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REVIEW

Stem cell therapy for Alzheimer's disease: An overview of experimental models and reality

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder. The pathology of AD is characterized by extracellular amyloid beta (Aβ) plaques, neurofibrillary tangles composed of hyperphosphorylated tau, neuronal death, synapse loss, and brain atrophy. Many therapies have been tested to improve or at least effectively modify the course of AD. Meaningful data indicate that the transplantation of stem cells can alleviate neuropathology and significantly ameliorate cognitive deficits in animal models with Alzheimer's disease. Transplanted stem cells have shown their inherent advantages in improving cognitive impairment and memory dysfunction, although certain weaknesses or limitations need to be overcome. This review recapitulates rodent models for AD, the therapeutic efficacy of stem cells, influencing factors, and the underlying mechanisms behind these changes. Stem cell therapy provides perspective and challenges for its clinical application in the future.

KEYWORDS
Alzheimer's disease, animal model, cognitive deficits, memory loss, stem cell therapy

1 | INTRODUCTION TO ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative disorder with insidious onset and slow progression. It is a growing health problem and has a huge impact on individuals and society. Epidemiological study has revealed that the number of AD patients aged 60 and above in China is close to 9.83 million with a 95% confidence interval of 9.39–10.29.[1] The incidence of population over 65 years of age is about 1%–3%.[2] After the age of 70, the risk of AD doubles every 5 years.[3] Clinically, patients may be in the preclinical period without overt symptoms for about 8–10 years.[2] Later, they can experience progressive memory decline, aphasia, apraxia, ignorance, executive dysfunction, personality changes, and behavioral symptoms. Once AD is diagnosed, the average survival time of patients is about 4.2 years for men and 5.7 years for women.[4] The pathological features of AD are manifested by extracellular amyloid beta (Aβ) plaques, hyperphosphorylated tau in intracellular neurofibrillary tangles, neuronal

death, synapse elimination, and brain atrophy.[5,6] These characteristics are highlighted through related mechanisms such as oxidative stress, free radical generation, metabolic dysfunction, and the release of inflammatory cytokines (e.g., tumor necrosis factor [TNF]-α and interleukin [IL]-1β). Detrimental factors activate cell death pathway and induce synaptic deficit in the hippocampus, leading to cognitive impairment and memory decline. Drug treatment for AD includes acetylcholinesterase inhibitors such as donepezil, galantamine, rivastigmine, and tacrine, *N*-methyl-d-aspartate (NMDA) receptor antagonist such as memantine, and Aβ-directed monoclonal antibody such as aducanumab.[7,8] Several natural compounds that can decrease amyloid plaques, neurofibrillary tangles, and neuroinflammation have been evaluated in clinical trials as well.[9,10] So far, no drugs have been demonstrated to prevent or delay the progression of AD. Stem cell therapy as a novel technology has been explored in animal models with AD. Acquirable research results have proved that the transplantation of stem cells can improve memory and learning abilities. The longer life expectancy well reflects the therapeutic effect of transplanted stem cells on different AD-like models.[11,12] However, the functional role of stem cells varies greatly, and there are some weaknesses or limitations that need to be overcome. The etiology of AD involves multiple risk factors, such as genotype, aging, infection, immunity, toxin intake, environmental pollutants, sociopsychological factors, and so on.[13–15] Genetically, the E4 allele of apolipoprotein E (APOE) on chromosome 19 is the susceptible locus for late-onset Alzheimer's disease.[16] APOE4 homozygotes dramatically increase the risk of AD, 14.5 times higher than APOE3 homozygotes. About 45%-50% of AD patients carry at least one APOE4 allele.[17–20] There is an interaction between APOE4 expression and herpes simplex virus type 1 in the progression of Alzheimer's disease.[21] Other infections are also related to neuroinflammation that leads to $A\beta_{1\text{-}42}$ production and tau pathology.[22–25] Nowadays, sporadic AD is generally considered to be the result of the interaction between genetic susceptibility and environmental factors.[26] Genetic traits can be modified by environment and lifestyle. Moreover, certain disorders, such as hypothyroidism, cerebrovascular disease, type 2 diabetes mellitus, immune-related disease, viral infection, epilepsy, depression, and schizophrenia, are predisposing factors for the development of AD. Altogether, the development of Alzheimer's disease is a multifactorial process characterized by a high degree of neuropathological heterogeneity.

