory deficits in Alzheimer's disease mice by modulation of immune responses, Stem Cells 28 (2010) 329–343.

[52] R.H. Lee, A.A. Pulin, M.J. Seo, D.J. Kota, J. Ylostalo, B.L. Larson, et al., Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6, Cell Stem Cell 5 (2009) 54–63.

[53] E. Levy-Lahad, W. Wasco, P. Poorkaj, D.M. Romano, J. Oshima, W.H. Pettingell, et al., Candidate gene for the chromosome 1 familial Alzheimer's disease locus, Science 269 (1995) 973–977.

[54] M. Li, K. Guo, S. Ikehara, Stem cell treatment for Alzheimer's disease, Int. J. Mol. Sci. 15 (2014) 19226–19238.

[55] Z. Li, C. Gao, H. Huang, W. Sun, H. Yi, X. Fan, et al., Neurotransmitter phenotype differentiation and synapse formation of neural precursors engrafting in amyloid-β 1-40 injured rat hippocampus, J. Alzheimers Dis. 21 (2010) 1233–1247.

[56] Akl Liu, Stem cell therapy for Alzheimer's disease: hype or hope? Bioscience Horizons 6 (2013) hzt011.

[57] Y. Liu, J.P. Weick, H. Liu, R. Krencik, X. Zhang, L. Ma, et al., Medial ganglionic eminence-like cells derived from human embryonic stem cells correct learning and memory deficits, Nat. Biotechnol. 31 (2013) 440–447.

[58] Y. Liu, J.P. Weick, H. Liu, R. Krencik, X. Zhang, L. Ma, et al., Medial ganglionic eminence–like cells derived from human embryonic stem cells correct learning and memory deficits, Nat. Biotechnol. 31 (2013) 440.

[59] Z.C. Liu, T.M. Chang, Preliminary study on intrasplenic implantation of artificial cell bioencapsulated stem cells to increase the survival of 90% hepatectomized rats, Artificial Cells, Blood Substitutes and Biotechnology 37 (2009) 53–55.

[60] T. Ma, K. Gong, Q. Ao, Y. Yan, B. Song, H. Huang, et al., Intracerebral transplantation of adipose-derived mesenchymal stem cells alternatively activates microglia and ameliorates neuropathological deficits in Alzheimer's disease mice, Cell Transplant. 22 (2013) (S113-S26).

[61] A. Mahmood, D. Lu, M. Lu, M. Chopp, Treatment of traumatic brain injury in adult rats with intravenous administration of human bone marrow stromal cells, Neurosurgery 53 (2003) 697–703.

[62] S. Mammana, A. Gugliandolo, E. Cavalli, F. Diomede, R. Iori, R. Zappacosta, et al., Human gingival mesenchymal stem cells (GMSCs) pre-treated with vesicular

