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FULL LENGTH REVIEW

Stem cell-based therapy as a promising approach in Alzheimer's disease: current perspectives on novel treatment

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Abstract Alzheimer's disease (AD) is a neuronal disorder with insidious onset and slow progression, leading to growing global concern with huge implications for individuals and society. The occurrence of AD has been increased and has become an important health issue throughout the world. In recent years, the care of more than 35 million patients with AD costs over $ 600 billion per year, it is approximately 1 percent of the global Gross Domestic Product. Currently, the therapeutic approach is not effective for neurological deficits especially after the development of these major neurological disorders. The discovery of the technique called cell-based therapy has shown promising results and made important conclusions beyond AD using the stem cells approach. Here we review recent progress on stem cell-based therapy in the context of AD.

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Introduction

Alzheimer's disease (AD), the commonest cause of dementia, leading to severe cognitive impairment and neuronal death (Selkoe 2001). AD is characterized by the precipitation of extracellular amyloid-beta (Aβ) plaques in the brain, the formation of neurofibrillary tangles, which is composed of the microtubule-associated protein (MAP) tau, neuroinflammation, neuronal injury, and damage to neuronal synapses (Selkoe 2001). AD-related neurodegeneration at first affects the entorhinal cortex, which that progresses to basal forebrain networks and the subiculum and Cornu Ammonis 1 (CA1) hippocampal subregion (Mann 1996; Francis et al. 1999). Atrophy of mentioned regions and the medial temporal lobe overall co-vary with verbal episodic memory deficits in AD patients and they progressively worsen with age, resulting in death (Delbeuck et al. 2003; Han et al. 2016).

By now, there is no effective treatment to address neurological deficits after the development of their destructing neurological disorders (Ohtake and Li 2015). Current advances in therapeutic strategies temporarily improve AD symptoms without an effective cure to reverse progressive disease. Earlier,

physicians considered that the central nervous system (CNS) is incapable of regeneration of new neurons due to physical and chemical barriers (Ohtake and Li 2015). Hence, the researches focused on different forms of stem cells due to their pluripotent feature in regulating brain homeostasis and it may offer a novel approach to CNS modulation. Due to the progressive nature of neurological diseases, successful stem cell-based therapy can target a well define clinical subset of patients (Duncan and Valenzuela 2017). Among stem cell types, mesenchymal stem cells (MSCs) can bring great promise in disease treatment especially in the fields of therapeutic gene delivery and regenerative medicine (Lee et al. 2009; Gao et al. 2001). Their therapeutic efficiency could initially relate to their migration and engraftment to the target site (Liew et al. 2017). In the transplanted region, stem cells have a potential role to modulate the microenvironment (Martino and Pluchino 2006). Stem cell grafts could provide neuroprotective impacts through the secretion of molecules with tissue trophic functions and immunomodulatory properties such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (Shen et al. 2017; Bagheri-Mohammadi et al. 2020a, b). In this review, we focus on recent advances in stem cell-based therapies that aim at relieving AD symptoms.

Alzheimer's disease prevalence, pathogenesis, and available treatments

Dementia afflicts 46.8 million people worldwide and this number seems to increase to 74.7 million by 2030 base on the World Alzheimer Report ("2018 Alzheimer's disease facts and figures," 2018). More than 35 million people are afflicted with AD and its deleterious deficits in memory and cognitive domains leading to death within 3–9 years (Prince et al. 2015). Although age is the main risk factor and its diagnosis exceeds one in three after the age of 85 years, AD is not necessarily a function of aging. Every 5 years after 65 years of age, the incidence of AD doubles which brings an increased social and economic burden on human populations (Prince et al. 2015; Choi et al. 2014).

The majority of AD patients are sporadic and late-onset. Sporadic AD accounts for almost 90% of cases, occurs in older cases. It has a multifactorial origin with partly a complex genetic profile by interaction with environmental factors (Bradshaw et al. 2013; Griciuc et al. 2013). The familial AD cases occur in less than 5% of cases and are due to highly penetrant autosomal mutations of presenilin (PSEN) 1, PSEN2, and, less frequently, amyloid precursor protein (APP) genes (Prince et al. 2015; Choi et al. 2014). Three genes involved in the production of PSEN1 (chromosome 14), PSEN2 (chromosome 1), and APP (chromosome 21) have been implicated in this type of AD. Excessive accumulation of amyloid plaques in AD patients is likely due to dysregulation of β-site APP-Cleaving Enzyme 1 (BACE1) which gives rise to Aβ from membrane-spanning APP (Vassar et al. 1999). Tau, as a microtubule-stabilizing protein, can be encoded by the MAP tau gene located on chromosome 17q21.31 containing 16 exons, with exons 2, 3, and 10 being alternatively spliced. Differential splicing giving rise to six different isoforms present in the adult human brain (Cacquevel et al. 2012). So far, more than fifty mutations in the MAP tau gene have been reported (Cacquevel et al. 2012; García-León et al. 2018). MAP tau mutations are related to frontotemporal dementia with parkinsonism which that linked to chromosome 17 but has also been reported in association with progressive supranuclear palsy, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, and globular glial tauopathies (Jack et al. 2013). Most mutations occur in exons 9–12 encoding repeat regions and adjacent introns with subsequent impact on both protein levels and/or alternative splicing of pre-mRNA (García-León et al. 2018).