2 | OVERVIEW OF STEM CELL THERAPY FOR ALZHEIMER'S DISEASE

Many different compounds, biochemicals, or mediators are used for intervention studies in animal models with Alzheimer's disease, such as microRNAs, cytokines, chemical inhibitors, and cell-derived exosomes.[11,27–29] Their therapeutic effects are altered with animal species, delivery approaches, evaluation indicators, and time intervals. A multitude of research data support that the transplantation of stem cells is associated with the improvement of synaptic plasticity and cognitive performance.[1,30,31] Therapeutic stem cells can transdifferentiate into neuronal lineage, which is a promising approach to stimulate neurogenesis circuitry.

2.1 | Types of stem cells

Based on the tissue source (e.g., embryo, placenta, amniotic fluid, bone marrow, fat, menstrual blood, or dental pulp), stem cells can be roughly classified into three categories: autologous, allogenic, or induced pluripotent stem cells (iPSCs). During a literature search, 75 preclinical studies that contain complete information on stem cell therapy were collected. Further analysis indicated that the common types of stem cells are brain-derived neural stem cells (NSCs), bone marrow-derived mesenchymal stem cells (BM-MSCs), human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs), and embryonic stem cells (ESCs) (Figure 1). Several types of stem cells are described in detail below.

2.1.1 | NSCS

The transplanted NSCs compensate for the loss of neurons and have a direct effect on the recipient tissue (Table 1). Moreover, transplanted NSCs can produce paracrine cytokines to exert indirect effect on neurogenesis. The function of transplanted NSCs can be enhanced through preconditioning. For instance, the transplantation of NSCs that express growth factor promotes neurogenesis and improves cognitive impairment in an AD-like rodent model.[32] NSCs overexpressing choline acetyltransferase can reverse spatial memory and learning deficits.[33] The underlying mechanisms are related to the paracrine release of neuroprotective factors, the attenuation of mixed proteinopathy (amyloid and tau), immunomodulation, the inhibition of neuroinflammation, and the promotion of neurogenesis/synaptogenesis.[11,34] However, the transplanted NSCs can also transdifferentiate into non-neuronal glia, which is an adverse event in its application.[35]

2.1.2 | BM-MSCS

Bone marrow-derived mesenchymal stem cells have been broadly investigated in the treatment of animal models with Alzheimer's disease. Because of their accessibility, relative ease of handling, and the wide range of cell types into which they can transdifferentiate, BM-MSCs are now one of the most frequently used stem cell types. The transplanted BM-MSCs can transdifferentiate into neurons, secrete acetylcholine neurotransmitters, and produce neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). Also, the transplanted BM-MSCs inhibit Aβ- and tau-related cell death. Meanwhile, the expression of anti-inflammatory cytokines such as IL-10 and IL-4 is upregulated, whereas the levels of pro-inflammatory cytokines such as TNF-α and IL-1β are downregulated. Furthermore, the intravenous administration of BM-MSCs that can

