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Mesenchymal stem cell application in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a type of degenerative disease that primarily affects in the central nervous system of elderly or pre-elderly individuals. The symptoms of Alzheimer's disease include memory impairment, aphasia, loss of function, dementia, and impairment of visual spatial ability, which in turn affects the physical health of patients. Mesenchymal stem cell therapy is a branch of regenerative medicine that primarily utilizes stem cells or their derivatives to stimulate the body's own healing process and repair damaged, diseased, or injured tissues. Its utilization in the treatment of autoimmune diseases and neurological disorders has been extensively documented. This review summarizes the preclinical and clinical applications of mesenchymal stem cells in AD, their underlying mechanisms and the application limitations of their application and potential solutions. It is hoped that researchers in this field will find it a useful foundation for further study of mesenchymal stem cell therapy.

1. Introduction

As China's population ages, the associated challenges, including the incidence rate, morbidity, and mortality of age-related diseases, have increased significantly, which will have substantial ramifications for the domestic society and economy [1–3]. Alzheimer's disease (AD) is a type of degenerative disease that manifests the symptoms including memory impairment, aphasia, loss of function, dementia, and impairment of visual spatial ability [4,5]. The etiology of AD is multifactorial, involving a complex interplay between genetic susceptibility, lifestyle choices, and environmental influences. The onset of AD is often insidious, progressing gradually and manifesting primarily as cognitive decline and a range of non-cognitive neuropsychiatric symptoms [6]. Statistical data have demonstrated that the number of individuals diagnosed with AD and other forms of dementia patients worldwide has reached 57 million. China has 17 million individuals diagnosed with AD and other forms of dementia, accounting for 29.82 % of the global population affected by the disease. Among them, 0.5 million deaths in China were attributable to AD and other dementia in 2021, accounting for approximately 25.2 % of the global population affected by the disease (0.5 million/1.9 million) [7,8]. According to statistical data, the annual total cost of AD patients in China accounted for approximately 1.47 % of the gross domestic product (GDP) in 2015. It is estimated that the social and economic cost of the disease will reach 3.2 trillion yuan by 2030. The total cost of moderate and severe AD is 1.3 and 2.1 times that of mild Alzheimer's disease. Furthermore, the incidence rate of AD in women is significantly higher than in men [9,10]. The combined pathological diagnosis of magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) has become the industry-recognized gold standard for clinical diagnosis of AD. The diagnosis of AD is complex, and the process of cerebrospinal fluid (CSF) testing is highly invasive to the human body. Typically, lumbar puncture is required to extract cerebrospinal fluid. AD patients must endure great pain, and the cost is high, resulting in a relatively low early diagnosis rate of AD [11,12]. The present status of nursing and treatment outcomes for AD is suboptimal, and the associated costs are considerable. These factors contribute to a substantial economic burden for patients and their families [13,14].

Stem cell therapy is the utilization of stem cells or their derivatives to stimulate the body's intrinsic healing mechanisms and repair damaged, diseased, or injured tissues. Its efficacy has been demonstrated in the treatment of various diseases and conditions [15,16]. Mesenchymal stem cells (MSCs) are a type of adult stem cell found in many body tissues. The subject has been demonstrated to possess pluripotency and multidirectional differentiation, and it can be isolated from bone marrow, adipose tissue, and muscle [17,18]. The evidence demonstrated that the subject has the anti-inflammatory and immune regulatory effects and it has the capacity to differentiate into osteocytes [19], neurons [20], and adipocytes [21]. In this review, we have summarized the

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preclinical and clinical applications of MSCs in AD. We have also discussed the underlying mechanisms of these cells, as well as their application limitations and the potential solutions. It is our hope that this review will serve as a foundational resource for researchers in this field, enabling them to gain a more profound understanding of stem cell therapy.