Over the last 10 years, therapeutic strategies primarily focus on targeting the production of Aβ by identifying key molecular regulators of BACE1 expression (Cacquevel et al. 2012). Scientists have also elucidated the role of human miRNA-339-5p which negatively modulates BACE1 in primary human brain cultures, and expression of miRNA-339-5p is reduced in AD patients. The reduced expression level of miRNA-339-5p in AD patients is seen (Cacquevel et al. 2012). The scientist tried out to demonstrate the efficacy of γ-secretase inhibitors for the treatment of AD patients by inhibiting the production of toxic Aβ42 peptides. However, side effects including skin cancers, weight loss, cognitive decline, and gastrointestinal infections were observed in clinical trials due to inhibition of Notch processing (De Strooper 2014; Coric et al. 2012). Current

pharmacological therapies are oral administration of rivastigmine, galantamine (cholinesterase inhibitors), donepezil, and memantine (*N*-methyl-D-aspartate receptor antagonist). Each has a therapeutic effect in the early stage of AD (Long et al. 2014; Tong et al. 2015). Dementia prevention trials using vitamin E and selenium, antihypertensive drugs, NSAIDs, and Ginkgo biloba did not reduce the risk of AD (Monacelli and Rosa 2014). After the amyloid cascade hypothesis, scientists began to develop drugs to target this cascade. Most recent clinical trials target steps in amyloid cascade via anti-tau approaches, BACE-1, β secretase inhibitors, and β vaccines (Monacelli and Rosa 2014). Besides, the cholinergic hypothesis postulates recued amounts of neurotransmitter acetylcholine as the event in the development of AD (Davies and Maloney 1976). Available treatments for AD such as pharmaceutical therapy and blocking neurotransmitter degradation, which that provide temporary relief in symptoms as palliative agents without alleviating pathophysiological disease burden and incapable to control disease progression (Monacelli and Rosa 2014; Powers et al. 2008; Kang et al. 2016).

As yet, there is no efficient treatment for neurological disorders which shows the shift to stem cell therapy as a recent therapeutic method in the treatment of neurological disease (Birks 2006). Recently, the application of stem cells brought a huge revolution for the treatment of neurological disorders such as AD (Lindvall and Kokaia 2006; Bagheri-Mohammadi et al. 2019a, b). By the advent of stem cell-based therapy, various types of cells have been a candidate for cell derivation and differentiation, cell therapy, and drug screening for AD such as MSCs, induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), and neural stem cells (NSCs) (Sundberg et al. 2013; Foltynie and Hariz 2010).

Stem cell therapy in Alzheimer's disease

AD represents the most significant medical, economic, and social crisis of our time. This condition of the neuronal and synaptic deficit is characterized by progressive neurodegenerative pathology (Song et al. 2017). Therapeutic approaches such as Pharmaceutical therapy to relieve symptoms of AD are palliative and incompetent in counteracting the disease processes and they can't able to replace the lost cells or effectively decelerate the neurodegeneration process (Song et al. 2017). But by the advent of cell-based therapy, it was suggested for the treatment of neurodegenerative disease (Song et al. 2017) and there are many experimental AD models to study the possibility of development of efficient cell-based therapies in animals (Hardy et al. 2008). Stem cells are able to differentiate into various cell types of different categories through self-mitosis and can be classified according to their differentiation potential as follows (Hardy et al. 2008). Stem cell characterization sheds light on a better understanding of general cellular processes and pathways related to development and senescence. Stem cells are also used as tools for predictive toxicology, drug target discovery, and cellular therapies such as tissue regeneration. Classification of stem cells can be done by measuring and quantifying distinct functional properties and/or molecular markers (Table 1) (Appasani and Appasani 2010). Also according to their sources, all stem cells can be categorized into five different groups (Fig. 1). By now, various cells are a candidate for neuron derivation and differentiation, cell therapy, and drug screening for neurological disorders (Sundberg et al. 2013; Kirkeby et al. 2012; Danielyan et al. 2011). The newly transplanted cells should incorporate and recapitulate a neural network similar to the healthy brain structure. Stem cells can provide environmental support to residing neurons by creating further neural networks and producing neurotrophic factors in affected areas (Zhang et al. 2016). Also, stem cells can modulation the environment with growth factors, such as glial-derived neurotrophic factor (GDNF), NGF, and, BDNF which would provide support at the main site of disease (Zhang et al. 2016; Behrstock et al. 2008; Blurton-Jones et al. 2009). Administrated stem cells to AD animal models moved to the brain passing through the blood–brain barrier (BBB) and exerted positive neuropathological impacts such as improvement in memory and scholastic skills (Lee et al. 2015a, b; Lee et al. 2015a, b). Engrafted stem cells are able to enhance neuronal differentiation, improve dendrite safety and induce proliferation of endogenous neural precursor cell and surrounding cells in the hippocampus (Lee et al. 2015a, b; Kim et al. 2012). Also, recent studies have suggested that acute beneficial effects of stem cells depend instead on their paracrine signalling actions which can modulate