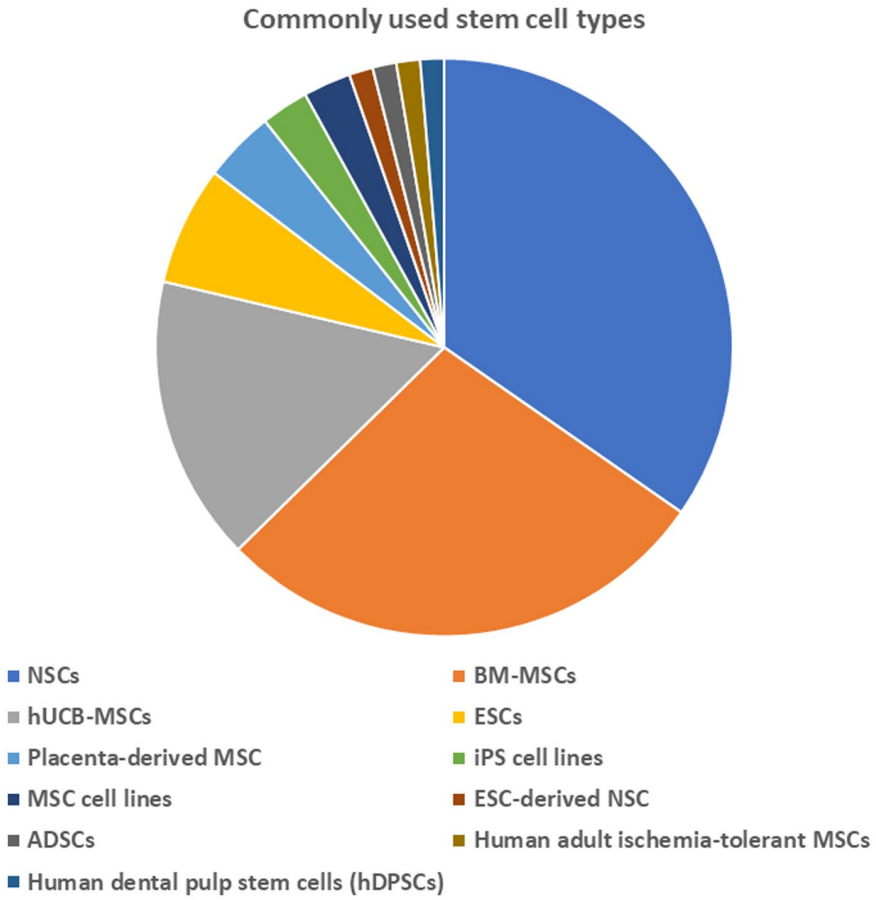

FIGURE 1 Types of stem cells in the treatment of Alzheimer's disease. During the literature review, 75 pre-clinical studies containing complete information on stem cell therapy are scrutinized. The most commonly used stem cell types are brain-derived neural stem cells (NSCs), bone marrow-derived mesenchymal stem cells (BM-MSCs), human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs), or embryonic stem cells (ESCs). However, each cell type has its weaknesses and limitations. For instance, ESCs and hUCB-MSCs have ethical and immunogenic issues. Autologous NSCs are not easy to be acquired in clinical practice. Relatively, BM-MSCs seem to have some advantages, but they are still complicated by various problems such as heterogeneity, low viability, and poor homing into lesional area. Also, therapeutic efficiency is affected by the source of stem cells, preconditioning, cell viability, and cell delivery methods. Moreover, the sample size of experimental animals for each cell type is limited. Based on the available data, it is difficult to determine the therapeutic efficiency of different stem cells

migrate to the hippocampus improves spatial learning, cognitive ability, and memory deficits. Intravenous delivery is a minimally invasive approach that has significant advantages over intracranial injection. Unfortunately, the infiltration of intravenous BM-MSC into multiple organs is still a problem. Another potential issue is that the transplanted BM-MSCs may cause thrombosis during stem cell therapy.[36]

2.1.3 | hUCB-MSCS

The beneficial characteristics of hUCB-MSCs include noninvasive collection, hypo- immunogenicity, superior tropism, high differentiation potentials, and paracrine activity.[37,38] Therefore, hUCB-MSCs have been emerging as an alternative source for allogeneic MSC-mediated therapy. The therapeutic effects of hUCB-MSCs have been verified in 5 × FAD mice and nontransgenic Sprague-Dawley rats.[37,39,40] Moreover, their safety and efficacy have also been evaluated through phase-I/IIa clinical trials (NCT02054208) in patients with Alzheimer's disease.[37] The secretome of hUCB-MSCs includes multifunctional molecules, such as the inhibitory effect of galectin-3 on aberrant tau phosphorylation, the role of ICAM-1 in the removal of Aβ plaques, and the effect of growth/differentiation factor 15 (GDF-15) on neurogenesis in AD models.[39,41,42] hUCB-MSCs may significantly reduce Aβ-dependent AD pathology, as demonstrated by the co-culture system of hUCB-MSCs and mouse primary hippocampal neurons. The paracrine thrombospondin-1 (TSP-1) of hUCB-MSCs can rescue neurons from the Aβ peptide-induced loss of synaptic density, thereby improving cognitive function in the AD-like mouse model.[37]

2.1.4 | ESCS

Transplanted mouse ESC-derived neuronal precursor cells can transdifferentiate into cholinergic cell phenotype, improving spatial

TABLE 1 Advantages and limitations of different stem cells in the treatment of AD