2. The pathogenesis of AD

The pathological phenomena of AD are complex. The accumulated experimental data have demonstrated that the classic symptoms of AD patients include the following: the presence of senile plaques, which are formed by the deposition of large amounts of β-amyloid protein; the presence of neurofibrillary tangles (NFTs), which are formed by abnormal phosphorylation of tau protein; neuronal loss; neuronal malnutrition, and synaptic loss. Ultimately, these symptoms of AD lead to the loss of neuronal function and neuronal death. A plethora of research has identified a multitude of factors that play a pivotal role in the development of the aforementioned condition. These include starch-like protein deposition, tau protein aggregation, abnormal apolipoproteins, vascular disease, heavy metal disorder, and oxidative stress [22]. The evidence demonstrated that the pathogenesis of AD is the result of a combination of genetic, lifestyle, and environmental factors, partially caused by specific genetic changes. Specifically, it has been reported that Presenilin-1 (PSEN1), Presenilin-2 (PSEN2), and apolipoprotein E (APOE) regulated the gain-of-function and loss-of-function to affect the pathogenesis of AD [23]. Furthermore, the smoke released by cigarette combustion contains various toxic substances that can cause damage to the nervous system, increase the mortality of AD [24]. Additionally, evidence has demonstrated that PM2.5 exposure has the potential to induce neuronal damage and inflammatory responses within the brain. This is achieved by increasing various inflammatory markers. Furthermore, PM2.5 has been observed to encapsulate lipopolysaccharide (LPS), a type of agonist for TLR4, to regulate immune and inflammatory signal pathways [25,26]. The sporadic nature of AD is well-documented, and the etiology of typical "late-onset Alzheimer's disease" is believed to be multifactorial, involving complex interactions between genetic and environmental factors. The prevailing hypothesis suggests that approximately 70 % of the risk of AD is attributable to genetic factors. Age, gender, unhealthy lifestyle choices, a positive family history of AD, and Down syndrome have been identified as the primary risk factors for developing AD [27–31].

The pathogenesis of AD remains to be fully elucidated at present. The gradual deposition of extracellular β-amyloid protein (Aβ protein) and the aggregation of intracellular tau protein in the brain are the primary causes of neuronal death and cognitive impairment in the AD [32,33]. It has been demonstrated that the Aβ protein is metabolized by amyloid precursor protein (APP), glycoprotein. Extracellular proteases of α-secretase can cleave APP, forming sAPPα. In addition, APP can also be cleaved into APPβ by aspartic protease of β-secretase 1 (BACE1), which can bind to the membrane to form fragment C99. The C99 protein is cleaved by a gamma secretase complex within the membrane. releasing the Aβ protein and intracellular peptides (AICD). The release of Aβ protein occurs in conjunction with heightened neuronal activity, resulting in the secretion of the protein into the interstitial fluid of cells. The protein subsequently aggregates, forming oligomers and fibrils that contribute to the development of plaques [34] (Fig. 1).

Tau protein has been demonstrated to fulfill a pivotal function in the process of microtubule assembly, the stability of neuronal axons, and the regulation of microtubule transport. This protein has been found to be intimately linked be closely associated with the progression of cognitive impairment [35]. In the human body, the tau protein generally exists in its natural monomeric form. However, the accumulation of tau in the olfactory cortex and medial temporal lobe results in misfolding along neuroanatomical connections in a fixed manner in patients with AD. The misfolded tau protein has been shown to promote further misfolding of natural tau monomers, resulting in pathological Tau protein aggregates [36]. Phosphorylation, acetylation, glycosylation, and O-GlcNAcylation of tau protein at different sites have been demonstrated to influence the progression of AD. The phosphorylation of Ser199, Ser422, Ser202, Thr205, and Thr231 has been identified as a marker for the varying stages of AD progression [37–39] (Fig. 2).

3. Current treatment strategies of AD

AD is a common neurodegenerative disease is a prevalent neurodegenerative condition, characterized by the progressive deterioration of cognitive abilities [40]. The prevailing principle of in the contemporary treatment of AD entails the following: diagnosis at an early stage, prompt treatment, and lifelong management [41]. Existing AD drugs have been shown to effectively improve and alleviate symptoms of the condition. However, there is a lack of evidence supporting the reversal or halting of its progression [42]. The therapeutic interventions for AD encompass both pharmacological and non-pharmacological approaches.

