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REVIEW

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Stem cells as a promising therapeutic approach for Alzheimer's disease: a review

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder that impairs memory formation and disrupts neurocognitive function. This neuropathy is characterized by neural loss, neurodegeneration, and formation of amyloid plaques and neurofibrillary tangles. Approved medications provide only symptomatic relief without affecting AD progression. Because of the multifactorial nature of AD and the absence of effective treatment, stem cell-based therapy has been regarded as an effective, safe, and innovative therapeutic approach to overcome AD. Different sources of stem cells are employed for AD treatment, such as neural stem cells (NSCs), mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs). There is a growing body of evidence supporting the promising therapeutic potential of stem cell transplantation, which might be attributed to the mechanistic actions exerted by stem cells such as inducing hippocampal neurogenesis, secreting paracrine factors, exerting anti-inflammatory activity, showing anti-amyloidogenic potential, and finally resulting in cognitive recovery. Although stem cell-based therapy faces potential hurdles, it holds a potential hope to provide a safe, effective, and feasible clinical application of stem cells in AD patients.

Keywords: Stem cell-based therapy, Alzheimer's disease, Neurodegeneration, Stem cell transplantation, Neurogenesis, Mechanistic actions

Background

Alzheimer's disease (AD) is an untreatable and age-related neurodegenerative disorder responsible for 50 to 70% of all dementia cases worldwide (Zhagn and Li 2014). AD, the most common form of dementia, is clinically identified by a slowly progressive decline in neurocognitive functions because of neural and synaptic loss, and deposition of neurotoxic proteins such as extracellular senile amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) (Popovic and Brundin 2006). AD is a proteinopathy due to excessive accumulation of misfolded and neurotoxic proteins like hyperphosphorylated tau protein and Aβ-42, which leads to neurotoxicity and subsequent synaptic failure (Reitz et al. 2011). AD neuropathy is a typical example of a complex multifactorial brain disorder that is considered to some extent a "stem cell disease," as deposition of Aβ-42 plaques has a negative impact on stem cell proliferation, and even newly generated neurons and glia ceased to survive in an AD-related microenvironment (Tincera et al. 2016).

Therefore, regenerative therapy, using stem cells, could be regarded as a promising and safe approach for regeneration of altered or lost cellular functions (Kocaoglu et al. 2014). Although the underlying mechanisms of stem cell-based therapy need more clarification, there are several preclinical studies demonstrated encouraging results (Kwak et al. 2018). This review demonstrates AD pathogenesis and summarizes the relevant stem cell research, mechanistic actions, and challenges in developing different stem cells for AD treatment.

The pathology of AD and current treatment

Alzheimer's disease (AD) is a multifactorial brain disorder, with several pathogenic factors including genetic factors, oxidative stress, Aβ-induced neurotoxicity, excitotoxicity, neuroinflammation, mitochondrial dysfunction, and cytoskeletal alteration of synapse components; therefore, it is complicated to determine its exact pathophysiologic cascade (Huang and Mucke 2012; Ferreiro et al. 2012). There are several assumptions that

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explain AD neuropathy such as cholinergic assumption, oxidative stress assumption, and amyloid cascade assumption (Bali et al. 2017). However, approximately one-third of AD patients showed no radiographic signs of amyloid plaques (Doraiswamy et al. 2014). Therefore, more advanced diagnostic approaches should be developed to enable the early diagnosis of AD (James et al. 2015; Sperling et al. 2011).

Amyloid cascade hypothesis assumed that the uncontrolled proteolytic processing of amyloid precursor protein (APP) results in the excessive accumulation of Aβ deposits (Querfurth and La Ferla 2010). APP is hydrolyzed through two major pathways; the non-amyloidogenic (α-secretase) pathway that leads to the generation of non-pathogenic amyloid products and the amyloidogenic (β- and ɣ-secretases) pathway that results in the formation of two forms of Aβ peptides: predominant Aβ-40 (90%) and fibrillogenic Aβ-42 (10%), involved in AD pathology (Portelius et al. 2010; Perneczky and Alexopoulos 2014; Bali et al. 2017). Accumulation of Aβ plaques induces neurotoxicity and triggers a cascade of pathological events leading to neuroapoptosis in the central nervous system (CNS) (Pallas and Camins 2006; Hardy 2009), (Fig. 1).

On the other hand, Tau is an "intracellular microtubule-associated protein" that plays an essential role in microtubule stabilization; therefore, atypical hyperphosphorylation of tau protein results in the formation of NFTs and disruption of microtubules (Khan and Bloom 2016; Bali et al. 2017). Moreover, microglial activation, and associated inflammatory mechanisms contribute to AD pathophysiology (Meraz-Ríos et al. 2013; Millington et al. 2014). In addition, metabolic dysfunction resulted in elevated levels of reactive oxygen species (ROS), reactive nitrogen species (RNS), and inflammatory mediators that generate neuroinflammation in AD subjects (Luque-Contreras et al. 2014). Another critical theory in AD pathogenesis is "Cholinergic hypothesis," which describes the impairment of cholinergic neurotransmission and the selective deficiency of the neurotransmitter acetylcholine (ACh) in AD brains (Zivin and Pregelj 2008).

Based on etiology, they are two classes of AD: early-onset familial (FAD)—approximately 10% of the cases—and late-onset sporadic (SAD)—90% of the cases (Bekris et al. 2010). Familial AD (FAD) is a very rare autosomal dominant AD disorder that affects patients under the age of 65 years (Amemori et al. 2015), its early onset is associated with mutations in specific genes such as APP, presenilin 1 (PS1), and presenilin 2 (PS2) (Bekris et al. 2010; Schipper 2011). Sporadic AD (SAD) appears to have a complex genetic profile and interacting environmental factors (Alzheimer's Association 2016). SAD is characterized by deposition of extracellular Aβ plaques, hyperphosphorylation of tau, microglial activation, and finally the massive neuronal and synaptic loss, resulting finally in brain atrophy in later stages of AD (Duncan and Valenzuela 2017), (Fig. 2).

Current medications for AD are symptomatic and are characterized by their neuromodulatory functions such as acetylcholinesterase (AChE) inhibitors (Coyle and Kershaw 2001), antioxidants (Zandi et al. 2004), and amyloid-β

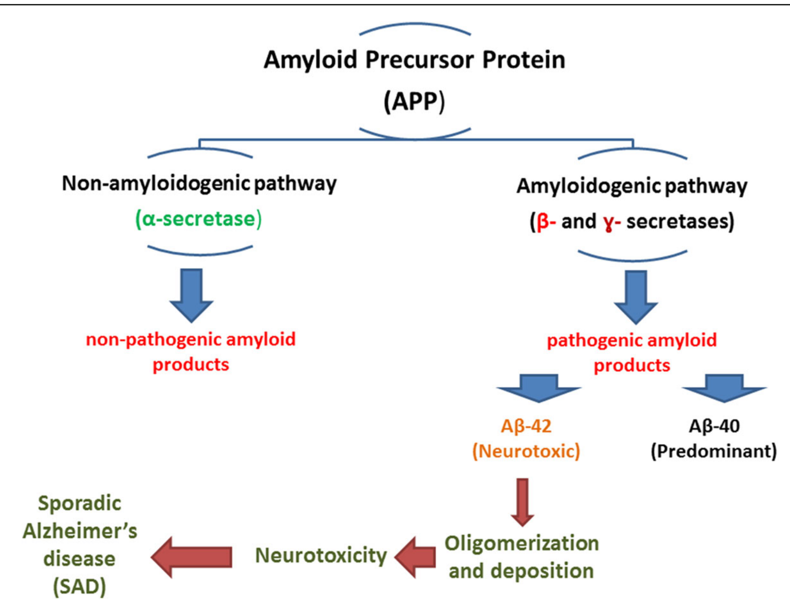

Fig. 1 The amyloidogenic and non-amyloidogenic pathways of the amyloid precursor protein (APP): APP is enzymaticaly hydrolyzed by either α- or β-secretase. The non-amyloidogenic pathway, implicating α-secretase, leads to the extracellular release of non-pathogenic products. The amyloidogenic pathway, involving β-secretase (BACE1) and ɣ-secretase, results in the generation of amyloid products of varying length (Aβ-40 and Aβ-42), accumulation of these neurotoxic proteins could lead to neurodegenration and might be the main cause of AD