Stem cell types	Advantages	Limitations/weaknesses	References
NSCs	Multipotent; easy adaption in brain; no need for transdifferentiation	Invasive collection; poor survival; tumorigenesis; non-neuronal glia; intrahippocampal or intraventricular stereotactic injection	*J. Neurosci*. 2012; 32:7926-7940. *Exp. Neurol*. 2013; 247:73-79. *Bioconjugate Chem*. 2013; 24:1798-1804.
BM-MSCs	Autologous transplantation; easy handling; multipotent; intravenous application; phase-I/II clinical trials	Low rate of neuronal differentiation; tumorigenesis; thrombosis; poor homing and multiple organ infiltration	*Cell Stem Cell*. 2008; 2:313-319. *Theranostics*. 2017 Jan 1;7(1):106-116. *Neuropathology*. 2003; 23:169-180. *Stem Cells Dev*. 2011; 20:1297-1308.
hUCB- MSCs	Noninvasive collection; easy handling; multipotent; phase-I/IIa clinical trials	Ethical and immunogenic issues; tumorigenesis; poor homing; stereotactic brain injection	*Alzheimers Dement*. 2015 Jul 26;1(2):95-102. *Alzheimers Res Ther*. 2021 Sep 14;13(1):154.
ESCs	Unlimited self-renewal; pluripotent	Ethical and immunogenic issues; uncontrolled differentiation and teratoma formation; only a few studies in experimental animals	*Development*. 2004; 131:5515-5525. *Am. J. Pathol*. 2005; 166:1781-1791. *Nat. Biotechnol*. 2002; 20:933-6.
iPSCs	Multipotent; autologous; multipotent	Only a few studies in experimental animals; possible pathological phenotype	*Hum Mol Genet*. 2014 Sep 15;23(R1):R17-26. *BMC Genom*. 2015; 16:84 *Hum. Mol. Genet*. 2014; 23:3523-3536.
Other (e.g., DPSCs, AD-MSCs, etc.)	Autologous; multipotent	Only a few studies in experimental animals	*Cell Stem Cell*. 2008; 2:313-319. *J. Neurosci. Res*. 2013; 91:660-670. *Aging*. 2013; 34:2408-2420. *Cell Biol Int*. 2017 Jun;41(6):639-650.

memory performance in ibotenic acid-induced AD-like rats.[43] When human ESCs are transplanted into mouse hippocampal slice, the stable generation of cholinergic neurons promotes synapse formation and functional circuit reconstruction.[44] Another study reports that human ESCs can transform into GABAergic and cholinergic neuronal subtypes, leading to improvements in spatial memory and learning ability in mouse model.[45] The cranial transplantation of human ESCs can rescue cognitive impairment in radiation-treated athymic nude rats.[46] Although ESC transplantation has shown the ability to improve cognitive function in rodent models, its clinical significance is limited due to the pluripotent uncontrolled cell growth and tumorigenesis.[47] Despite much preclinical research, there are inherent ethical and immunogenic limitations in the use of allogeneic ESC-based therapies.[48]

2.1.5 | iPSCS

iPSCs are a product of autologous source using up-to-date cell technology. Human iPSCs have been generated from primary fibroblasts that are isolated from patients with familial AD or from healthy individuals.[49] In iPSCs from sporadic AD, APOE4 can be converted to APOE3 to attenuate multiple AD-related pathologies, such as Aβ aggregates and hyperphosphorylated tau.[50,51] The transplantation of iPSCs has shown long-term survival and efficacy in preclinical studies, including ischemic stroke rodent model and APP transgenic mice.[52,53] The therapeutic effect of iPSC-derived somatic cells on patients with familial AD is being evaluated through clinical trial NCT00874783. Human iPSC-derived precursors can differentiate into mature cholinergic neurons and form synaptic networks, improving neurological function and ameliorating memory impairment.[52,54] iPSC-NSCs can reduce pro-inflammatory factors through a neurotrophin-associated bystander effect after their implantation in the ipsilesional hippocampus.[53] However, the benefits of autologous iPSCs are limited by the phenotypic neuropathology of neurons generated from AD patients, including abnormal Aβ level, increased p-tau, decreased neurite length, and susceptibility to inflammatory challenge.[55–57]

2.2 | Delivery methods of stem cells

2.2.1 | Intravenous

Intravenous administration is a relatively convenient method for stem cell delivery, which can be implemented multiple times through the peripheral vein. However, the transfused stem cells travel in the systemic circulation, and they may infiltrate into different organs, with especially large accumulation in the lungs. Stem cells injected through the tail vein take time to cross the blood-brain barrier and enter the hippocampus for functional activities. Hence, the therapeutic efficiency of the intravenous method needs to be improved.