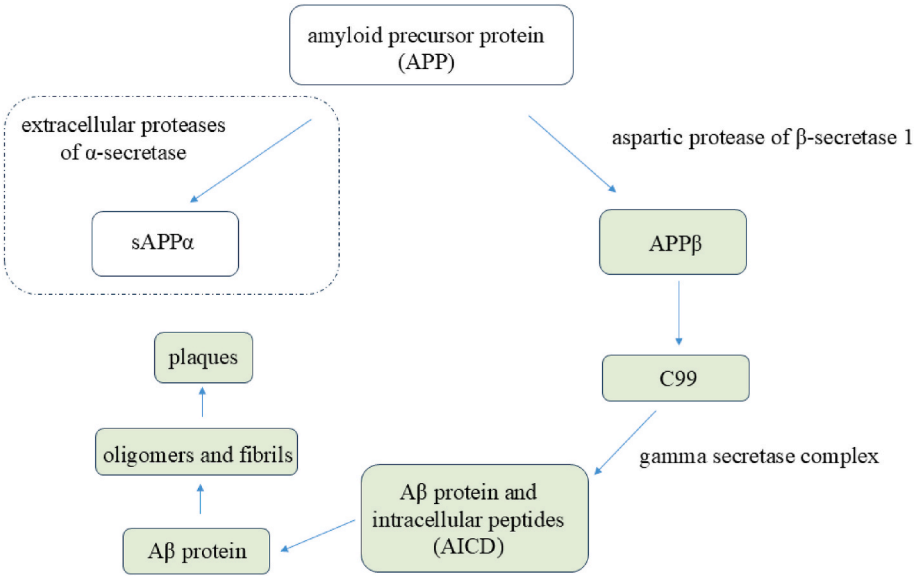

Fig. 1. The pathological process of AD mediated by β-amyloid protein.

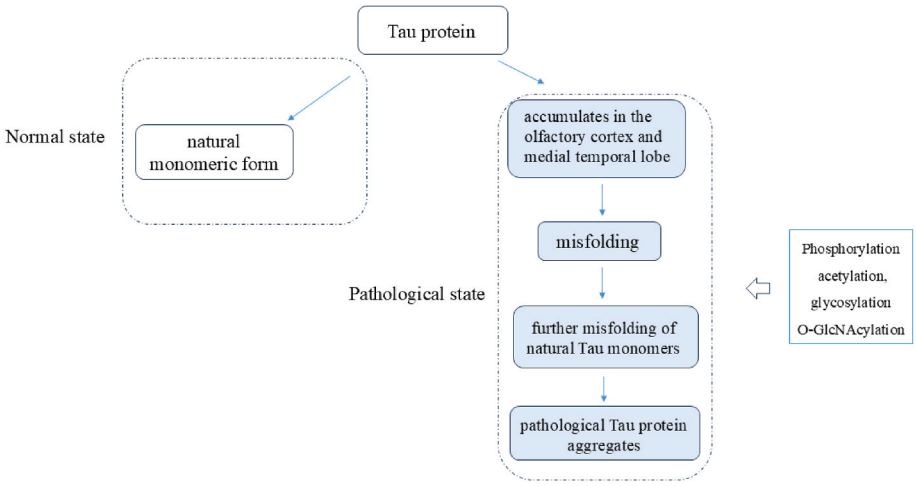

Fig. 2. The pathological process of AD mediated by Tau protein.

Drug treatments include cholinesterase inhibitors [43], excitatory amino acid receptor antagonists [44], monoclonal antibody drugs, and symptomatic treatment drugs. These pharmacological agents have been shown to exhibit favorable neuroprotective properties, demonstrate good safety profiles, and enhance cognitive function. However, their therapeutic efficacy remains limited, and there is an absence of evidence suggesting that they to modify the progression of AD. Furthermore, these agents have been associated with significant adverse effects, including diarrhea, nausea, vomiting, and dizziness [45].