Moringin nanostructures as a new therapeutic approach in a mouse model of spinal cord injury, J. Tissue Eng. Regen. Med. (2019).
[63] F. Mangialasche, M. Kivipelto, P. Mecocci, D. Rizzuto, K. Palmer, B. Winblad, et al., High plasma levels of vitamin E forms and reduced Alzheimer's disease risk in advanced age, J. Alzheimers Dis. 20 (2010) 1029–1037.
[64] R.A. Marr, E. Rockenstein, A. Mukherjee, M.S. Kindy, L.B. Hersh, F.H. Gage, et al., Neprilysin gene transfer reduces human amyloid pathology in transgenic mice, J. Neurosci. 23 (2003) 1992–1996.
[65] P. Martinez-Morales, A. Revilla, I. Ocana, C. Gonzalez, P. Sainz, D. McGuire, et al., Progress in stem cell therapy for major human neurological disorders, Stem Cell Rev. Rep. 9 (2013) 685–699.
[66] C. Matrone, R. Marolda, S. Ciafrè, M. Ciotti, D. Mercanti, P. Calissano, Tyrosine kinase nerve growth factor receptor switches from prosurvival to proapoptotic activity via Abeta-mediated phosphorylation, Proc. Natl. Acad. Sci. 106 (2009) 11358–11363.
[67] L.M. McGinley, O.N. Kashlan, E.S. Bruno, K.S. Chen, J.M. Hayes, S.R. Kashlan, et al., Human neural stem cell transplantation improves cognition in a murine model of Alzheimer's disease, 8 (2018) 14776.
[68] D. Mechlovich, T. Amit, O. Bar-Am, S. Mandel, M. BH Youdim, Ojcar Weinreb, The novel multi-target iron chelator, M30 modulates HIF-1α-related glycolytic genes and insulin signaling pathway in the frontal cortex of APP/PS1 Alzheimer's disease mice, 11 (2014) 119–127.
[69] F.H. Moghadam, H. Alaie, K. Karbalaie, S. Tanhaei, M.H.N. Esfahani, H. Baharvand, Transplantation of primed or unprimed mouse embryonic stem cell-derived neural precursor cells improves cognitive function in Alzheimerian rats, Differentiation 78 (2009) 59–68.
[70] S. Mueller-Steiner, Y. Zhou, H. Arai, E.D. Roberson, B. Sun, J. Chen, et al., Antiamyloidogenic and neuroprotective functions of cathepsin B: implications for Alzheimer's disease, Neuron 51 (2006) 703–714.
[71] Y. Naaldijk, C. Jaeger, C. Fabian, C. Leovsky, A. Blüher, L. Rudolph, et al., Effect of systemic transplantation of bone marrow-derived mesenchymal stem cells on neuropathology markers in APP/PS 1 Alzheimer mice, 43 (2017) 299–314.
[72] G.D. Nicol, M.R. Vasko, Unraveling the story of NGF-mediated sensitization of nociceptive sensory neurons: ON or OFF the Trks? Mol. Interv. 7 (2007) 26.
[73] M. Noetzli, C.B. Eap, Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease, Clin. Pharmacokinet. 52 (2013) 225–241.
[74] J. Oliveira, A. Alcyr, H.M. Hodges, Alzheimer's disease and neural transplantation as prospective cell therapy, Curr. Alzheimer Res. 2 (2005) 79–95.
[75] D. Park, H.J. Lee, S.S. Joo, D.-K. Bae, G. Yang, Y.-H. Yang, et al., Human neural stem cells over-expressing choline acetyltransferase restore cognition in rat model of cognitive dysfunction, Exp. Neurol. 234 (2012) 521–526.
[76] D. Park, G. Yang, D.K. Bae, S.H. Lee, Y.H. Yang, J. Kyung, et al., Human adipose tissue-derived mesenchymal stem cells improve cognitive function and physical activity in ageing mice, J. Neurosci. Res. 91 (2013) 660–670.
[77] D. Park, Y.-H. Yang, D.K. Bae, S.H. Lee, G. Yang, J. Kyung, et al., Improvement of cognitive function and physical activity of aging mice by human neural stem cells over-expressing choline acetyltransferase, Neurobiol. Aging 34 (2013) 2639–2646.
[78] S.E. Park, J. Lee, E.H. Chang, J.H. Kim, J.-H. Sung, D.L. Na, et al., Activin A secreted by human mesenchymal stem cells induces neuronal development and neurite outgrowth in an in vitro model of Alzheimer's disease: neurogenesis induced by MSCs via activin A, 39 (2016) 1171–1179.
[79] S.E. Park, N.K. Lee, J. Lee, J.W. Hwang, S.J. Choi, H. Hwang, et al., Distribution of human umbilical cord blood-derived mesenchymal stem cells in the Alzheimer's disease transgenic mouse after a single intravenous injection, 27 (2016) 235–241.