Table 1 The most common features of stem cells

Types of stem cells	Surface markers	Gene expression, profiling, and proteomics	Advantages of stem cells	Disadvantages of stem cells
Human ESCs	EpCAM (CD326), E-cadherin (CD324), CD90, SSEA-3, SSEA-4, SSEA-5, CD9, TRA-1–60, and TRA-1–81	box A2 (Foxa2) β-III-tubulin, Arterial Smooth Muscle Actin (ASMA) Oct-4, Sox2, Nanog	Ability to self-renew and neural cell differentiation	Tumor formation, graft failure, immunorejection, social, and ethical limitation
Human iPSCs	EpCAM (CD326), E-cadherin (CD324), CD90, SSEA-3, SSEA-4, SSEA-5, CD9, TRA-1–60, and TRA-1–81	Oct3/4, Sox2, Klf4 and c-Myc	Creation cell models for diseases	Teratoma formation
Human NSCs	GFAP (GLAST), CD133/Prominin, EGF receptor, CD15, and Nestin S	Activator-type bHLH genes: Neurogenin 2 (Ngn2), Mash1 and Math repressor-type bHLH genes: Hes genes	Remarkable property to develop various neural cells	Difficult process of collection
Human MSCs	CD90, CD73,CD105, CD133, CD146, CD271, stro1, and MSCA1 (W8B2)	GPC4, LTBP1, ECM2, CSPG2 I/B [NFIB], HOXA5, HOXB6, inhibitor of differentiation/DNA binding (ID1)., fibronectin 1 (FN1)	Ability to promote endogenous neural growth, induce synaptic formation, multipotency features, less immunological reaction, feasibility of preparation, and lack of gliosis	May be resulted in mitochondrial dysfunction

brain homeostasis (Lee et al. 2015a, b; Kim et al. 2012).

Over the last 10 years, scientists were showed that the application of MSCs into the brain of an induced AD animal model can reduce the Aβ protein levels and accelerated the activation of microglia cells, compared to sham-transplanted animals (Oron and Oron 2016; Gavish et al. 2008). Also, MSCs have the ability to eliminate amyloid deposits by means of a cell-specific phagocytic mechanism (Tuby et al. 2009; Thomson et al. 1998). Based on the aforementioned observations, recent studies identified the positive effects of MSCs administration in a progressive stage of the AD animal model (Tuby et al. 2009). Thus, it may have a possible effect in clinical practice for the application of AD (Fig. 2). Hence, cellular therapy by different types of stem cells such as iPSCs, NSCs, and MSCs has emerged as an encouraging therapeutic route in modern medicine.

Induced pluripotent stem cells

Human iPSC technology is a novel approach for the assessment of neurological disorders. Compared with other stem cells, iPSCs are available to create disease models for purposes of drug discovery and pathophysiological researches (Robbins and Price 2017). This technology opened new horizons for studying human cells without the need for immortalized or embryonic cells (Doi et al. 2012). Human iPSCs derived from patients' somatic cells could serve as an appropriate cell source for transplantation therapy without induction of immunologic rejection. In this

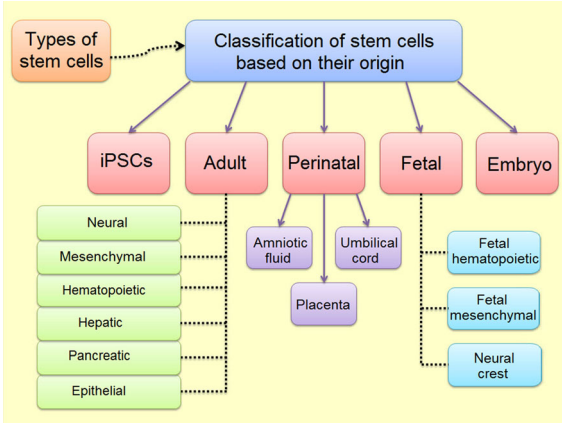

Fig. 1 Classification of stem cells based on their origin. Stem cells can collect in many different sources, they share many common properties, still differ in terms of rates of differentiation, secretion of trophic factors, as well as the ability to be stimulated by endogenous signaling mechanisms under pathologic conditions. According to their origin, all stem cells can be categorized into five different groups including Adult stem cells, iPSCs, perinatal stem cells, fetal stem cells, and embryonic stem cells. Perinatal stem cells can be easily achieved at birth from extra-embryonic structures such as amniotic fluid, umbilical cords, and placenta membranes. Fetal stem cells are cell types that can collect from fetal tissues and can differentiate into the various organ systems of the body. Fetal stem cells can be divided into, fetal hematopoietic stem cells, fetal mesenchymal stem cells, and neural crest stem cells. Adult stem cells can be categorized as neuronal stem cells, mesenchymal stem cells, hematopoietic stem cells, hepatic stem cells, pancreatic stem cells, and epithelial stem cells

way, ethical issues related to ESCs are not any more concerns, but the risk of teratoma formation is still present (Klincumhom et al. 2012; Xu et al. 2013). Besides, transplantable neural progenitors or neurons had generated from ESCs and iPSCs.