Non-pharmacological therapies encompass a range of approaches, including cognitive training [46], exercise therapy [47], sensory stimulation therapy [48], environmental therapy [49], and dietary intervention [50]. These therapeutic interventions offer several benefits, including the capacity to reduce neurological and psychiatric symptoms, the advantage of being cost-effective, and the minimal side effects observed. Nonetheless, it is imperative to acknowledge the inherent limitations of these therapeutic interventions. These limitations encompass the possibility of diminished treatment efficacy and the

Table 1
The summary of the advantages and disadvantages of MSCs therapy, drug treatments, and non-pharmacological therapies in AD.

Treatment method	Classification	Therapeutic effect	Staging of AD	Advantages	Disadvantages
MSCs therapy	/	slow down brain atrophy and improve cognitive function	/	multi-target therapy; neuroprotection; immune regulation and anti-inflammatory effects, and high safety	cell survival and targeting issues; standardization difficulties; high treatment costs
Drug treatments	cholinesterase inhibitor	improve cognitive function, overall function, and daily function	mild to moderate AD	reduce mortality risk, benefit from reducing anticholinergic load, diverse dosage forms	limited therapeutic effect and no change in AD progression, side effects (diarrhea, nausea, vomiting, dizziness)
	excitatory amino acid receptor antagonists	improve cognitive function, daily living ability, comprehensive ability	moderate to severe AD	good neuroprotective effect; good safety	limited therapeutic effect and no change in AD progression, side effects (diarrhea, nausea, vomiting, dizziness)
	monoclonal antibody drugs	improve cognitive function, delay the progression of AD	moderate to severe AD	clear targeted pathological mechanisms, personalized therapeutic potential, and convenient administration way	safety issue; limited therapeutic effect, and high costs
	symptomatic treatment drugs	improve illusion, delusions, impulsive aggressive behavior	symptoms are dangerous, severe, and/or cause severe pain to patients	good therapeutic effect and high safety	unable to delay disease progression, limited long-term efficacy; side effects (constipation, cardiovascular symptoms)
Non-pharmacol-ogical therapies	cognitive training	stimulate brain function and delay cognitive decline	/	non-invasive and highly safety; low costs	limited treatment effectiveness, compliance challenges, and significant individual differences
	exercise therapy	improve cognitive decline	preclinical AD and moderate to severe AD	reduce neurological and psychiatric symptoms, low cost, low side effects, multiple health benefits	limited treatment effectiveness, compliance challenges, and significant individual differences
	acupuncture	improve cognitive decline	mild to moderate AD	multi-target regulation, high safety, and low side effects	limited treatment effectiveness, compliance challenges, significant individual differences, lack of standardization
	sensory stimulation therapy	improve autobiographical memory function	mild AD	non-invasive and highly safety; low costs	limited treatment effectiveness, significant individual differences, lack of standardization
	environmental therapy	relieve anxiety	/	non-invasive and highly safety; low costs	significant individual differences, high costs
	dietary intervention	improve cognitive function	mild AD	multi-target regulation, high safety, low cost	limited treatment effectiveness, significant individual differences

requirement for adherence, a component that can present a substantial challenge for certain individuals [51]. The comparison of the MSCs therapy, drug treatments, and non-pharmacological therapies were summarized in Table 1.

4. The preclinical applications of MSCs in AD

MSCs are a type of multipotent cell that can be obtained from multiple sources, including bone marrow, adipose tissue, umbilical cord,

Table 2
The summary of the recent research progress of MSCs applications in AD.