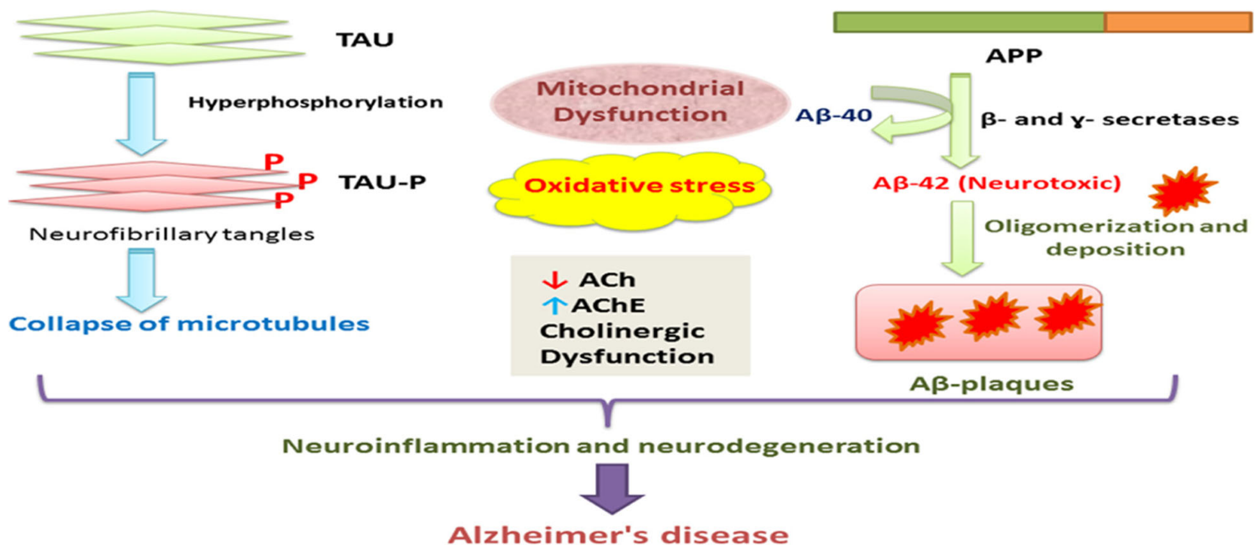

Fig. 2 Pathological events related to underlying AD neurodegeneration. These events include the amyloid deposition in the brain due to the uncontrolled cleavage of APP and the degeneration of neurotoxic Aβ-42 peptides, hyperphosporhylation of tau protein and the formation of intracellular neurofibrillary tangles, the deficiency of acetylcholine (ACh) due to its increased hydrolysis by acetylcholinesterase (AChE), oxidative stress, and mitochondrial dysfunction

targeting medications (Cummings et al. 2017). For example, AChE inhibitors can ameliorate cholinergic function through blocking neurotransmitter degradation and increasing the brain content of neurotransmitters (Confaloni et al. 2016; Stella et al. 2015). However, this type of treatment can only provide temporary symptomatic relief without attenuating AD progression (Monacelli and Rosa 2014). Another type of treatment, such as anti-Aβ aggregation agents and β-secretase inhibitors, is aimed to prevent amyloid plaque formation and to facilitate amyloid clearance (Huang and Mucke 2012; Salloway et al. 2014). However, several Aβ-targeting treatments failed to restore neurocognitive function (Coric et al. 2012; Doody et al. 2013; Kile et al. 2017). Actually, the “one alteration, one disease, one drug” strategy is not applied for AD (Kimura, 2016); therefore, different targets in the brain should be considered (Fang et al. 2018). Moreover, therapeutic interventions should be introduced at the early AD stages (Tong et al. 2015). Hence, it is very important to understand the etiology of AD for clinical application of alternative therapeutic approaches such as stem cell-based therapy (Banik et al. 2015).

Stem cell-based therapy for AD

Stem cell-based therapy is a promising, safe, and effective therapeutic strategy for several neurodegenerative diseases, including AD (Kocaoglu et al. 2014; Chang et al. 2014; Wernig et al. 2008). Stem cell-based-approach is still under development but rapid achievements indicate its therapeutic potential for reversing AD-associated neurodegeneration, as well as, improving cellular and structural functions (Lee et al. 2015; Kwak et al. 2018). This therapeutic potential might be partly attributed to the neurosecretory (paracrine) effect, as several neurotrophic factors are implicated in neuromodulation of various cellular functions that ameliorate the pathological features and neurocognition in AD animal models (Fang et al. 2018).

Stem cells are capable of spontaneous self-renewal and subsequent differentiation into specialized cells, such as neurons and glial cells (Eriksson et al. 1998; Paspala et al. 2009). Based on the differentiation capacity, there are three types of stem cells: totipotent cells that have the potential to create an organism, pluripotent cells that can be transformed into all cell types, and multipotent cells that can be differentiated into cell types in their own tissues (Yoo et al. 2013). Based on origin, stem cells are divided into embryonic, fetal, and adult types (Takahashi et al. 2008). Choosing the suitable cell source is an important step to develop a stem cell-based therapy (Duncan and Valenzuela 2017). The most commonly utilized stem cells in AD-related studies are embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) (Takahashi et al. 2006), mesenchymal stem cells (MSCs) (Drela et al. 2013), and neural stem cells (NSCs) (Kim et al. 2013). This review attempts to provide a simplified idea of stem cell-based therapy for AD. We described the underlying pathology of AD and demonstrated the different stem cells used in AD animal models and referred to their possible mechanistic actions as summarized in Table 1.

Table 1 Transplantation studies of stem cells in AD animal models

Stem cell type	AD subject	Therapeutic outcome and mechanism of action	References
NSCs	Aged Tg-AD mice	-Improved cognition -paracrine support (BDNF)	Blurton-Jones et al. 2009
NSCs	AD rats	Improved learning and memory function	Xuan et al. 2009
NSCs	APP /PS1 Tg mice	-Enhanced expression of synaptic proteins -Improved spatial memory	Zhang et al. 2014
NSCs	APP /PS1 Tg mice	-Ameliorated cognitive deficits -Anti-inflammatory activity * No difference was found in Aβ levels	Zhang et al. 2015a
NSCs	APP /PS1 Tg mice	-Enhanced mitochondrial biogenesis -Reduced cognitive deficits	Zhang et al. 2015b
overexpressing ChAT-NSCs	Cognitive decline-rat model	Restored cognition	Park et al. 2012
overexpressing ChAT-NSCs	Aged mice	Improved memory function	Park et al. 2013
Human NSCs	Tg2576 mice	-Enhanced neurogenesis -Improved cognition	Lilja et al. 2015
Human NSCs	-3xTg-AD mice -CaM/Tet-DT(A) model of neuronal loss	-Improved cognition -Enhanced synaptogenesis	Ager et al. 2015
NEP-expressing NSCs	-3xTg-AD -Thy1-APP mice	Anti-amyloidogenic effect	Blurton-Jones et al. 2014
MSCs	Aβ-treated mice	Modulated Wnt signaling pathway	Oh et al. 2015
UCB-MSCs	APP /PS1 Tg mice	-Rescued memory deficits -Anti-amyloidogenic effect -Paracrine support	Yang et al. 2013
UCB-MSCs	AD model	promoted hippocampal neurogenesis and synaptic activity	Kim et al. 2015
UCB-MSCs	APP/PS1 Tg mice	Anti-amyloidogenic effect *via* SCAM-1	Kim et al. 2012
Human UCB-MSC	APP/PS1Tg mice	-Improved memory function -Anti-amyloidogenic effect -Anti-hyperphosphorylation of tau	Lee et al. 2012b
adipose-derived MSCs	AD mice	- Microglial activation -Ameliorated neuropathological deficits	Ma et al. 2013
AT-MSCs	APP/PS1 Tg mice	-Enhanced neurogenic activity -Improved cognitive impairment	Yan et al. 2014
VEGF overexpressing BM-MSCs	2xTg-AD mice	-Anti-amyloidogenic effect -Improved cognitive impairment	Garcia et al. 2014
BM-MSCs	Aβ mice	-Induced microglial migration when exposed to Aβ in vitro -Increased release of CCL5, NEP, IL-4 -Anti-amyloidogenic effect -Improved cognitive impairment	Lee et al. 2012a
BM-MSCs	APP/PS1 Tg mice	-Anti-amyloidogenic activity -Anti-inflammatory effect -Anti- hyperphosphorylation of tau -Improved cognitive function	Lee et al. 2010
BM-MSCs	Aβ-injected C57BL/6 mice	-Microglial activation -Anti-amyloidogenic activity	Lee et al. 2009
PD-MSC	Aβ mouse model	-Regulated neurogenesis, glial cell activation and altering cytokine expression	Yun et al. 2013
MSCs	AD models	-Enhanced autophagy -Anti-amyloidogenic activity -Upregulated BECN1/Beclin 1 expression	Shin et al. 2014
Encapsulated human -MSCs	Double Tg-AD mouse	-Anti-amyloidogenic activity -Anti-inflammatory activity	Klinge et al. 2011
hESC	Radiation-induced cognitive impairment	-Improved cognitive function	Acharya et al. 2009
ESC-derived NPCs	Aβ rats	Improved cognitive function	Tang et al. 2008