Neural progenitor cells (NPCs) derived from iPSCs or ESCs can differentiate into astrocytes, neurons, or oligodendrocytes. This is a good option for treatment of various neurodegenerative disorders such as AD (Wang et al. 2017; Zhang et al. 2018) and also for drug screening for chemical agents with the ability to prohibit neuronal toxicity induced by Aβ (Emsley et al. 2005; Shivraj Sohur et al. 2006). Recently, a line of iPSCs generated from dermal fibroblasts of a patient with APP gene mutation, which is useful for drug screening and assessment of pathomechanism of AD (Wang et al. 2017; Kohyama et al. 2008). Stem cell technology by using iPSCs can represent a novel strategy toward disease models for different types of neurodegenerative disease and it can represent an unlimited source of native phenotypes of cells which that involved in neuronal death (Kang et al. 2016; Bagheri-Mohammadi et al. 2019a, b).

Neural stem cells

In the brain of adult mammals, neurogenesis can consider to occurring throughout life including humans; it contributes thousands of new neurons each day to the hippocampal formation to assist in the maintenance of normal cognition and memory function in humans (Hamilton and Fernandes 2018). In AD pathogenesis, neurogenesis can associate epigenetic mechanisms which that altered due to changes in intracellular programs and surrounding microenvironments of stem cells (Winner and Winkler 2015). Adult neurogenesis and NSCs activity are relevant regulators of the adult brain and its impairment results in various psychiatric and neurodegenerative conditions (L'episcopo et al. 2018; Spalding et al. 2013). NSCs produce inhibitory neurons that can modulate existing circuits, excitatory neurons with the ability to form neo-circuits and or glial cells that are essential for neuronal functions (Spalding et al. 2013; Bjorklund and Kordower 2013). Human NSCs as the immune practical value can be proper for scientists and their clinical trials (Bjorklund and Kordower, 2013; Park et al. 2013). Researchers can obtain human NPCs from the olfactory bulb and hippocampal formation (Kang et al. 2016; Xuan et al. 2008). In vitro acquisition and expansion of enough NSCs from the brain into a sufficient amount of donor cells is generally difficult. The culture medium of NSCs should be supplement with mitogenic growth factors, such as epidermal growth factor and basic fibroblast growth factor (Dhivya and Balachandar 2017; Parmar 2018). The overexpression of NSCs showed to restore the synaptic integrity and cognitive performance in animal models which attributed to changes in neurotrophins (Birch et al. 2013; Tuszynski et al. 2015; Tincer et al. 2016). Adult NSCs from the subventricular zone (SVZ) found out to be a promising candidate for neurogenesis due to cell differentiation and migration into damaged brain areas (Birch et al. 2013; Tuszynski et al. 2015; Tincer et al. 2016). Potential NSC-based therapies for AD aim to provide a convenient microenvironment to suppress neurodegeneration

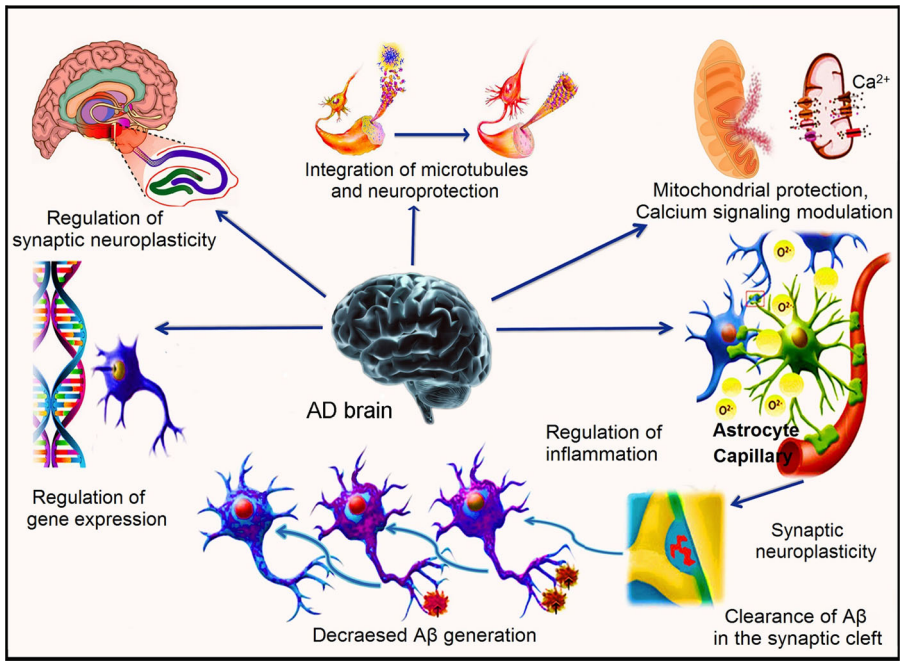

Fig. 2 Stem cell therapy by using mesenchymal stem cells (MSCs) in Alzheimer's disease (AD) brain. Stem cell administration by using MSCs could enhance gene expression, protect mitochondria, modulate calcium signaling, clear amyloid-beta (Aβ) in the synaptic cleft between neuron and astrocyte, establish normal neuronal connectivity, decrease Aβ generation, integrate microtubules, regulate inflammation, regulate synaptic neuroplasticity, and contribute to higher cognitive functions. Moreover, administration of the transfected MSCs markedly mitigated cognitive deficits, promoted amyloid plaque clearance, decreased the activation of microglia, and reduced neuronal cell death. However, the poor proliferation capacity and low survival rate of engrafted MSCs in the hostile microenvironment of AD limit their therapeutic efficiency