2.2.2 | Intrahippocampal

Intrahippocampal delivery avoids the blood-brain barrier but requires 3-dimensional positioning device and imaging system. Moreover,

stereotactic injection is a traumatic operation that reaches the functional area of the hippocampus. Therefore, it is inappropriate to perform multiple injections, which limits its clinical application. In addition, the local pressure can be increased after the stem cells are injected into the hippocampus. This pressure change may generate a physical impact, but its potential influence remains to be determined. In contrast, peripheral vein delivery does not have this type of problem.

2.2.3 | Intracerebroventricular

Intracerebroventricular method is similar to intrahippocampal administration, and also requires 3-dimensional positioning device and imaging system. The physical pressure in the cerebral ventricle is elevated after the injection of stem cells. Accordingly, the physical pressure of cerebral tissue is proportional to the volume of transplanted stem cells and depends on the delivery method. Sometimes, even if the same cell type (i.e., BM-MSCs) is used, the volume of stem cells has to be adjusted due to different delivery procedures.[11]

2.2.4 | Intranasal

The intranasal route is a noninvasive and convenient way that can easily and repeatedly deliver drugs, exosomes, and stem cells to the brain.[58,59] This injury-free method shows clinical feasibility and has important advantages over conventional injection or intracranial transplantation.[60] The intranasal delivery of stem cells has been performed in APP/PS1 transgenic mice, and the functional improvement has been verified.[59] Currently, nanotechnology has been combined with the intranasal administration of stem cells, which has exhibited a synergistic effect on the treatment of neurological diseases.[60,61] The therapeutic efficiency of intranasal administration has not yet been proven.

2.3 | The functional mechanism of stem cells

Preclinical studies have shown that there is a complex signal network involved in the improvement of cognitive function following stem cell therapy. Representative signal pathways and potential mechanisms are summarized as follows.

2.3.1 | Neurogenesis/Synaptogenesis

The transplanted stem cells contribute to hippocampal neurogenesis and synaptic plasticity (Figure 2). hUCB-MSCs can be stereotactically injected into the hippocampus of APP/PS1 transgenic mice, which stimulates neurogenesis and synaptic plasticity through paracrine GDF-15.[39] AD-MSCs improve endogenous neurogenesis in both the subgranular and subventricular zones, and reduce cognitive decline in APP/PS1 mice.[62] BM-MSCs are transfused into APP/PS1 mice via the tail vein to promote hippocampal neurogenesis.[11,63] The transplanted stem cells can up- regulate the expression of galectin-3, activate the Wnt signaling pathway, and facilitate the secretion of autocrine and paracrine cytokines such as BDNF and NGF, which are associated with the improvement of cognitive ability.[39,64–66]

2.3.2 | Amyloid-β and tau pathologies

The deposition of Aβ aggregates and the formation of neurofibrillary tangles are related to the neuronal death and synaptic loss. The administration of hUCB-MSCs mitigates the hyperphosphorylation of tau and ameliorates memory impairment in mice. Furthermore, the secretion of essential galectin-3 takes part in the removal of aberrant tau tangles by modulating protein-protein interactions.[42] The intrahippocampal transplantation of hAM-MSCs remarkably decreases Aβ deposits and improves memory function in APP/PS1 mice.[67] BM-MSCs not only reduce the production of Aβ peptides in the cortex and hippocampus, but also promote the degradation and transport of Aβ proteins. Moreover, BM-MSCs can attenuate the phosphorylation level of tau protein in the APP/PS1 mice.[11]

2.3.3 | Inflammation and immunoregulation

The therapeutic effect of BM-MSCs on APP/PS1 transgenic mice involves immunoregulatory mechanisms, including peripheral monocyte recruitment, microglial M1/M2 polarization, pro-/anti-inflammatory cytokines, neurotrophin-mediated synaptic plasticity, and so on.[68] BM-MSCs can regulate the microenvironmental immune activity by inhibiting the excessive activation of microglia. The expression of pro-inflammatory TNF-α and IL-1β is downregulated, whereas the level of anti-inflammatory IL-10 is upregulated. Moreover, BM-MSCs dramatically reduce the number of astrocytes and microglia.[69,70] Human menstrual blood-derived MSCs are able to reduce the level of several pro-inflammatory cytokines such as IL-1β and TNF-α, which are associated with an altered microglial phenotype in APP/PS1 transgenic mice.[71] Inflammation/immunoregulation is a key axis associated with the improvement of synaptic function and cognitive performance.