[80] C. Patterson, J.W. Feightner, A. Garcia, G.-Y.R. Hsiung, C. MacKnight, A.D. Sadovnick, Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease, Can. Med. Assoc. J. 178 (2008) 548–556.
[81] D.G. Phinney, D.J. Prockop, Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair—current views, Stem Cells 25 (2007) 2896–2902.
[82] J. Pizzicannella, A. Gugliandolo, T. Orsini, A. Fontana, A. Ventrella, E. Mazzon, et al., Engineered extracellular vesicles from human periodontal-ligament stem cells increase VEGF/VEGFR2 expression during bone regeneration, Front. Physiol. 10 (2019) 512.
[83] R. Potter, B.W. Patterson, D.L. Elbert, V. Ovod, T. Kasten, W. Sigurdson, et al., Increased in vivo amyloid-β42 production, exchange, and loss in presenilin mutation carriers, Sci. Transl. Med. 5 (2013) 189ra77–ra77.
[84] M.S. Rafii, T.L. Baumann, R.A. Bakay, J.M. Ostrove, J. Siffert, A.S. Fleisher, et al., A phase1 study of stereotactic gene delivery of AAV2-NGF for Alzheimer's disease, 10 (2014) 571–581.
[85] G. Ren, L. Zhang, X. Zhao, G. Xu, Y. Zhang, A.I. Roberts, et al., Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide, Cell Stem Cell 2 (2008) 141–150.
[86] P.G. Ridge, M.T. Ebbert, J.S. Kauwe, Genetics of Alzheimer's disease, Biomed. Res. Int. 2013 (2013).
[87] R. Rikhtegar, M. Pezeshkian, S. Dolati, N. Safaie, A.A. Rad, M. Mahdipour, et al., Stem cells as therapy for heart disease: iPSCs, ESCs, CSCs, and skeletal myoblasts, 109 (2019) 304–313.
[88] R. Rikhtegar, M. Yousefi, S. Dolati, H.D. Kasmaei, S. Charsouei, M. Nouri, et al., Stem cell-based cell therapy for neuroprotection in stroke: a review, J. Cell. Biochem. 120 (6) (2019) 8849–8862.
[89] J.M. Ringman, A. Goate, C.L. Masters, N.J. Cairns, A. Danek, N. Graff-Radford, et al., Genetic heterogeneity in Alzheimer disease and implications for treatment strategies, Current neurology and neuroscience reports 14 (2014) 1–9.
[90] J.P. Robbins, Price JJPm, Human Induced Pluripotent Stem Cells as a Research Tool in Alzheimer's Disease, vol. 47, (2017), pp. 2587–2592.
[91] P.H. Rosado-de-Castro, F.R. Schmidt, V. Battistella, S.A. Lopes de Souza, B. Gutfilen, R.C. Goldenberg, et al., Biodistribution of bone marrow mononuclear cells after intra-arterial or intravenous transplantation in subacute stroke patients, Regen. Med. 8 (2013) 145–155.
[92] A.M. Salem, H.H. Ahmed, H.M. Atta, M.A. Ghazy, H.A. Aglan, Potential of bone marrow mesenchymal stem cells in management of Alzheimer's disease in female rats, Cell Biol. Int. 38 (2014) 1367–1383.
[93] P. Schelterns, H. Feldman, Treatment of Alzheimer's disease; current status and new perspectives, The Lancet Neurology 2 (2003) 539–547.
[94] S.D. Schwartz, J.-P. Hubschman, G. Heilwell, V. Franco-Cardenas, C.K. Pan, R.M. Ostrick, et al., Embryonic stem cell trials for macular degeneration: a preliminary report, Lancet 379 (2012) 713–720.
[95] A. Serrano-Pozo, M.P. Frosch, E. Masliah, B.T. Hyman, Neuropathological alterations in Alzheimer disease, Cold Spring Harbor perspectives in medicine 1 (2011) a006189.
[96] J.W. Shin, J.K. Lee, J.E. Lee, W.K. Min, E.H. Schuchman, H.K. Jin, et al., Combined effects of hematopoietic progenitor cell mobilization from bone marrow by granulocyte colony stimulating factor and AMD3100 and chemotaxis into the brain using stromal cell-derived factor-1α in an Alzheimer's disease mouse model, 29 (2011) 1075–1089.
[97] J.Y. Shin, H.J. Park, H.N. Kim, S.H. Oh, J.-S. Bae, H.-J. Ha, et al., Mesenchymal stem cells enhance autophagy and increase β-amyloid clearance in Alzheimer disease models, Autophagy 10 (2014) 32–44.
[98] S.E. Sullivan, Young-Pearse TLJBr, Induced pluripotent stem cells as a discovery tool for Alzheimer' s disease, 1656 (2017) 98–106.
[99] T. Suzuki, H. Motohashi, Yamamoto MJTips, Toward clinical application of the Keap1–Nrf2 pathway, 34 (2013) 340–346.