Table 1 Transplantation studies of stem cells in AD animal models *(Continued)*

Stem cell type	AD subject	Therapeutic outcome and mechanism of action	References
ESC-derived NPCs	AD rats	Improved cognitive function	Moghadam et al. 2009
iPSC-derived NPCs	APP-Tg mice	-Cholinergic function -Improved spatial memory	Fujiwara et al. 2013
human IPSC-ML/NEP2	5XFAD AD mouse	Anti-amyloidogenic activity	Takamatsu et al. 2014

Abbreviations: *Aβ* amyloid beta, *AD* Alzheimer's disease, *Tg* transgenic, *APP /PS1: Tg mice* amyloid precursor protein (APP)/PS1 transgenic (Tg) mice, *ChAT* choline acetyltransferase, *UCB-MSCs* umbilical cord-derived MSCs, *AT-MSCs* adipose tissue-derived mesenchymal stem cells, *BM-MSCs* bone marrow-derived MSCs, *NEP* neprilysin, *PD-MSC* placenta-derived MSCs, *hESC* human embryonic stem cells, *NPCs* neuronal precursor cells, *IPSC-ML/NEP2* iPSC-derived macrophages expressing Neprilysin-2, *2xTg-AD mice* double transgenic mice model of AD express APP and PS1 mutation, *3xTg-AD mice* triple transgenic mice model of AD express APP, PS1 and microtubule-associated protein tau (MAPT) mutation, *5XFAD* mice overexpress 3 APP mutations and 2 PS1 mutations

Stem cells used for the treatment of AD

Neural stem cells (NSCs)

NSCs are derived from the embryonic or adult brain and are responsible for the generation of all neural cell types such as neurons, astrocytes, and oligodendrocytes (Kim et al. 2013; Shroff 2018); their presence is restricted to neurogenic niches of the subventricular zone (SVZ) and the granular layer of the hippocampal dentate gyrus (DG) (Duncan and Valenzuela 2017). Multipotent NSCs are capable of self-renewal and differentiation into functional glia, neurons, astrocytes, and oligodendrocytes (Gage 2002) and can be obtained from fetal and postmortem neonatal brain tissues (Martínez-Morales et al. 2013) or differentiated from iPSCs and ESCs (Hermann and Storch 2013; Yu et al. 2013a, 2013b).

The mechanistic action of NSCs is regulated by metabolic processes such as oxygen consumption and energy production (Almeida and Vieira 2017; Fatt et al. 2015; Wang et al. 2012a). Mitochondrial dysfunction is implicated in AD progression (Swerdlow et al. 2014); therefore, more research is required to estimate the connection between the metabolic switch of NSCs and AD pathogenesis (Fang et al. 2018).

Experimentally, it was found that engrafted NSCs could survive, migrate, proliferate, and differentiate into cholinergic neurons, astrocytes, and oligodendrocytes, resulting in increased synaptic strength and amelioration of cognitive function in AD animal models (Yamasaki et al. 2007; Xuan et al. 2009; Blurton-Jones et al. 2009). Most NSC transplantation studies successfully recovered cognitive dysfunction in AD animal models but failed to decrease Aβ plaques (Blurton-Jones et al. 2009; Zhang et al. 2015a; Ager et al. 2015). In another study, Park et al. (2012) demonstrated that transplantation of human choline acetyltransferase (ChAT)-NSCs into (AF64A-cholinotoxin-induced) AD rats improved cholinergic neuronal integrity through elevating ACh in cerebrospinal fluid (CSF). In addition, NSCs might exert "paracrine neuroprotection" through enhancing the expression and release of neurotrophic factors such as brain neurotrophic factor (BDNF) and nerve growth factor (NGF), increasing neurogenesis, and finally improving neurocognitive function in AD rat model and aged primate (Blurton-Jones et al. 2009; Chen and Blurton-Jones 2012; Park et al. 2013; Fan et al. 2014). Moreover, transplanting NSCs, derived from the hippocampus of neonatal rats, into AD rats resulted in the generation of new cholinergic neurons and improvement of cognitive function (Xuan et al. 2009).

Interestingly, the transplantation of human NGF-expressing NSCs (genetically modified) ameliorated cognitive function in AD mice (Lee et al. 2012a). In addition, transplantation of BDNF-overexpressing NSCs improved synaptic density and restored memory formation (Wu et al. 2016). On the other side, transplantation of genetically modified NSCs that express neprilysin (NEP), the Aβ-degrading enzyme, into the hippocampi of AD transgenic (Tg) mice, reduced Aβ pathology and improved synaptic plasticity and function (Blurton-Jones et al. 2014). In accordance, transplantation of fetal NSCs into the cerebral lateral ventricles of AD mice resulted in activation of Akt/GSK3β pathway, the subsequent inhibition of tau hyperphosphorylation, and the final improvement of memory function (Lee et al. 2015). Therefore, NSC transplantation attenuated both tau- and Aβ neuropathy and could represent an effective treatment against AD proteinopathy.

Altogether, transplanted NSCs mitigate neuroinflammation, enhance neurogenesis, promote synaptogenesis, and rescue cognitive functions of AD animal models (Yang et al. 2016; Lilja et al. 2015; Ager et al. 2015; Zhang et al. 2015b). Moreover, NSC transplantation resulted in modulation of cross talk between NSCs and endothelial cells (Li et al. 2006). Thus, NSC-based therapy for AD could provide a suitable neural microenvironment to inhibit neurodegeneration and to sustain the survival of mature neurons (Xuan et al. 2009). However, they are limitations to NSCs such as failure to improve Aβ pathology, limited differentiation capacities to generate sufficient numbers of NSCs and cholinergic neurons, unwanted generation of non-neuronal cell types, and uncontrolled differentiation into glial cell types (Xuan et al. 2009; Ager et al. 2015; Lee et al. 2016). Moreover, NSC content in the human brain declined with age (Manganas et al. 2007). This age-associated decline in NSCs might affect the efficacy of transplantation.

NSCs showed relatively low risks in tumorigenesis and immunogenicity; that renders them the ideal candidates for neuronal transplantation in the human brain (Kim et al. 2013). As an alternative strategy for neuronal replacement, NSCs could represent a promising and safe approach to deliver potential therapeutic agents and disease-modulating proteins (Liu 2013, Martínez-Morales et al. 2013, Chen and Blurton-Jones 2012, Dunnett and Rosser 2014; Blurton-Jones et al. 2014).

Mesenchymal stem cells (MSCs)

MSCs can be derived from various origins as demonstrated in (Fig. 3). MSCs, under certain conditions, can differentiate into different cell types of mesodermal origin such as chondrocytes, cardiomyocytes, adipocytes, osteoblasts, myocytes, and tendon cells. Interestingly, MSCs are featured by their regenerative potential due to self-renewal capacity and multipotency (Hsun and Yang 2018).

MSCs are multipotent progenitors derived from different adult tissues and are capable of in vitro self-renewal (Lanza and Atala 2014). Moreover, MSCs are capable of supporting hematopoiesis and cartilage regeneration (Bianco et al. 2013). MSCs have several modulatory features such as accessibility, ease of handling, availability, and a broad range of differentiating potential (Divya et al. 2012). MSCs are characterized by the Blood-Brain Barrier (BBB)-crossing ability, active homing ability, and efficient migratory capacity toward damaged brain regions; moreover, MSCs could be clinically used in AD patients, because of their less-invasive systemic administration (intravenously), without inducing tumorigenicity or immunogenicity, besides lacking ethical concerns (Oh et al. 2015, Ra et al. 2011, Fang et al. 2018).

MSC transplantation into AD models demonstrated neuroprotective potential through modulating neuroinflammation, boosting survival signaling, enhancing endogenous hippocampal neurogenesis, suppressing neuroapoptosis, and augmenting the Wnt signaling pathway (Oh et al. 2015; Heppner et al. 2015; Laroni et al. 2015). For instance, transplantation of Bone marrow-derived MSCs (BM-MSCs) into murine AD models attenuates neuroinflammation, improves both neuropathology and neurocognitive functions (Huang and Mucke 2012). Moreover, transplantation of BM-MSCs into APP/PS1 Tg mice reduced the size of pE3-Aβ plaque (Naaldijk et al. 2017). BM-MSCs demonstrated their ability to upregulate expression of "Nestin and ChAT-positive cells" and decreased hippocampal Aβ plaques at the damaged brain region (Bali et al. 2017). Furthermore, placenta-derived MSCs (PD-MSC) improved memory dysfunction in Aβ-42-infused AD mice (Yun et al. 2013).