and to maintain the survival of mature neurons by supplying neurotrophic factors (Birch et al. 2013). For instance, infusions of NGF in aged murine models have been shown to improve cognitive function (Birch et al. 2013; Tuszynski et al. 2015; Tincer et al. 2016). Phase 1 clinical trials of NGF gene therapy were performed in AD patients and resulted in an improvement in cognitive behavior and activation of neuronal responses with no adverse effects (Tincer et al. 2016). On a large scale of clinical application of NSCs is still lacking and there are legal and ethical complications of fetal tissue (Tuszynski et al. 2015; Tincer et al. 2016).

Mesenchymal stem cells

MSCs are negative for CD40, CD80, CD86, HLA-DR which makes them immune-privileged and let them suppress T-cell proliferation with subsequent tolerogenicity (Yun et al. 2013; Kim et al. 2013; Ding et al. 2017). MSCs possess immunomodulation key markers (HLA-G and indoleamine 2,3-dioxygenase). These cells retain the safety aspect of decreasing telomere length with increased passage number (Bagheri-Mohammadi et al. 2020a, b; Park et al. 2015). Cell-based therapies can be applied for the treatment of various neurodegenerative disorders like AD. Among proposed cells for clinical purposes, MSCs are good candidates due to their versatility, ease of acquisition, anti-inflammatory, and immunomodulatory properties (Moradian Tehrani et al. 2018; Jun et al. 2019). MSCs have good homing and integration capacity to injured tissue following both intracranial and intravenous transplantation as well as low immunogenic potentials due to lack of major histocompatibility complex II (MHC-II) (Bagheri-Mohammadi et al. 2019a, b; Lindroos et al. 2011; Emmerson and Gargett 2016). These cells could afford more efficient gene delivery alongside reduced systemic toxicity due to their preferential tumor tropism and their local activities (Tincer et al. 2016; Lindroos et al. 2011). Human bone marrow-

MSCs (HBM-MSCs) are multilineage differentiation into bone, clonogenicity, plastic adherence, and marrow lineages (osteocytes, chondrocytes, adipocytes) in vitro and a surface phenotype (CD29 +, CD44 +, CD73 +, CD90 +, CD105+, CD146 +, CD312, CD342, and CD452) distinguishing them from hematopoietic stem cells (HSCs) also resident in the marrow (Bagheri-Mohammadi et al. 2019a, b). Human CD146 + PDGFR-b + and SUSD2 + [sushi domain containing-2 (previously W5C5 +)] and human endometrium-derived stem cells (HEDSCs) have similar in vitro properties with HBM-MSCs (Bagheri-Mohammadi et al. 2019a, b). In animal studies, umbilical cord blood and bone marrow-MSCs can use to generate new cells (Morandi et al. 2008; Wu et al. 2007). Stem cell-based therapy with MSCs in animal models of AD also contributed to the clearance of abnormal Aβ plaques via microglial activation and prevented neuronal death (Wu et al. 2007). Furthermore, MSCs can safely restore cognitive ability such as memory in animal analyses (Zhang et al. 2012; Takata et al. 2007). Besides, Scientists show MSCs can play roles in activating proinflammatory cytokines that are beneficial to the recovery of damaged neuronal microenvironments (Yun et al. 2013; Kim et al. 2013; Takata et al. 2007). Many investigations by using MSCs revealed they can promote endogenous neural growth, induce synaptic formation, reduce levels of free radicals in the microenvironment, and decrease apoptosis and regulate inflammation (Kim et al. 2013; Ding et al. 2017; Bagheri-Mohammadi et al. 2019a, b). The safety and tolerability of intrathecal therapy using MSCs-NPCs for patients were shown (Turgeman, 2015; Losurdo et al. 2020). MSCs are involved in oligodendrogenesis, neuroprotection, and inhibition of gliosis, thus this multitasking cell is considered a promising tool for stem cell-based therapy in AD (Turgeman, 2015; Losurdo et al. 2020).