[100] T.M. Swi Chang, 50th anniversary of artificial cells: their role in biotechnology, nanomedicine, regenerative medicine, blood substitutes, bioencapsulation, cell/stem cell therapy and nanorobotics, Artificial Cells, Blood Substitutes and Biotechnology 35 (2007) 545–554.
[101] J. Tang, H. Xu, X. Fan, D. Li, D. Rancourt, G. Zhou, et al., Embryonic stem cell-derived neural precursor cells improve memory dysfunction in Aβ (1–40) injured rats, Neurosci. Res. 62 (2008) 86–96.
[102] P. Taupin, Adult neural stem cells, neurogenic niches, and cellular therapy, Stem Cell Rev. 2 (2006) 213–219.
[103] L.M. Tong, H. Fong, Y. Huang, Stem cell therapy for Alzheimer's disease and related disorders: current status and future perspectives, Exp. Mol. Med. 47 (2015) e151.
[104] G. Turgeman, The therapeutic potential of mesenchymal stem cells in Alzheimer's disease: converging mechanisms, Neural Regen. Res. 10 (2015) 698.
[105] M.H. Tuszynski, L. Thal, M. Pay, D.P. Salmon, R. Bakay, P. Patel, et al., A Phase 1 Clinical Trial of Nerve Growth Factor Gene Therapy for Alzheimer Disease, vol. 11, (2005), p. 551.
[106] R. Volkman, D. Offen, Concise review: mesenchymal stem cells in neurodegenerative diseases, Stem Cells 35 (2017) 1867–1880.
[107] Y. Wang, X. Ji, R.K. Leak, F. Chen, G. Cao, Stem cell therapies in age-related neurodegenerative diseases and stroke, Ageing Res. Rev. 34 (2017) 39–50.
[108] X. Wei, X. Yang, Han Z-p, Qu F-f, L. Shao, Shi Y-f, Mesenchymal stem cells: a new trend for cell therapy, Acta Pharmacol. Sin. 34 (2013) 747–754.
[109] M. Wernig, A. Meissner, R. Foreman, T. Brambrink, M. Ku, K. Hochedlinger, et al., In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state, Nature 448 (2007) 318–324.
[110] R.S. Wilson, E. Segawa, P.A. Boyle, S.E. Anagnos, L.P. Hizel, D.A. Bennett, The natural history of cognitive decline in Alzheimer's disease, Psychol. Aging 27 (2012) 1008.
[111] Q.-Y. Wu, J. Li, Z.-T. Feng, T.-H. Wang, Bone marrow stromal cells of transgenic mice can improve the cognitive ability of an Alzheimer's disease rat model, Neurosci. Lett. 417 (2007) 281–285.
[112] R.D. Wyse, G.L. Dunbar, J. Rossignol, Use of genetically modified mesenchymal stem cells to treat neurodegenerative diseases, Int. J. Mol. Sci. 15 (2014) 1719–1745.
[113] H. Xu, X. Fan, J. Tang, G. Zhou, L. Yang, X. Wu, et al., A modified method for generation of neural precursor cells from cultured mouse embryonic stem cells, Brain Res. Protocol. 15 (2005) 52–58.
[114] H. Xu, X. Fan, X. Wu, J. Tang, H. Yang, Neural precursor cells differentiated from mouse embryonic stem cells relieve symptomatic motor behavior in a rat model of Parkinson's disease, Biochem. Biophys. Res. Commun. 326 (2004) 115–122.
[115] A. Xuan, D. Long, H. Gu, D. Yang, L. Hong, S. Leng, BDNF improves the effects of neural stem cells on the rat model of Alzheimer's disease with unilateral lesion of fimbria-fornix, Neurosci. Lett. 440 (2008) 331–335.
[116] N. Yahata, M. Asai, S. Kitaoka, K. Takahashi, I. Asaka, H. Hioki, et al., Anti-Aβ drug screening platform using human iPS cell-derived neurons for the treatment of Alzheimer's disease, PLoS One 6 (2011) e25788.
[117] T.R. Yamasaki, M. Blurton-Jones, D.A. Morrissette, M. Kitazawa, S. Oddo, LaFerla FMJJoN, Neural Stem Cells Improve Memory in an Inducible Mouse Model of Neuronal Loss, vol. 27, (2007), pp. 11925–11933.
[118] H. Yang, Z.H. Xie, L.F. Wei, H.N. Yang, S.N. Yang, Z.Y. Zhu, et al., Human umbilical cord mesenchymal stem cell-derived neuron-like cells rescue memory deficits and reduce amyloid-beta deposition in an AβPP/PS1 transgenic mouse model, Stem Cell Res Ther 4 (2013) 76.
[119] G. Yilmaz, S. Vital, C.E. Yilmaz, K.Y. Stokes, J.S. Alexander, D.N. Granger, Selectin-mediated recruitment of bone marrow stromal cells in the postischemic cerebral microvasculature, Stroke 42 (2011) 806–811.