MSCs can induce hippocampal neurogenesis through secretion of neurotrophic factors (Tfilin et al. 2010). The neuronal replacement potential of MSCs is mediated by the released neurotrophic factors (Oh et al. 2015; Teixeira et al. 2015). Transplantation of BM-MSCs into the lateral ventricles of the brain in Tg AD mouse model increased expression of vascular endothelial growth factor (VEGF) that improved the endothelial dysfunction and enhanced synaptic plasticity (Garcia et al. 2014) and could be employed as a therapeutic approach for AD. In addition, MSCs demonstrated anti-inflammatory and immunomodulatory activities, such as upregulating neuroprotective mediators, downregulating pro-inflammatory cytokines, and, activating microglial activity to improve Aβ pathology (Lee et al. 2012a; Yang et al. 2013). These mechanistic actions exerted by MSC could render them as possible candidates for effective neuronal replacement.

In the CNS, there are two opposite microglial phenotypes: M1 (pro-inflammatory) and M2 (anti-inflammatory). M1 microglia release pro-inflammatory cytokines such as IL-1β. M2 microglia are induced by IL-4, IL-13, apoptotic

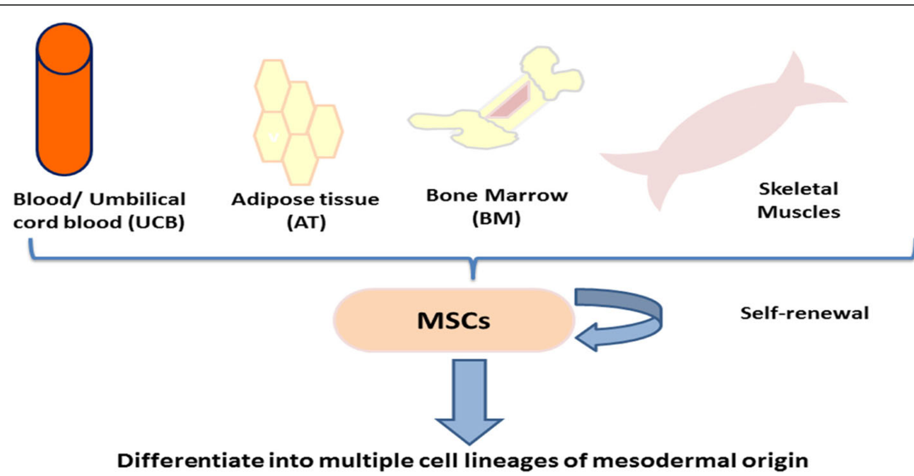

Fig. 3 Origin of mesenchymal stem cells (MSCs). MSCs can be isolated from the umbilical cord blood, bone marrow, and adipose tissue. MSCs are capable of self-renewal and differentiation into multiple cell lineages

cells, or other anti-inflammatory cytokines (Tang and Le 2016). M2 microglia are involved in ameliorating Aβ neuropathy after transplantation (Ma et al. 2013; Yang et al. 2013). Therefore, targeting the balance of M1/M2 microglia and activation of M2-like microglia is a potential strategy to ameliorate AD-associated neuroinflammation (Lee et al. 2012b; Darlington et al. 2013). The anti-inflammatory and anti-amyloidogenic activities of MSCs might be attributed to microglial activation (M2 microglia) and their ability to express CCL5, a chemoattractive factor secreted by transplanted BM-MSCs, to enroll additional microglial cells (Lee et al. 2009; Lee et al. 2012b; Turgeman 2015). Bi-lateral transplantation of human umbilical cord-derived MSCs (hUCB-MSCs) into double transgenic mice released soluble intracellular adhesion molecule-1 (sICAM-1), enhanced microglial expression of Aβ-degrading enzymes *via* the sICAM-1/LFA-1 signaling pathway, and subsequently decreased hippocampal Aβ plaques (González and Pacheco 2014, Kim et al. 2012), through microglial activation (Giunti et al. 2012). This proves the multi-targeting therapeutic potential of MSCs, and the activation of cell plasticity in AD brain, especially when coupled with therapeutic substances such as NEP (Laroni et al. 2015; Kim et al. 2012).

Furthermore, transplantation of BM-MSCs and UCB-MSCs into AD animal models was able to activate endogenous microglia, to suppress monocyte-derived dendritic cells, to generate cholinergic neurons, and to decrease Aβ plaques and safely recover cognitive function (Sun et al. 2013; Zhang et al. 2012). In addition, human MSCs are capable of promoting autophagy, enhancing Aβ clearance, and boosting neuronal survival in Aβ-induced AD mice (Shin et al. 2014).

Moreover, adipose tissue-derived MSCs (AT-MSCs) might have a common transcriptional profile with BM-MSCs (Peroni et al. 2008). AT-MSCs secrete neurotrophic factors and differentiate into neuron-like and astrocyte-like cells (Gutiérrez-Fernández et al. 2013; Ikegame et al. 2011). Intracerebral transplantation of AT-MSCs into APP/PS1 Tg AD mice enhances neurogenesis (Yan et al. 2014). In addition, AT-MSCs, when co-cultured with Aβ, secrete active NEP-containing exosomes (Katsuda et al. 2013b). Exosomes are cell-derived membrane vesicles that regulate physiological or pathological pathways through acting as mediators of cell-to-cell communication and transferring genetic information to recipient cells (Record et al. 2011). Furthermore, administration of exosomes could represent an alternative therapy for AD (Fang et al. 2018; El Andaloussi et al. 2013). Intravenous administration of MSC-derived exosomes enhances functional recovery in stroke-induced rats (Bang et al. 2016); this might be attributed to "miR delivery to target cells," thereby regulating the expression of genetic information and promoting a therapeutic response (Juranek et al. 2013). For instance, MSC transplantation raised miR-133b expression in the brains of stroke-induced rats and regulated neurite outgrowth (Xin et al. 2012).

Recently, three-dimensional (3D) modeling aimed to simulate the in vivo-like microenvironment of the stem cells, to preserve their characteristics and to enhance their mechanism of action (Sart et al. 2014; Frith et al. 2010); this approach could assist the clinical application of stem cells (Bang et al. 2016). For example, "3D MSCs" expresses higher neuromodulating factors (Frith et al. 2010); thereby this type of MSCs could present a higher therapeutic potential.

Finally, we could consider that MSCs, a double-edged weapon in neurodegenerative disorders, provide both neuroprotection and immunomodulation, and at the same time, MSCs have an uncontrolled homing mechanism to lesion sites in aged AD models due to their low efficacy (Laroni et al. 2015; Fabian et al. 2017). Therefore, more research is required to understand the homing mechanism of MSCs to optimize their migration capacities and to promote the therapeutic potential of transplanted MSCs that home directly to the brain (Fang et al. 2018; De Becker and Riet 2016).

Embryonic stem cells (ESCs)

Pluripotent ESCs are stem cells derived from the inner cell mass of developing blastocysts and give rise to all cell types during the embryonic development (Lerou 2011). ESC transplantation resulted in a safe recovery of neurocognitive function in rodent models of brain injury (Acharya et al. 2009). However, because of their pluripotent differentiation capacity, ESCs demonstrated drawbacks such as the risk of tumorigenesis and uncontrolled cell growth, besides the risk of immunogenic rejection (Acharya et al. 2009; Fong et al. 2010; Ratajczak et al. 2014; Chen et al. 2015).

Nonetheless, it was suggested that ESC-derived NSCs could be safely transplanted without the risk of tumor formation (Araki et al. 2013, Tang et al. 2008). In vitro pre-differentiation of ESCs into NSCs and their subsequent transplantation into an AD rodent model resulted in the generation of cholinergic neurons and memory enhancement (Moghadam et al. 2009).

The conversion of ESCs into medial ganglionic eminence-like progenitor cells, and their subsequent transplantation into a murine brain injury model, resulted in amelioration of neurocognitive function through generating cholinergic and dopaminergic neuronal subtypes (Liu 2013). Transplantation of ESC-derived neural progenitor cells (NPCs) into AD animal models can result in a therapeutic outcome, through differentiation into astrocytic and neuron-like cells and enhancing memory performance (Tang et al. 2008). In addition, transplanting "neuron-like cell (NLC)-derived mouse ESCs (mESCs)" into AD-induced rats enhanced the neuronal connectivity and reduced brain lesions (Hoveizi et al. 2018).

They are several successful trials to differentiate ESCs into different neural cell types, including dopaminergic neurons (Krencik et al. 2011, Kriks et al. 2011, Lee et al. 2007). Human ESCs (hESCs) were able to generate astroglial cells, spinal motor neurons, and dopaminergic neurons (Lee et al. 2007). In addition, an ex vivo slice culture study reported stable functional integration of cholinergic neuron from hESCs (Bissonnette et al. 2011). However, hESCs in FDA-approved clinical trials elicit ethical concerns (Liras 2010).