MSC type	Animal	Modeling type	Therapeutic effect	Mechanism	References
BMMSC-derived EVs	mouse	5 × FAD	decrease amyloid plaque deposition	/	[52]
bovine UMSCs conditioned medium	rat	TMT 8 mg/kg BW intraperitoneally	increase the number of neurons	regulating IL1β and TNFα	[53]
HSPCs	mouse	5 × FAD	decrease neuroinflammation, Aβ aggregation and improved memory	/	[54]
HDPSCs	mouse	3xTg	improve the damaged neurons	regulating AKT-GSK3β-Nrf2	[55]
NSC-derived exosomes	mouse	SIRT1 conditional knockout; 5 × FAD	inhibit astrocyte activation	regulating SIRT1-PGC1α	[56]
UCMSCs, DPSCs,ADSCs	mouse	5 × FAD	improve behavioral disturbances	regulating gut microbiota	[57]
BMMSCs	mouse	5 × FAD	enhance cognitive function	/	[58]
BMMSCs	mouse	5 × FAD	improve cognitive function	regulating AKT/IAPs	[59]
dental pulp stem cells	mouse	3xTg-AD	improve cognitive impairment	regulating Wnt/β-catenin	[60]
BMMSCs	rat	Aluminum chloride ($AlCl_3$)-induced	impair the rats' behavior	/	[61]
BMMSCs-EVs	mouse	Aβ1-42 oligomer injection	promote hippocampal neurogenesis	regulating BDNF/TrkB	[62]
olfactory ecto MSCs	rat	Aβ1-43 oligomer injection	reduce Aβ accumulation	regulating BDNF and the NMDA	[63]
olfactory mucosa MSCs	mouse	Aβ1-44 oligomer injection	attenuate cognitive impairment	regulating LRP1	[64]
MSC-EVs-SHP2	mouse	Aβ1-45 oligomer injection	improve synaptic loss and cognitive decline	regulating NF-κB/ERK/JNK	[65]
Wharton's jelly MSCsiron oxide nanoparticle	murine	Aβ1-46 oligomer injection	improve brain retention efficiency	/	[66]
BMMSCs-Exos	mouse	STZ injection	alleviate cognitive decline	regulating neuroinflammation	[67]
Nasal Olfactory Mucosa MSCs	mouse	APPswe/PS1dE9	promote Aβ clearance	immunomodulation	[68]
human exfoliated deciduous teeth MSCs	mouse	SAMP8	improve neuronal protection	regulating PPARγ	[69]
Hydrogen sulfide and MSCs-MVs	rat	LPS-induced	improve cognitive function	regulating TNF-α, miR-155, and pAKT	[70]
ADMSCs	rat	amyloid β injection	improve spatial learning and memory	/	[71]
BMMSCs	rat	$AlCl_3$	improve neurocognitive function	regulating SIRT1/MiR-134/GSK3β	[72]
ADMSCs	rat	amyloid β injection	improve cognitive impairment	regulating SIRT1	[73]
ADMSCs-Exos	rat	STZ-induced	improve cognition and memory deficiency	regulating BDNF and SOX2	[74]
ADMSCs	rat	$AlCl_3$	improve cognitive impairment	/	[75]
tanshinone IIA pretreated MSCs	rat	Aβ25-35 induced	attenuate Aβ accumulation	regulating AMP-activated protein kinase	[76]
Fe_3O_4@PDA-labeled hUC-MSCs	mouse	5 × FAD	improve memory and cognitive ability	/	[77]
dimethyl fumarate pretreated ADMSCs	rat	Aβ1-42 induced	rescue learning and spatial memory deficits	regulating Bcl2, BDNF, and NGF	[78]
Hypoxic pretreated ADMSCs-Exos	mouse	5 × FAD	improve cognition	regulating microglial M1/M2 polarization	[79]
NSCs-secretome	mouse	Aβ1-42	improve neurogenesis	regulating Wnt/β-Catenin	[80]
neprilysin expressing NSCs-Evs	mouse	APPswe/PS1dE9	improve neural regeneration	regulating Wnt/β-catenin	[81]
BMMSC-Evs	rat	Aβ1-42	improve neural regeneration	regulating Wnt/β-catenin	[82]
BMMSCs	mouse	3xTg	reduce the β-secretase cleavage	/	[83]
BMMSC-Exos	mouse	5 × FAD	improved cognitive function	regulating sphingosine kinase/ sphingosine-1-phosphate	[84]
UCMSC-EVs	mouse	APP/PS2	improve spatial learning and memory abilities	regulating synaptic vesicle cycle	[85]
Neural stem cell-derived EVs	mouse	5 × FAD	decrease amyloid-β plaque accumulation	/	[86]
ADMSC-Exos	mouse	5 × FAD	improve nerve function and motor ability	regulating NLRP3	[87]
MSC-CM	rat	Aβ1-42	attenuate the retinal pathology	regulating SIRT1/pAKT/pGSK3β/ β-catenin	[88]