[120] K. Yokokawa, N. Iwahara, H. Suzuki, M. Emoto, S. Hisahara, T. Saito, et al., Transplantation of rat bone marrow-derived mesenchymal stem cells regulates oxidative stress in Alzheimer's disease transgenic mouse model, 381 (2017) 1031.
[121] J.E. Young, L.S. Goldstein, Alzheimer's disease in a dish: promises and challenges of human stem cell models, Hum. Mol. Genet. 21 (R1) (2012) R82–R89 dds319.
[122] S.H. Yuan, J. Martin, J. Elia, J. Flippin, R.I. Paramban, M.P. Hefferan, et al., Cell-surface marker signatures for the isolation of neural stem cells, glia and neurons derived from human pluripotent stem cells, PLoS One 6 (2011) e17540.
[123] L. Zhang, X. Tan, C. Dong, L. Zou, H. Zhao, X. Zhang, et al., In vitro differentiation of human umbilical cord mesenchymal stem cells (hUCMSCs), derived from Wharton's jelly, into choline acetyltransferase (ChAT)-positive cells, 30 (2012) 471–477.
[124] Q. Zhang, Hh. Wu, Y. Wang, Gu Gj, W. Zhang, Xia RJJon, Neural stem cell transplantation decreases neuroinflammation in a transgenic mouse model of Alzheimer's disease, 136 (2016) 815–825.
[125] Y. Zhao, X. Chen, Y. Wu, Y. Wang, Y. Li, Xiang CJFimn, Transplantation of human menstrual blood-derived mesenchymal stem cells alleviates Alzheimer's disease-like pathology in APP/PS1 transgenic mice, 11 (2018) 140.
[126] H. Zheng, M. Fridkin, Youdim MJPimc, New Approaches to Treating Alzheimer's Disease, vol. 7, PMC. S13210, 2015.