The neurocognitive decline in AD patients may occur because of degeneration of basal forebrain cholinergic neurons (BFCNs) and the subsequent cholinergic dysfunction. Yue and Jing (2015) successfully differentiated both mouse and human ESCs into BFCNs from a highly pure population of BFCN progenitors. Both mouse and human ESC-derived BFCN progenitors were transplanted into transgenic AD mice and gave rise to functional cholinergic neurons that resulted in neurocognitive recovery. Therefore, BFCNs might be a typical model of donor cells; however, more research is required to elucidate the potential of transplanted BFCNs.

Induced pluripotent stem cells (iPSCs)

IPSCs are pluripotent stem cells reprogrammed (in vitro) from adult somatic cells (Ye et al. 2013). Takahashi et al. (2006) discovered that four transcription factors (TFs) [Sox2, Oct4, Klf4, and c-myc] could reprogram murine fibroblasts, through retroviral transduction, to ESC-pluripotency state.

iPSCs are more available, easily generated, less immunogenic, and less ethically controversial. Furthermore, iPSCs have the capacity to provide an unlimited source for different cell types. Additionally, iPSCs are regarded as "disease modeling" approach for drug screening and testing, identifying novel drugs, and patient-tailored (personalized) cell therapy (Tang 2012; Araki et al. 2013), (Fig. 4). iPSC-derived neurons are structurally and functionally mature and can form active synaptic circuits (Pang et al. 2011).

Moreover, applications of iPSCs in AD have been more concerned with the development of cell-based AD models (Kwak et al. 2018). Actually, using iPSC-derived neurons to recap AD pathogenesis in vitro has significant applications in screening for potential therapeutic drugs (Pen and Jensen 2017). The first AD model using iPSCs was generated using five transcription factors (OCT4, SOX2, KLF4, LIN28, and NANOG) from fibroblasts of FAD patients; these iPSCs were then differentiated into neurons that may increase Aβ-42 expression to mimic Aβ pathology; thus, these iPSCs could represent a potential strategy for the development of therapeutic drugs against AD (Yagi et al. 2011). For example, the intra-hippocampal transplantation of human iPSC-derived cholinergic NPCs into a transgenic AD mouse model improved spatial memory performance by generating mature cholinergic neurons (Fujiwara et al. 2013). In addition, iPSCs could be used to generate NEP-secreting macrophages (Takamatsu et al. 2014).

To establish a successful iPSC-based therapeutic approach against AD, we should consider the following factors: examining the haplobanks of human leukocyte antigen (HLA), defining standardized and optimized

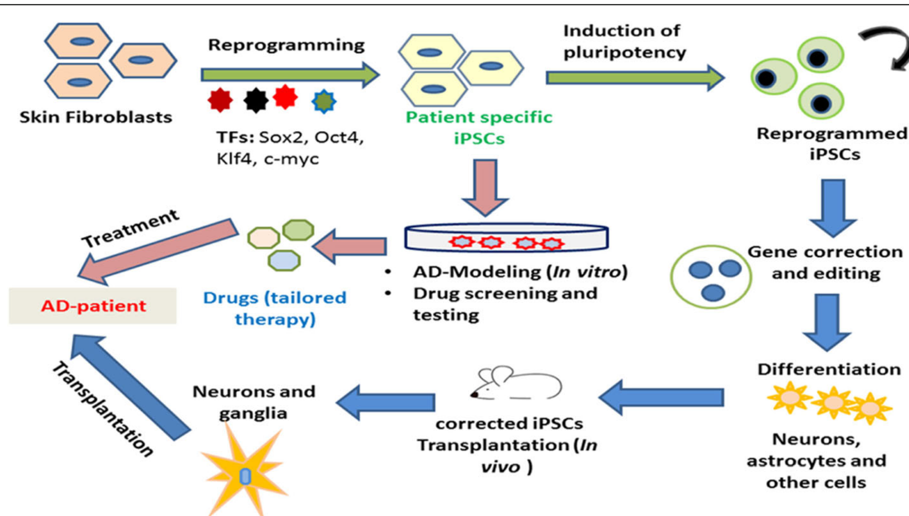

Fig. 4 The potential applications of iPSC-based therapy for AD. iPSC-based therapy is a therapeutic approach for replacing lost or damaged neural tissues. iPSCs could be used for generation of healthy neurons and astrocytes, by genetic modification, for in vivo transplantation. Moreover, iPSCs could act as an in vitro tool for AD modeling and anti-AD drug screening and testing

protocols to generate NSCs or hippocampal neurons, and establishing an astrocyte-generation technique for providing neurotrophic agents (Pappas et al. 2015; Hunsberger et al. 2016). Moreover, chimeric modeling and three-dimensional (3D) modeling were used to imitate different cellular interactions (such as amyloidogenic pathway) in the AD brains; in addition, genome-editing techniques were employed to enable isogenic comparison of different mutations while keeping a constant genetic background (Fang et al. 2018).

Interestingly, human iPSCs derived from somatic cells of either FAD or SAD patients contain a patient-specific (personalized) pathogenic background and can present an effective method for AD modeling, which could represent a link between preclinical (animal models) and clinical application. Moreover, it could aid in the understanding of AD pathogenesis, identifying therapeutic targets, and drug screening of the novel treatments against AD (Yang et al. 2016). Furthermore, it was found that human iPSC lines have only a 10–50% differentiation potential for neurons, as compared to ESCs, which have a nearly 90% differentiation potential (Wang et al. 2015), that is why, the possibility of employing iPSCs as a tool for the development of specific and tailored AD patient model systems remains challenging (Tang 2012). More interestingly, degeneration of basal forebrain cholinergic neurons (BFCNs) is closely associated with a neurocognitive decline in AD. Thus, the generation of tailored BFCNs from AD patient-specific iPSCs is crucial for in vitro disease modeling and for the development of novel AD treatments (Yang et al. 2016). BFCNs derived from SAD-iPSCs showed a significant elevation in Aβ plaque formation which is regarded as a typical AD (Duan et al. 2014). Recently, Schöndorf et al. (2018) derived iPSCs from dermal fibroblasts of two SAD patients and three controls to examine SAD pathogenesis. In addition, Najar et al. (2018) generated iPSCs from two FAD patients. Thus, these studies might contribute to explain the etiology of AD and to influence the future treatment of AD. Therefore, iPSCs could provide unique platforms to detect the early-AD phenotypes that may help to uncover the underlying mechanisms of this neuropathy (Yang et al. 2016).

However, there are several hurdles concerning the clinical application of iPSCs such as long-term safety and efficacy, tumorigenicity, immunogenicity, patient-derived genetic defects, optimal reprogramming, and ethical issues (Kwak et al. 2018; Lomax et al. 2013). For instance, using integrating (e.g., viral) vectors to generate patient-specific iPSCs results in genetic mutation and disruption of endogenous genes (Stadtfeld and Hochedlinger 2010). Additionally, viral delivery system (using retroviral or lentiviral vectors) is efficient and reproducible in reprogramming to induce iPSCs (Sommer et al. 2012); however, the random viral integration increases the risk of tumorigenesis (Okita et al. 2007). This can be avoided through transfection of linear DNA by poly-cistronic vectors, but this would result in lower reprogramming efficiency. Fortunately, many viral integration-free systems for iPSCs generation have been utilized, such as adenovirus, episomal vectors, and direct protein delivery (Yang et al. 2016).

In addition, several murine iPSCs conceal epigenetic abnormalities and continue to keep the epigenetic memory of their donor cells, as well as the absence of efficient targeting strategies to repair mutant alleles (Panopoulos et al. 2011). Therefore, generating high-fidelity cells of known-fate is required for a long-lasting effect of the transplantation and will have to be guaranteed before the clinical use of reprogrammed cells (Pen and Jensen 2017).

Other cells

Novel sources of stem cell have demonstrated potential in neuronal-regeneration, including neural crest stem cells, hematopoietic stem cells, human dental pulp stem cells (DPSCs), and olfactory ensheathing cells (Kwak et al. 2018). For example, DPSCs are being examined as a potential stem cell source for transplantation in AD models (Apel et al. 2009; Ahmed et al. 2016). DPSCs are cranial neural crest-derived MSCs that facilitate their neural differentiation (Mead et al. 2017). Moreover, DPSCs are easily harvested, available, less invasive, and less immunogenic and demonstrate neurotrophic potential (Luo et al. 2018). Notably, the somatic cell nuclear transfer procedure involving olfactory ensheathing cells, *via* the intranasal route, is another promising technology (Baig and Khan 2014; Baig 2014).

Remarkably, there are very few reports registered at https://www.clinicaltrials.gov/ of transplantation of stem cells in AD patients. In 2011, Medipost *Co Ltd.* completed an open level, phase I safety and efficacy trial on Korean AD patients, but the outcomes were not revealed (Bali et al. 2017). There has been increasing commercial interest to convert preclinical studies into clinical practice on AD patients. Actually, the growing interest in stem cell transplantation should be controlled by governmental regulations (Fang et al. 2018). Several laws and guidelines under agencies like the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and others control stem cell-based therapy (Frese et al. 2016).