2.3.4 | Paracrine and autocrine cytokines

Injected hUCB-MSCs can secrete paracrine GDF-15 in the hippocampus of APP/PS1 transgenic mice, which promotes neurogenesis and synapse formation.[39] Also, hUCB-MSCs produce galectin-3 to reduce the hyperphosphorylation of tau, thereby lessening aberrant tau tangles.[42] BM-MSCs can stimulate the hippocampal angiogenesis through vascular endothelial growth factor (VEGF) expression.[70] Moreover, BM-MSCs regulate the expression of Nrf2, reduce oxidative stress, and decrease neuronal

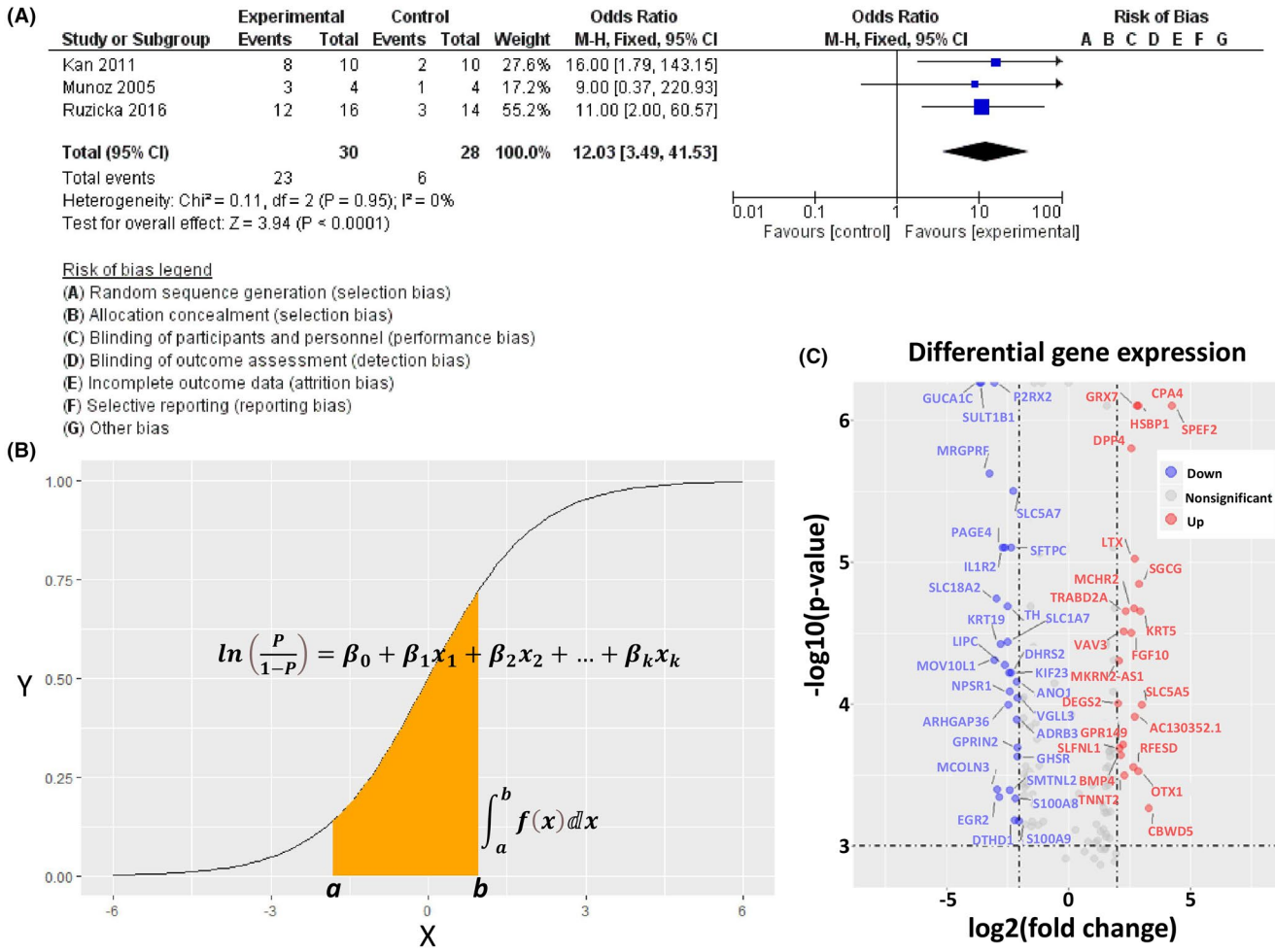

FIGURE 2 Neurogenesis subsequent to stem cell therapy. The exact mechanisms of neurogenesis remain to be determined in animal models with Alzheimer's disease. Anyway, neurogenesis plays a crucial role in the improvement of synaptic plasticity and cognitive function. A, Mata-analysis provides the potential trend of neurogenesis following the transplantation of stem cells. The forest plot is acquired based on relative ratios or values as experimental group was assigned as 1. The 95% confidence interval is computed from the observed data to estimate the theoretical range of true parameter. B, Sigmoid curve and logistic regression equation for the quantitative analysis of gene expression. C, Differential gene expression in the brain is compared between normal control and patients with Alzheimer's disease

apoptosis.[72,73] The upregulation of neurotrophic factors such as BDNF and NGF raises the number of NeuN-positive neurons and boosts neuronal repair.[63,74,75]