Human umbilical cord-MSCs

The potential role of human umbilical cord-MSCs (HUC-MSCs) in neural differentiation and their released paracrine neutrophins make them promising candidates for stem cell-based therapy for neurological diseases (Park et al. 2015; Zhou et al. 2015; Harris et al. 2018; Thomi et al. 2019). For recipient patients in stem cell-based therapy, HUC-MSCs as allogeneic stem cell has low immune reaction feature, so it cannot motivate allocative lymphocyte proliferation (Bagheri-Mohammadi et al. 2019a, b). HUC-MSCs had collected with a noninvasive method (Bagheri-Mohammadi et al. 2019a, b; Thomi et al. 2019). After cell therapy in the animal models, HUC-MSCs have a low risk for teratoma formation in the transplantation region (Bagheri-Mohammadi et al. 2020a, b; Mennan et al. 2016). Treatment of the APP/PS1 AD mice model with HUC-MSCs, leading to a reduction of the Aβ burden in the cortex and the hippocampus which is correlating with a reduction of the cognitive loss (Obtulowicz et al. 2016). MSCs transplantation was associated with attenuated Aβ deposition in an AD mouse's brain with consequent improvement in memory and learning capacity (Harris et al. 2018). Besides, HUC-MSCs have the ability to increase paracrine action and clear Aβ by microglial cells (Wang et al. 2018). HUC-MSCs can regulate GDF-15 secretion and promote the Aβ clearance by microglial cells, thus elucidating a therapeutic mechanism for AD (Wang et al. 2018). As we know, the GDF-15 belongs to the transforming growth factor β (TGF-β) superfamily which play key roles in immunosuppression, neuroprotection, and regulation of cell growth and also differentiation (Moradian Tehrani et al. 2018; Kim et al. 2010, 2018; Boutajangout et al. 2017). In the brain, GDF-15 is a powerful neurotrophic factor for therapeutic aims, and its expression can important for the treatment of brain disorder. Moreover, GDF-15 may increase hippocampal neurogenesis and synaptic activity in AD animal models, whereas lacking GDF-15 in animals show progressive motor and sensory neuron loss after birth (Moradian Tehrani et al. 2018; Kim et al. 2010; Weiss, and Attisano, 2013). Also, the TGF-BRII is a member of the TGF–TGF-β superfamily, and it is a receptor and mediator in the GDF-15 signalling pathway (Weiss and Attisano, 2013; Li et al. 2006; Caraci et al. 2012). Based on Kim et al. (2018) study, the TGF-BRII is associate with the regulation of insulin-degrading enzyme expression in microglia by GDF-15 secreted by HUC-MSCs, and that GDF-15 is able to promote TGF-BRII expression (Kim et al. 2018). It should be noted that the TGF-BRII can mainly express in microglia and neurons. Interestingly, scientists showed that the level of TGF-BRII can decrease in human AD as well as in AD animal models (Kim et al. 2018). Decrease the TGF-BRII signalling and function in the AD patient can

potentially promote Aβ accumulation and neurodegeneration (Kim et al. 2018; Strelau et al. 2009). HUC-MSCs, have emerged as relatively safe and effective neuro-protectors and immune-modulators and showed to diminish behavioral impairment in AD animal models (Lee et al. 2015a, b). HUC-MSCs specifically cells derived from mononuclear fraction, can reduce amyloidogenic APP processing, β- amyloid plaques, Aβ levels, reactive microgliosis, and cognitive impairment in animal models of AD (Lee et al. 2015a, b; Lee et al. 2015a, b; Wang et al. 2014). These cells could remain viable for years after cryopreservation. HUC-MSCs retain their immunologically immature phenotype because they didn't have exposure to immunologic challenges (Tesseur et al. 2006; Das, and Golde, 2006). HUB-MSCs progenitor posse up to an eightfold proliferative capacity compared to similar bone marrow cells and carries as much as four times as many CD34 + cells (Ehrhart et al. 2016). Therapeutic benefits of HUC-MSCs are passes through the evoking modulation of peripheral and central inflammatory processes (Lee et al. 2015a, b; Lee et al. 2015a, b). Besides, in stem cell-based therapy for a rat model of neuronal injury, HUC-MSCs have the ability to differentiating into target cells and it can improve the disease (Potkin 2002; Cui et al. 2017).

The studies identify that the differentiation and neuroprotection of neurons have related to the neurturin genes (Potkin 2002; Cui et al. 2017; Gasmi et al. 2007). Researchers can be transfected of HUC-MSCs with neurturin gene by recombinant adenovirus, result in increasing of neurturin concentration and neuron-specific markers in cell differentiated such as Nestin, TH, β-tubulin III, and MAP-2 caused the survival of animal fetal midbrain (Potkin 2002; van de Ven et al. 2007; Yang et al. 2013). Another research revealed that cell-based therapy can improve the symptoms of neuronal injury in monkeys and by immunohistochemistry analysis identified there were donor neuronal-like cells that can survive in the brain (Yang et al. 2013; Fu et al. 2006). Applied HUC-MSCs can reduce Aβ deposition in AD animal's brain and improve memory. Similarly, the beneficial effects of transplanted neuronlike cells differentiated from MSCs have also been demonstrated (Yang et al. 2013). Ultimately, stem cell-based therapy using HUC-MSCs can introduce a new gateway of hope for the treatment of neurological diseases like AD.