Mechanistic actions of transplanted stem cells for treatment of AD

Regenerative medicine using stem cells could represent a promising therapeutic approach for the management of chronic disorders like AD; this is mainly attributed to the potential actions exerted by stem cells such as improving the neurogenic potential, exerting anti-inflammatory effect, presenting neurotrophic support, and having an anti-amyloidogenic potential (Fig. 5, Table 1).

Induction of endogenous neurogenesis (neurogenic potential)

Neurogenesis (neural regeneration) is the process of differentiation of neural progenitor cells (NPCs) into specific, functional, and fate-known new neurons, which synaptically integrated into the pre-existing neural circuit of the host (Ming and Song 2005; Jin and Galvan 2007). It takes place in the subgranular zone (SGZ) of the dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricles (Alvarez-Buylla and Garcia-Verdugo 2002). In humans, the neurogenic potential declines normally with age and is associated with AD progression (Donovan et al. 2006; Klempin and Kempermann 2007; Lopez-Toledano and Shelanski 2007a), impaired neurogenesis plays a role in AD pathogenesis (Hollands et al. 2016). AD murine models demonstrated dysfunction of neurogenesis; this refers to the imbalance between neuroregeneration and neurodegeneration (Haughey et al. 2002). Neurogenesis is associated with maintenance of neurocognitive function; therefore, stimulation of adult neurogenesis has been the main target in AD treatment (Li et al. 2015). Several effector molecules are both involved in AD pathogenesis, and, in the modulation of neurogenesis; such as apolipoprotein E (ApoE), PS1, APP, neurotrophic factors, transcription factors, metabolic factors, and epigenetic regulators (Yang et al. 2011; Gadadhar et al. 2011; Ghosal et al. 2010; Horgusluoglu et al. 2017). Therefore, neurogenesis is enhanced as a self-repairing mechanism in the early stages of AD; however, the survival of newly generated neurons was hampered by the progression of neurodegeneration (Chen et al. 2008). For instance, deposited Aβ plaques could impair neurogenesis in AD animal model (Veeraraghavalu et al. 2010). Therefore, application of stem cell-based therapy for AD depends on the neurogenic capacities of stem cells, identifying key molecules in the modulation of endogenous neurogenesis (Zhang and Jiang 2015; Fang et al. 2018).

Transplanted stem cells can enhance endogenous neurogenesis to replace damaged neurons in the AD brain (Mu and Gage 2011; Kanno 2013). Novel neurons, derived from donor cells or activated neurogenesis, demonstrated their ability to mediate structural and functional integration in the pre-existing network and to modulate neurogenesis (Yu et al. 2013a, 2013b; Bonaguidi et al. 2011). These new neurons are capable of secreting neurotrophic factors (Enciu et al. 2011) and increasing brain ACh levels, thus improving neurocognitive functions in AD animal models (Park et al. 2013; Park et al. 2012; Yang et al. 2013; Ma et al. 2013; Njie et al. 2012). Furthermore, genetically reprogrammed stem cells can possess the migratory capacity and can be employed as vehicles to deliver neurotrophic factors or to enhance genetic expression that can alter the AD pathway (Mucke 2009). As demonstrated in AD animal models, transplanted stem cells have the potential to improve several cellular functions, such as synaptic connectivity (Blurton-Jones et al. 2009), neurogenesis (Kim et al. 2015), microglial activity (Yang et al. 2013), angiogenesis

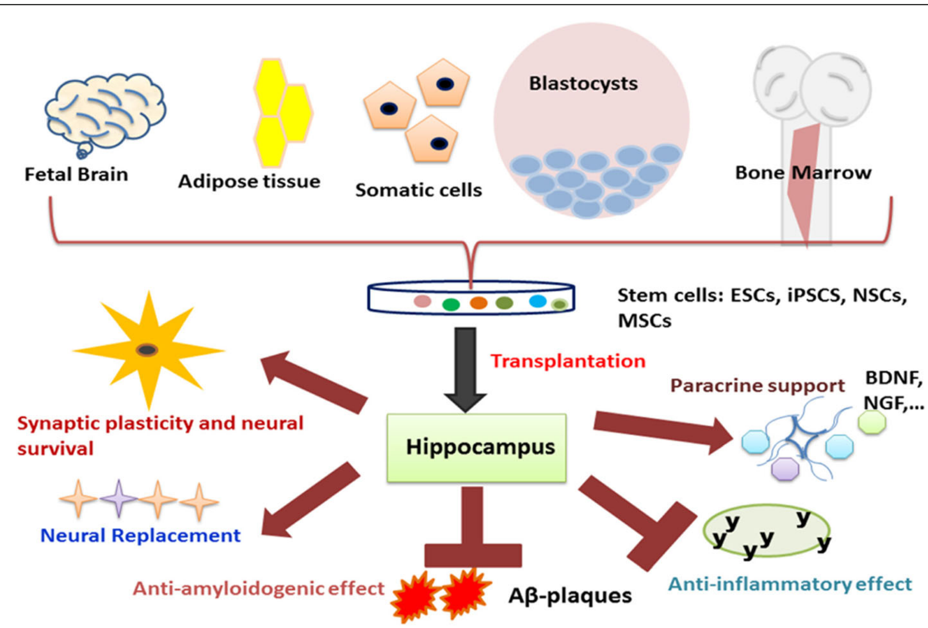

Fig. 5 The potential mechanistic actions exerted by stem cells against Alzheimer's disease

(Garcia et al. 2014), mitochondrial function (Zhang et al. 2015b), and autophagy (Shin et al. 2014). Therefore, stem cell transplantation could represent a promising and safe approach to treat AD, as it affects this disease through multiple mechanisms that result in re-building the neural integrity and improving the neurocognitive function (Fang et al. 2018; Lee et al. 2016; Choi et al. 2014a).

However, it has been suggested that engrafted stem cells are not the sole source of the newly generated neurons (Sullivan et al. 2015; Zhang et al. 2013). Hence, rather than using the cell-replacement model in AD, activation of endogenous NPCs and stimulation of neurogenesis could improve the microenvironment, support neuroregeneration, and enhance the survival of injured neurons (Lunn et al. 2011), and prevent secondary neuronal damage, through the neurotrophic support (Burns et al. 2009).

Neurotrophic and neuroprotective activity

Transplanted stem cells demonstrated neurotrophic/paracrine potential (Martino and Pluchino 2006), through increasing the levels of different neurotrophic factors such as brain-derived neurotrophic factor (BDNF)—the classic paracrine mediator—(Blurton-Jones et al. 2009), glial cell line-derived neurotrophic factor (GDNF) (Kim et al. 2012), insulin-like growth factor 1 (IGF-1) (Klinge et al. 2011), glucagon-like peptide-1 (GLP-1) (Zhang et al. 2014), nerve growth factor (NGF) (Jin et al. 2002), and vascular endothelial growth factor (VEGF) (Garcia et al. 2014). For example, NSCs, ESCs, and MSCs can express high levels of BDNF and NGF, which are important positive neuroregulators in endogenous neuronal survival and synaptic plasticity (Yan et al. 2014). Moreover, Blurton-Jones et al. (2009) showed that NSC transplantation into the brains of transgenic AD models elevated brain BDNF levels and enhanced the hippocampal synaptic density. Similarly, Yan et al. (2014) demonstrated that MSC transplantation induced endogenic activity in the hippocampal SGZ and SVZ and improved cognitive function in APP/PS1 transgenic AD mice. In addition, transplantation of NGF-expressing human NSCs (hNSCs) into the hippocampi of ibotenic acid-injected mice (a model of neurocognitive dysfunction) exerted neuroregenerative potential and restored memory formation (Wang et al. 2012b). Furthermore, Chen and Blurton-Jones (2012) found that delivery of recombinant BDNF could resemble the potential of NSC transplantation in AD transgenic animals.

BDNF and CREB (cAMP response element-binding protein) play a major role in the process of memory formation and consolidation (Song et al. 2015; Dominguez et al. 2016). Since CREB is a DNA-binding protein and acts as a transcription factor for BDNF, it is possible that a relationship exists between the role of BDNF expression and its regulation by CREB in restoring memory function (Lee et al. 2013). Suzuki et al. (2011) reported that elevated BDNF levels were associated with improvement of both long-term memory (LTM) and short-term memory (STM), suggesting that CREB-mediated BDNF expression plays an intrinsic role in memory formation. Besides secreting neurotrophic factors, the therapeutic potential of stem cell-derived extracellular vesicles was also investigated (Katsuda et al. 2013a).