2.3.5 | Enhancement of synapse formation

The transplanted BM-MSCs have effects on synapse formation and endogenous neurogenesis. Potential mechanisms involve (i) the generation of neurotrophic factors, with stem cell transplantation improving cognitive performance, which may attribute to the recovery of synaptic connectivity through the release of neurotrophins (i.e., growth-associated protein-43 [GAP-43], BDNF)[73,76]; and (ii) the proliferation of regulatory T cells. The immunoregulation of the central nervous system depends on the interaction between microglia and T cells. The microglia-mediated proliferation of Aβ-reactive Th2 cells is linked with the expression of cytokines IL-4 and IL-10, which may counterbalance the toxic level of nitric oxide (NO) induced by the Aβ protein.[77,78] MSCs can stimulate the proliferation of regulatory T cells.[79,80] T cells mediate synaptic plasticity by shaping the cross-talk of distinct immune cells or specialized immune networks.

2.3.6 | Novel balance theory

Stem cell therapy for AD is related to the integrative effect of different mechanisms, such as inflammation, immunoregulation, oxidative stress, apoptosis, autophagy, and angiogenesis (Figure 3).[11] These mechanisms alter the regional homeostasis in the hippocampus and mediate functional reconstruction by establishing a new balance.[34] The new balance theory involves many advanced subjects, such as stem cell heterogeneity and therapeutic effect, the role of