Human bone marrow-MSCs

Human bone marrow-MSCs (HBM-MSCs) with self-renewal properties, rapid proliferation, pluripotency, tissue regeneration, ability of repair, immunosuppression, and low immunogenicity features, can use in regenerative medicine (Li et al. 2014; Naaldijk et al. 2017; Tirino et al. 2011). Besides, bone marrow-MSCs have the ability to homing in lesion tissues, secreting different neurotrophic growth factors, and they can promote regeneration and neuroprotection in CNS (Yu et al. 2018; Bagheri-Mohammadi et al. 2020a, b). In AD animal models, HBM-MSCs capable of enhancing memory by reducing the level of Aβ in the hippocampal formation and Aβ deposition through the activation of M2-like microglia and modulation neuroinflammation in an AβPP/PS1 transgenic AD mouse model (Yu et al. 2018). Moreover, HBM-MSCs were improved Aβ immunoreactivity and autophagosome induction decreased intracellular Aβ levels, and promoted Aβ clearance in AD models, leading to increase neuronal survival against Aβ toxicity (Yu et al. 2018). Cell therapy could trigger selective AD indicator-1 (Seladin-1) is an important neuroprotective effector. Seladin-1 and Nestin expression showed to be enhanced after stem cell therapy with BM-MSC through activation of extracellular signal-regulated kinase (ERK1/2) signalling pathways and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) in AD animal models (Yu et al. 2018). Also, a recent study revealed that the anti-apoptotic role of let-7f-5p in Aβ 25–35-induced cytotoxicity, as well as the protective effect of let-7f-5p on the survival of grafted MSCs by targeting caspase-3 in AD models (Fig. 3) (Frederiksen et al. 2019; Han et al. 2018). Therefore, stem cell-based therapy using HBM-MSCs has promise translational significance as evidenced by emerging scientific data showing therapeutic benefits in AD (Frederiksen et al. 2019).

Human adipose-MSCs

Recently, adult adipose cells were showed by several scientists to be a source of multipotent stem cells from progenitor cells including adipocytes, osteoblasts, chondrocytes, and myocytes for cell therapy while others reported adipose cells may also have subpopulations of stem cells with neurogenic potential