It is essential to upregulate (either pharmacologically or with gene therapy) the neurotrophic factors (Jin et al. 2002). Nonetheless, this is complicated by several obstacles, such as the age-dependent decline of hippocampal neurogenesis, the massive loss of hippocampal neurons in AD patients, and the possible effect of AD pathology on neurogenesis (Lopez-Toledano et al. 2007a, 2007b). Moreover, endogenous NSCs demonstrated a limited capacity to compensate for damaged cells, as well as, NSCs become "gliogenic" rather than neurogenic (Li et al. 2010). Therefore, the comprehensive mechanism of endogenous neuroregeneration needs more clarification (Tang 2012).

Immunomodulation and anti-inflammatory activity

Chronic inflammation is involved in neurodegenerative diseases, including AD (Voloboueva and Giffard 2011). Certain stem cell types such as NSCs and MSCs showed anti-inflammatory activities by decreasing pro-inflammatory cytokines and upregulating anti-inflammatory factors (Ylostalo et al. 2012). MSCs represent a good source of inflammatory mediators and growth factors (Caplan and Dennis 2006). Moreover, MSCs could deliver therapeutic molecules such as proteins (Hsun and Yang 2018).

UCB-MSC transplantation into transgenic AD mice attenuated neuroinflammation, induced microglial expression of neprilysin (NEP), decreased hippocampal Aβ plaques, and ameliorated neurocognitive function (Kim et al. 2012). Moreover, intra-hippocampal transplantation of NPCs into Aβ-42 peptide-injected hippocampi in AD rats is neuroprotective and attenuates inflammatory reactivity (Ryu et al. 2009).

Noteworthy, "Cholinergic anti-inflammatory pathway" is mediated by ACh, which has anti-inflammatory activity, through inhibiting production of tumor necrosis factor (TNF-α) and IL-1β and suppressing the activation of nuclear factor-kB (NF-kB) (Pavlov and Tracey 2006). Transplantation of ChAT-overexpressing human NSCs (HB1.F3.ChAT) into AD animal models restored neurocognitive function and improved memory function; this might be attributed to the elevated levels of ACh in CSF and the successful migration of transplanted cells to affected brain regions (Naert 2012; Kim et al. 2012). Therefore, cell-based therapies that simultaneously increase neurotransmitters and growth factors could achieve better outcomes (Choi et al. 2014a).

Anti-amyloidogenic potential

Alzheimer's disease (AD) is characterized by the deposition of neurotoxic Aβ plaques (Walsh and Selkoe 2004). Therefore, stem cells transplantation is an effective and promising strategy for functional recovery for AD (Choi et al. 2014a), through enhancing the clearance of Aβ plaques. For instance, transplanted MSCs into murine AD models increased NEP expression, cleared Aβ aggregates, and enhanced neural survival (Bales et al. 2006; Szabo et al. 2008; Choi et al. 2014a). Moreover, NSCs can express metalloproteinase 9 (MMP9) which is regarded as a degrading enzyme for Aβ peptides (Miller et al. 2003). Similarly, adipose tissue-derived stem cells (ADSCs) demonstrated a similar anti-amyloidogenic potential coupled with anti-inflammatory activity (Melchor et al. 2003). Moreover, transplanting stromal cell-derived factor-1 into AD transgenic animals resulted in clearance of Aβ plaques (Xue et al. 2012). Additionally, engrafted MSCs cleared Aβ plaques, through differentiating into microglia or recruitment of activated microglia (Lee et al. 2012a).

Autophagy plays a critical role in maintaining Aβ homeostasis by enhancing the clearance of Aβ deposits in the brain (Shin et al. 2014). Autophagy acts as a cytoprotective response, under stress conditions, for the degradation of abnormal and aggregated proteins (Cuervo et al. 2010). Dysfunction in the autophagic system may lead to deposition of Aβ plaques (Shin et al. 2014). They are several autophagic vacuoles (AVs) that accumulate in the AD brains (Lee et al. 2010). Autophagy markers (e.g., ATG5, ATG12, and microtubule-associated protein 1 light chain 3 [LC3]) are correlated with Aβ neuropathology (Ma et al. 2010). Moreover, the immunofluorescent analysis showed that MSC transplantation raised fusion of Aβ-containing auto-phagosomes (LC3-II) and lysosomes (LAMP2), raised activity of lysosomal enzymes, and enhanced the autolysosome formation and catabolic function, which may be accompanied with neuronal survival. This neuroprotective potential might be attributed to lysosomal activity mediated through autolysosome formation. Thus, using MSCs to modulate the autophagy mechanism might be a promising therapeutic strategy for AD (Shin et al. 2014). It was evidenced that some compounds can reduce Aβ levels through activation of autophagy or lysosomal proteolysis (Parr et al. 2012; Lai and McLaurin 2012). MSC transplantation into an AD animal model (Aβ intoxicated) resulted in a marked increase in autophagosome induction and a significant decrease in Aβ levels (Shin et al. 2014). This confirms the potential role of MSCs as an autophagy modulator that enhances clearance of neurotoxic Aβ deposits; thus, a therapeutic strategy for AD is to enhance Aβ clearance through induction of the autophagy-lysosome pathway (Caplan and Dennis 2006; Shin et al. 2014).

Challenges in stem cell-based therapies of AD

They are several challenges concerning the clinical translation of stem cell-based therapy such as tumorigenicity, immune rejection, contamination, genetic modification, uncontrolled migration and growth, and unintended trans-differentiation (Kwak et al. 2018). Therefore, more research is required to set protocols for standard preparation of cells suitable for transplantation, to clarify the mechanism underlying symptomatic relief upon transplantation, and to determine the immune response after transplantation (Yue and Jing 2015). Furthermore, the safety and efficacy of transplanting genetically-engineered cells in humans have not yet been legitimized, as well as, there is a need for stem cell genome alteration which could encounter ethical restrictions (Fang et al. 2018). Some of those issues are listed below:

Time of transplantation

Regarding that AD is a progressive chronic disease that takes several years before clinical manifestation of symptoms; it is essential to determine the appropriate time window for transplantation during AD progression (Fang et al. 2018). It was suggested that NSC transplantation, at the onset of AD, is more effective when the brain suffers the fewest alterations in microenvironment detrimental to neurogenesis (Fan et al. 2014). Moreover, the hippocampus, in the early stage of AD, could be the main therapeutic target (Stensola et al. 2012). For example, one study used the transgenic (Tg2576) murine model (12-month--old), demonstrated age-related neurocognitive decline, showed that transplantation restored neurocognition, and improved AD neuropathology, while transplantation failed in a 15-month-old mice (Kim et al. 2015). Therefore, the therapeutic approach will become more complicated and less effective, as the AD associated neurodegeneration progresses.

MSC transplantation into elder stroke-patients, who already have a limited content of NSCs/NPCs and BM-MSCs, will be of no significance because of loss of regenerative capacity of MSCs (Bang et al. 2016). This attenuation of the potential of stem cell-based therapy in aged patients could result from aging in either the donor cells or the host cells (Manganas et al. 2007). In addition, the neurogenic activity of BM-MSCs declined with age; this implies the significance of the "aging/rejuvenation of donor cells" to the efficiency of stem cell-based therapy (Bang et al. 2016).

Location of transplantation

Determining the ideal site for introducing the new population of neurons/stem cells is of great importance and may play a critical role in the treatment of AD. The NSC-rich regions like the hippocampus and the lateral ventricles are possible candidates (Bock et al. 2011). Therefore, the hippocampus is the typical target site for introduction of transplanted cells in AD patients (Igarashi et al. 2014).

The recognition of grid cells and functionally specialized neurons and the establishment of computational models of grid cells make it possible to detect the damaged neurons and affected neural circuits (Giocomo et al. 2011). However, it is still difficult to attain an accurate grid map of the brain due to its complex structure and overlapping functions in AD. Therefore, it is necessary to develop more precise brain grid charts to estimate the ideal locations for cell transplantation for each AD patient (Li et al. 2015).

Donor-to-donor heterogeneity

Identifying "genetic and epigenetic backgrounds" of donor cells is essential for successful transplantation. Although the brain is immune-privileged, the human leukocyte antigen (HLA) profile of donor cells must be examined to avoid the immune response after transplantation (Chen et al. 2012). During the production of neuronal cells for transplantation, the genetic defects responsible for AD symptoms must be corrected in the donor cells (Yagi et al. 2011). For instance, heterogeneity between iPSC clones from the same individual and iPSCs from different individuals is the major obstacle in the application of iPSC-technology (Arber et al. 2017); this could be achieved by genetic editing with molecular scissors such as CRISPR (Marchetto et al. 2009). Selecting pure donor cells could reduce variability and improve functional outcomes in the newly generated products (Yuan et al. 2011).