Abbreviations: BMMSCs, bone marrow mesenchymal stem cells; 5 × FAD, transgenic mice with five familial Alzheimer's disease; IL-1β, Interleukin-1β; TNF, tumor necrosis factor; HSPC, Hematopoietic stem and progenitor cells; HDPSCs, Human dental pulp stem cells; NSCs, Neural stem cells; ADSCs, adipose-derived stem cells; STZ, Streptozotocin; GSK3β, Glycogen synthase kinase 3 beta; NF-κB, nuclear factor kappa-B; Bcl-2, B-cell lymphoma-2; NRF2, Nuclear factor-erythroid 2 related factor 2; LPS, lipopolysaccharide; PPARγ, peroxisome proliferators-activated receptor γ coactivator I alpha; NLRP3, NOD-like receptor family pyrin domain containing 3; Ccl2, C–C motif ligand 2; Wnt, the wingless-related integration site; AMP, adenosine monophosphate; TNF, tumor necrosis factor; TGFβ1, transforming growth factor-β; SMAD3, SMAD family member 3; PPARγ, Peroxisome proliferators-activated receptors; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; SOX2, SRY-box transcription factor 2; SAMP8, the senescence accelerated mouse-prone 8; pAKT, phosphorylated protein kinase; $AlCl_3$, aluminium chloride; CM, conditional medium; Exo, exosomes; EVs, extracellular vesicles.

and placenta. The various application advantages of the subject include the following: low immunogenicity, multi-directional differentiation, immune regulatory ability, anti-apoptotic and anti-inflammatory ability, exhibiting the strong application advantages in several types of diseases, including AD. For example, Hevi Wihadmadyatami et al. investigated the effect of bovine umbilical mesenchymal stem cells derived conditional medium (BUMSC-CM) on the AD rats. The data demonstrated that BUMSC-CM exhibited a potential neuroprotective effect by increasing the levels of brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NGF), and decreasing the levels of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in rats [53]. Rita Milazzo et al. demonstrated that hematopoietic stem cells (HSCs) exhibited the expansion, distribution and myeloid differentiation potential in within the central nervous system (CNS). Furthermore, transplantation of HSCs was observed to decrease the Aβ degradation and phagocytosis in AD animals [54]. And Yalan Lu et al. demonstrated that the administration of BMMSCs-derived cytokines to rats with AD resulted in enhanced cognitive function, reduced β-amyloid deposition, and decreased neuronal apoptosis. This effect was attributed to the regulation of the AKT/IAP signaling pathway [59]. We summarized the recent research progress of MSCs applications including the therapeutic effect and the mechanisms in AD in Table 2.