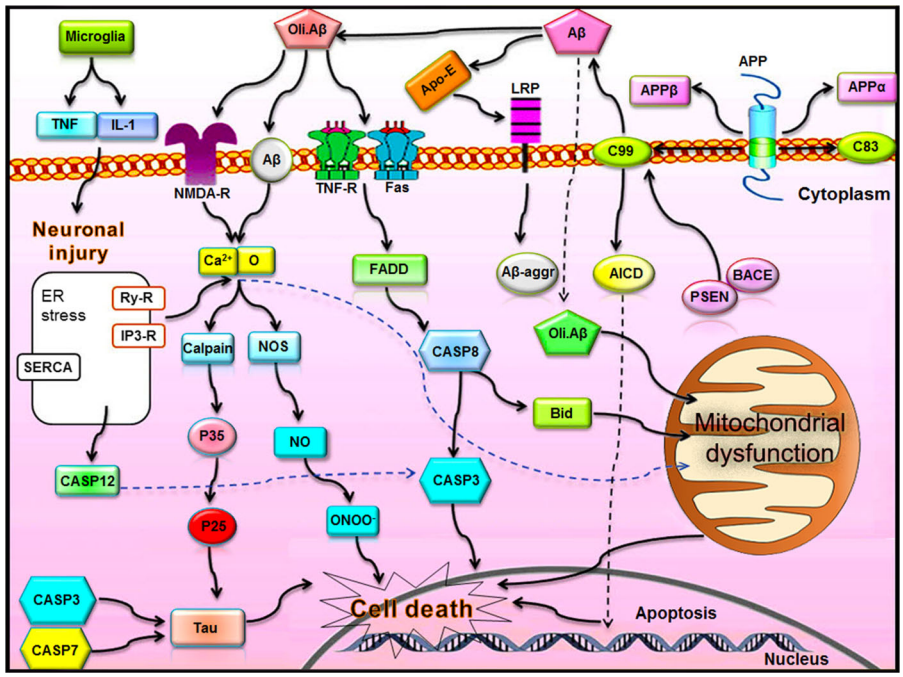

Fig. 3 AD-associated neuronal death in *in-vitro* mouse models (KEGG pathway). Cell death can be achieved in a variety of ways in AD. Both extracellular amyloid deposits and intracellular Aβ protein may activate caspases, leading to cleavage of nuclear and cytoskeletal proteins, including tau protein. Also, after stress to the endoplasmic reticulum (ER), including the release of Ca^{2+} from intracellular stores, caspase-12 is activated. Activated initiator caspases, such as caspase-8, activate executioner caspases, including caspase-3. The activated caspase-3 may be a factor in functional decline and may have an important role in neuronal cell death and plaque formation in AD brain. Proteolysis of tau may be critical to neurofibrillary degeneration, which correlates with dementia. Fas receptors and Fas ligand are expressed on both astrocytes and neurons in normal rats and the human brain. The binding of Fas to its receptor leads to the trimerization of the receptor and results in the recruitment of an intracellular adapter protein, FADD. FADD also contains a separate death effector domain at its N-terminal, which interacts directly with a homologous region in the prodomain of pro-caspase-8. Pro-caspase-8 subsequently undergoes autocatalytic cleavage to yield its active form. Caspase-8 may then cleave and activate caspases-3, caspases-6, and caspases-7 directly, thereby leading to cell death. Alternatively, caspase-8 may cleave Bid to form truncated Bid. Based on studies, scientists were revealed that there are at least two signaling pathways that occur after death-inducing signaling complex formation. One pathway involves mitochondrial amplification of caspase activation, while the other results in mitochondrial dysfunction that occurs only after activation of caspases-8 and caspases-3. The protective effects of stem cells on the survival of grafted MSCs could be induced by targeting caspase-3 in AD models. Many stem cell therapies showed their effects as a powerful tool to modulate calcium signaling in neurological diseases which can be considered as a proper strategy for the treatment of Alzheimer's disease. Abbreviations: APP, Amyloid precursor protein; Apo-E, Apolipoprotein E; Oli. Aβ, Oligomeric amyloid-beta; LRP, Low-density lipoprotein receptor-related protein; TNF-R, Tumor necrosis factor receptor; Fas, Cell surface death receptor; NMDA-R, N-Methyl-D-aspartate receptor; FADD, Fas-associated protein with death domain; BACE, Beta-secretase; PSEN, Presenilin; AICD, Amyloid precursor protein intracellular domain; Aβ.aggr, Aβ Aggregation; CASP, Caspase; No, Nitric oxide; NOS, Nitric oxide synthase; ER, Endoplasmic reticulum; SERCA, Sarco/endoplasmic reticulum Ca^{2+}-ATPase; Ry-R, Ryanodine receptor; IP3-R, Inositol 1,4,5-trisphosphate receptor.

in vitro (Chang et al. 2014; Gerth and Thaller 2019; Bagheri-Mohammadi et al. 2020a, b). The term adipose-MSCs (AD-MSCs) was the original term used to refer to these stem cells based on their potential for multi-lineage specification (McCoy et al. 2008). Despite significant progress in the characterization of cell surface markers for AD-MSCs (Safford et al. 2002), the therapeutic benefit derived from transplantation of AD-MSCs has yet to be demonstrated in animal models of neurological disease such as AD (Chang et al. 2014; Gerth and Thaller 2019). Transplantation of AD-MSCs can improve animal models of neuronal injury, like tremor recovery and motility in combination-transplanted monkeys (Guilak et al.

2006). AD-MSCs treatment can restore the increased serum TGF–TGF-β, BDNF, and monocyte chemoattractant protein 1 (MCP-1) levels in animals (Zhou et al. 2013). Also, AD-MSCs transplantation in the lesioned brain showed beneficial effects on adult neurogenesis in the SVZ and dentate gyrus (DG), memory function, and peripheral cytokines in an animal model (Chang et al. 2014). AD-MSCs can localize around blood vessels or in the arachnoid mater, and provide a protective condition for the survival and differentiation of stem cells due to their stem cell niche-like characteristics (Chang et al. 2014). AD-MSCs can increase the generation and survival of neurons in the DG (Schwerk et al. 2015). Furthermore, the treatment of animal models with neuronal injury using AD-MSCs, revealed that in the hippocampus not only neurogenesis was increased, but also in the subventricular area it can be increased (Chang et al. 2014).

The therapeutic potential of intracerebral or intravenous administration of human AD-MSCs was previously reported by Chang et al. (2014), in an AD mouse model (Tg2576 transgenic mice). Besides, their investigation showed that intravenously transplanted AD-MSCs can be passed the BBB and migrated into the brains of transgenic mice (Chang et al. 2014; Schwerk et al. 2015; Janvin et al. 2006). Intracerebral or intravenous administration of AD-MSCs significantly improved learning and memory and restored neuropathology conditions including Aβ deposition in transgenic mice (Schwerk et al. 2015; Johnston et al. 2008). Besides, elevating endogenous neurogenesis and synaptic and dendritic stability were showed in AD-MSCs treated transgenic mouse brains (Schwerk et al. 2015; Johnston et al. 2008). However, IL-10 and vascular endothelial growth factor (VEGF) were upregulated in AD-MSCs-treated animals (Schwerk et al. 2015; Johnston et al. 2008). Among stem cells, autologous human AD-MSCs elicit no immune rejection responses, tumorigenesis, or ethical problems (Kim et al. 2012). Also after the injection of human AD-MSCs in transgenic mice brain (AD model), the number of amyloid plaques and Aβ levels significantly decreased (Kim et al. 2012). In addition, human AD-MSCs can decrease the Aβ generation and reverse upregulated p53 and foxo3a protein levels in the AD mice brain (Liu et al. 2017). Furthermore, AD-MSCs transplantation can reduce oxidative stress and alleviated cognitive impairment in the AD mice model (Ma et al. 2013a, b; Yan et al. 2014). Taken together, stem cell-based therapy using AD-MSCs shows a novel advanced tool for the treatment of AD (Ma et al. 2013a, b; Yan et al. 2014).

In conclusion, advances in the field of stem cell-based therapy can improve the quality of life for patients suffering from AD. Though our understanding of the AD, brain functions, and mechanism action of stem cells can provide a long way, there are still significant challenges for future researches.

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Compliance with ethical standards

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