Instead of using the immunosuppressive agents (Freed et al. 1992), "cell encapsulation techniques" were used to avoid the possible immune rejection of the transplanted cells; the encapsulated cells are protected with a polymeric semi-permeable membrane, which permits the exchange of essential molecules for cellular metabolism, from the immune response for a stable delivery of therapeutic agents. For example, encapsulated somatic cells were employed to deliver trophic factors to treat AD (Garcia et al. 2010; Spuch et al. 2010; Eriksdotter-Jönhagen et al. 2012; Wahlberg et al. 2012). For example, encapsulated MSCs transfected with GLP-1 were capable of inhibiting inflammatory events (Klinge et al. 2011). Moreover, in vivo or *in situ* reprogramming of iPSCs might represent a solution for the possibilities of transplantation rejection and tumorigenesis (Qu et al. 2001, Zhou et al. 2008).

Functional integration

Stem cell-based therapy for AD should be accompanied by the administration of antioxidants and neurotrophic factors. NSC transplantation exerts a neurogenic potential by providing paracrine support to existing NSCs rather than forming new functional neurons (Feng et al. 2009). Additionally, the transplantation of stem cells is often accompanied by massive death of transplanted cells in the brain (Limke and Rao 2003). New strategies such as "deep brain stimulation" showed positive outcomes in relieving AD symptoms (Gratwicke et al. 2013; Hescham et al. 2013).

Ethical issues and safety concerns

Stem cell-based therapy is an ethically challenging process; it is considered an invasive procedure that could cause several clinical complications and direct harm to the already damaged areas. Ethically, it is important to estimate the efficacy of transplantation-based therapy, to decrease the risk of therapeutic misconception, to reduce the risk of pain, and to highlight the importance of informed consent (Ciervo et al. 2017; King and Perrin 2014). Actually, the debate of ethical concerns in stem cell-based therapy showed the difficult equilibrium between the imperatives of caution and the progress for clinical trials (King and Perrin 2014). Translation of preclinical studies into successful clinical trials for AD provokes several ethical and safety concerns. For instance, the unlimited and undesired differentiation capacity of iPSCs raises the risk of non-ethical generation of genetically modified human embryos, human cloning, and human-animal chimeras, as well as, the risk of tumorigenesis. Similarly, MSC transplantation provokes safety issues concerning their capacity to induce tumor growth and metastasis (Volarevic et al. 2018). The ethical issue concerning the destruction of a human embryo hindered the development of clinical application of hESC; moreover, the pluripotent nature of hESCs renders them more prone to form tumors due to their uncontrolled growth after in vivo transplantation (Nussbaum et al. 2007). Thus, iPSCs are considered morally superior to hESCs (Meyer 2008); however, the main safety challenge regarding iPSC-based therapy is the risk of teratoma formation due to the uncontrolled differentiation (Wernig et al. 2008). In addition, the difference between the niche of the host cells and that of the in vitro cultured cells reduces the proliferative and differentiating capacity (Marks et al. 2017).

Reprogramming of somatic adult cells into NSCs could solve the problem of the immune rejection by "autologous transplantation" and evade the ethical limitations associated with the use of embryonic (fetal)-derived stem cells. Besides ethical and safety concerns, the efficiency of reprogramming and the epigenetic background of stem cells are among the obstacles that should be avoided before the clinical translation of iPSCs (Ciervo et al. 2017). On the other side, MSCs can be obtained easily from patients allowing "autologous transplantation" and avoiding ethical limitations related to the use of ESCs (Lewis and Suzuki 2014).

In vitro senescence of stem cells

The incomplete success to translate preclinical studies into clinical application might be attributed to the age-related regenerative activity between AD animal models and AD patients (Bang et al. 2016). Stem cells such as MSCs are subjected to "*in vitro* senescence" which might affect their performances through losing their characteristics (e.g., homing capacity, proliferation, paracrine function) during "*ex vivo* culturing" (Bonab et al. 2006; Li et al. 2008). In addition, AD occurs mostly in aged patients, thus "aged" MSCs derived from aged AD patients showed the characteristics of senescence, such as losing the differentiation capacity.

Therefore, it is important to evade age-associated defects such as shorter telomere length in transplanted cells (Yang et al. 2018). This could take place by presenting "retroviral vectors that carry the gene for the catalytic subunit of telomerase" to MSCs and therefore guarantee the normal proliferation and differentiation capacity during "large-scale expansion" (Hsun and Yang 2018). Finally, the in vitro approach of "large-scale expansion" is aimed to generate a massive population of stem cells for clinical therapy; this is accompanied with the use of anti-aging (senolytic) drugs such as nicotinamide riboside, quercetin, and danazol (Grezella et al. 2018). In addition, transplanted stem cells should be differentiated on large-scale "in vitro," without affecting their cellular identity and genetic profile, to ensure their efficacy (Zonari et al. 2017; Marks et al. 2017).

Future directions of stem cell-based therapy against AD

Future research should be directed to define a standardized protocol for isolation and differentiation of stem cells, through identifying their sources and designing methodologies for their isolation and differentiation into different lineages (Avinash et al. 2017). More research is required to define the sources, types, stages, doses, and routes of stem cell transplantation in AD animal models to validate their optimum therapeutic outcome (Banik et al. 2015).

Administration of anti-oxidative nutraceuticals such as polyphenols could help to prevent AD progression (Borai et al. 2017). For example, resveratrol, a grape-derived polyphenolic compound, facilitates transplantation of hUC-MSCs into the brains of AD mice and promotes functional outcomes of MSCs through activating SIRT1 signaling pathway and stimulating NPCs proliferation, and finally enhances neurocognitive function (Wang et al. 2018).

Moreover, using nanomaterials in combination with stem cells could introduce several applications in brain regenerative studies (Alipour et al. 2018). Nanomaterials provide an ideal platform for enhancing the efficacy of stem cell treatment (Misra et al. 2016), imaging and tracking of stem cells (Sibov et al. 2014), implying genetic modifications to mediate stem cell proliferation and differentiation (Tiwari et al. 2013), and improving neuronal differentiation of stem cells into neurons (Stephanopoulos et al. 2014). For example, administration of curcumin-encapsulated PLGA nanoparticles (Cur-PLGA-NPs) into Aβ-treated rats upregulated the genes necessary for the NSC proliferation and differentiation, activated Wnt signaling pathway, and improved neurocognitive function (Tiwari et al. 2013).

In time, more advanced stem cell therapies hold the potential for the clinical treatment of AD (Li et al. 2014). The safe and ethical future of stem cell-based therapy for AD will be slow, expensive, and tightly regulated (Dunnett and Rosser 2014).

Conclusion

This review has summarized the relevant use of stem cell-based therapy for the management of Alzheimer's disease (AD). Treatment of complicated AD requires targeting multiple pathogenic pathways; therefore, stem cell-based therapy might represent a multi-target therapeutic intervention that enhances neuroregeneration and suppresses neurodegeneration through exerting anti-inflammatory, anti-amyloidogenic, immunomodulating, and neuroprotective activities. However, more research is required to evaluate the most effective combination of therapeutic actions of stem cells to amend AD pathology, to apply supporting approaches that could improve mechanistic actions of stem cells such as genetic editing and 3D modeling and to provide supporting synergistic treatments such as administration of natural products, nanoparticles, and antioxidants. Several preclinical trials provided an optimistic prospect for treating AD and paved the way for the subsequent clinical application of stem cell-based therapy, which requires standardized protocols for the isolation and expansion of stem cells to get the desired therapeutic outcome. Finally, moving forward in the rapidly advanced stem cell research demands the proper combination of creativity, accuracy, and caution.

Abbreviations

ACh: Acetylcholine; AD: Alzheimer's disease; ADSCs: Adipose tissue-derived stem cells; ApoE: Apolipoprotein E; APP: Amyloid precursor protein; Aβ plaques: Amyloid-β plaques; BDNF: Brain neurotrophic factor; BFCNs: Basal forebrain cholinergic neurons; cAMP: Cyclic adenosine monophosphate; CNS: Central nervous system; CREB: cAMP response element-binding protein; Cur-PLGA-NPs: Curcumin-encapsulated PLGA nanoparticles; DG: Dentate gyrus; DPSCs: Dental pulp stem cells; ESCs: Embryonic stem cells; GDNF: Glial cell line-derived neurotrophic factor; GLP-1: Glucagon-like peptide-1; HLA: Human leukocyte antigen; IGF-1: Insulin growth factor-1; iPSCs: Induced pluripotent stem cells; LTM: Long-term memory; MMP9: Metalloproteinase 9; MSCs: Mesenchymal stem cells; NEP: Neprilysin; NF-kB: Nuclear factor-kB; NFTs: Neurofibrillary tangles; NGF: Nerve growth factor; NPCs: Neural progenitor cells; NSCs: Neural stem cells; PS1: Presenilin 1; PS2: Presenilin 2; ROS: Reactive oxygen species; STM: Short-term memory; SVZ: Subventricular zone; TFs: Transcription factors; UCB: Umbilical cord blood; VEGF: Vascular endothelial growth factor

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