5. The clinical applications of MSCs in AD

To conduct systematic drug development, confirm the clinical, pharmacological, the pharmacological effects, and determine the safety and efficacy of the MSCs application in AD, several clinical trials of MSCs in AD have been conducted. For example, Hee Jin Kim et al. designed and conducted a phase I clinical trial with nine subjects diagnosed with AD dementia. The participants were divided into two groups: the first group received an injection of hUCB-MSCs at a dose of 1.0 × 107 cells/2 mL, while the second group received an injection of hUCB-MSCs at a dose of 3.0 × 107 cells/2 mL, administered thrice with 4-week intervals between each injection. The data demonstrated that hUCB-MSCs could decrease the levels of total tau, phosphorylated tau, and Aβ42 in all participants at the first day after the injection. The adverse events including fever, headache, nausea, and vomiting were observed within 36h after injection [89]. And Ngoc-Huynh Ton Nguyen et al. conducted a phase I study to evaluate the safety and efficacy of adipose-derived stromal vascular fraction (ADSVF, including 8 % HSCs and 7.5 % ADSCs) in 31 patients by intraventricular injections. The data demonstrated that this particular ADSVF could enhance cognitive function and reduce the levels of P-tau and β-amyloid in AD patients. Specifically, there was an increase in hippocampal volume from the 5th percentile to the 48th percentile after a 2-year follow-up period, and eight SVF injections were administered to one patient with AD. The side effects associated with ADSVF injection included transient meningismus, headache, fever, and the need for hospitalization [90].

6. Conclusion and prospects

AD is a type of degenerative neurological disease characterized by progressive cognitive impairment and behavioral damage to the central nervous system. It can result in a range of symptoms, including aphasia, loss of function, and misidentification, which can have a significant impact on patients' physical health, quality of life, and financial well-being, as well as on their families. MSCs, as a type of multipotent cell, possess characteristics that make them a convenient source, regulate the immune system, and differentiate into multiple cell types. These characteristics suggest that MSCs have significant application advantages and prospects. But there are several application limitations should be considered: (1) Heterogeneity of MSCs. The evidence has demonstrated that the heterogeneity of MSCs includes phenotypic heterogeneity, functional heterogeneity, and source heterogeneity. Phenotypic heterogeneity is mainly manifested in the limitations of existing isolation and purification methods. In fact, the isolation and purification of MSCs primarily relies on surface markers, with different combinations of these markers yielding the various subtypes of MSCs. Furthermore, MSCs may exhibit variations in functionality. The discrepancy under discussion may encompass a number of hierarchical levels, including metabolic pathways, cell signaling and cell secretion. The heterogeneity of MSCs has a significant impact on the applications of these cells. The establishment and continuous improvement of legislation pertaining to the treatment of MSCs, the regulation of multiple aspects of MSC research, preparation, transportation, storage, and clinical application, the enhancement of MSC preparation methods, the improvement of the purity and quality of MSCs, the exploration of new transplantation methods, the development of personalized treatment plans and conducting personalized treatments based on the patients' conditions and individual differences of patients, is conducive to improving the safety of MSC treatment and reducing the application limitations caused by MSCs. (2) The clinical applications of MSCs. Numerous animal experiments have demonstrated that the efficacy of MSCs in alleviating the symptoms of AD and achieving positive therapeutic outcomes in animal models. However, the clinical application of MSCs in the treatment of AD remains limited. The clinical trials that are currently underway have reported significant adverse effects, including headaches, fever, and the need for hospitalization. Therefore, It is imperative that larger-scale and more standardized clinical trials are carried out, and that the clinical trial process is supervised in a standardized manner. Furthermore, there is a necessity to enhance the management of clinical data, with a view to facilitating the detection of adverse events. In addition, exploration of stem cell therapy strategies, such as combination therapy and personalized therapy is essential. Finally, there is a necessity for the enhancement of international cooperation in stem cell research, with the objective of promoting the integration of stem cell technology, experience, and resources, and accelerating the application of MSCs in AD. Consequently, with the rapid development of life technology and the resolution of the aforementioned issues, MSCs applications in AD will make rapid progress.

Consent to participate

Not applicable.

Ethical approval

Not applicable.

Availability of data and material

Not applicable.

Consent for publication

Not applicable.

Author contributions

Study concept and design: Qianying Feng and Junzheng Yang; Data extraction: Qianying Feng and Junzheng Yang; Drafting of the manuscript; Qianying Feng and Junzheng Yang, and Critical revision of the manuscript: Fengxia Chen, Rui Liu, Dan Li, Huigen feng.

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Declaration of competing interest

All the authors declared that there was no the conflict of interests in

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