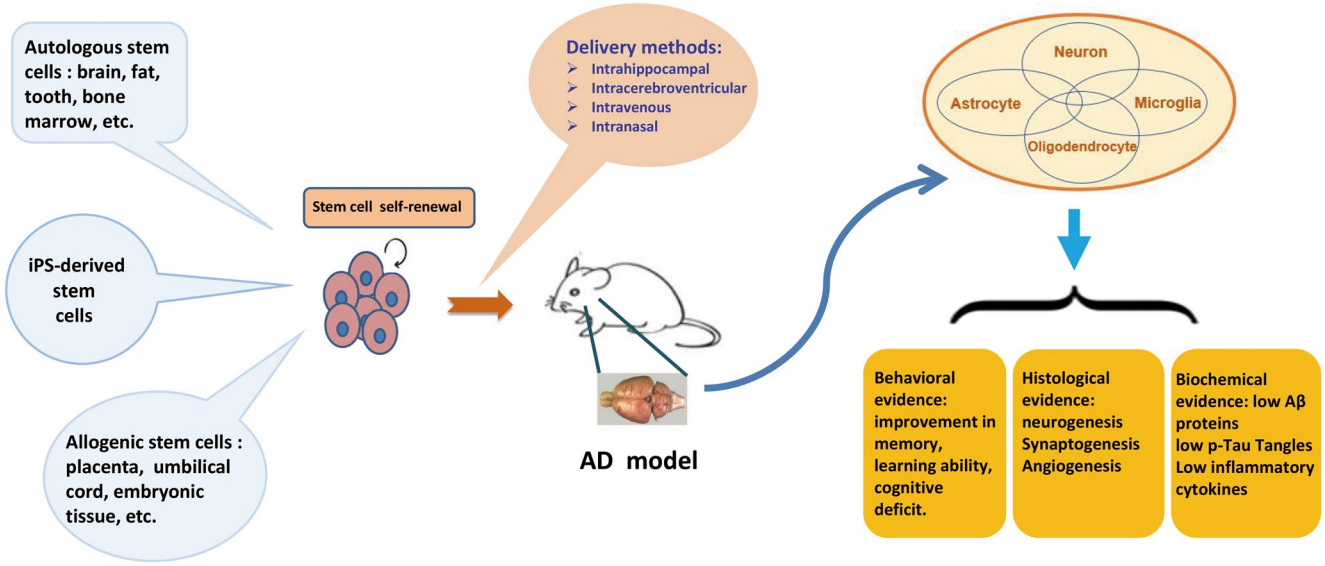

FIGURE 3 Stem cell therapy is a novel therapeutic strategy for Alzheimer's disease. The transplantation of stem cells alters the pathological state by affecting different cell types such as neurons, oligodendrocytes, astrocytes, and microglia in the hippocampus. Intercellular interactions establish a new dynamic balance through functional reconstruction. The therapeutic effect of stem cells is demonstrated by alleviating neuropathology in animal models with Alzheimer's disease. Cognitive improvement is confirmed by behavioral performance tests such as Morris water maze test, Y-maze alternation test, plus-maze discriminative avoidance task, etc

stem cell-derived extracellular vesicles or exosomes, and synaptic plasticity mediated by the crosstalk between T cells and microglia.

3 | THERAPEUTIC EFFICACY OF STEM CELLS AND ITS INFLUENCING FACTORS

3.1 | The evaluation of therapeutic effect

Stem cells such as NSCs, BM-MSCs, hUCB-MSCs, ESCs, and iPSCs have been investigated in different AD-like animal models. Furthermore, hUCB-MSCs, hPD-MSCs, hBM-MSCs, and hAD-SVF are being tested in different clinical trials. The evaluation of therapeutic efficacy involves (i) behavioral performance tests in animal models, and (ii) biochemical and pathohistological indicators. Examples of behavioral performance tests include Morris water maze, Barnes maze, Y-maze, T-maze, zero-maze, 8-arm maze, plus-maze discriminative avoidance task, shuttle box test, step down test, open field test, and dark avoidance.[59,81] In clinical trials, the disease-related severity of all subjects is evaluated based on symptoms, cognitive function, memory, and quality of life. Biochemical and pathohistological changes of the AβPP/PS/tau triple transgenic model are informative in assessing co-evolving amyloid and tau pathologies, which are related to the pathomechanism of Alzheimer's disease.[82] The pathophysiological changes of Aβ and tau in the human brain occur before the onset of AD symptoms. There are high levels of $A\beta_{42}$, t-tau, and p-tau in peripheral neurogenic exosomes and cerebrospinal fluid, which is powerful evidence for the diagnosis of AD.[83,84].

3.2 | Selection of animal models

Many animal models with Alzheimer's disease mimic the pathological characteristics of amyloidosis, such as the injection of Aβ proteins (e.g., $A\beta_{1\text{-}42}$, $A\beta_{1\text{-}40}$, $A\beta_{25\text{-}35}$) and transgenic models.[85–88] The advantages of the injection method include high success rate, good stability, rapidness, and ability to use different animal species. However, this method inevitably causes mechanical damage to the cerebral tissue during the injection process, resulting in unpredictable injury. By employing genetic modification of APP, PS1, PS2, and APOE4, over-produced Aβ proteins are deposited in the brain to induce cognitive dysfunction. Of note, end-stage amyloid and tau pathologies in 3× transgenic AD mice are similar to those in sporadic AD, but the comprehensive investigation of AβPP, amyloid-β, and tau reveals key differences in biochemical and pathological characterization.[82] Hyperphosphorylated tau is expressed along with AβPP/Aβ from an early age, whereas abundant extracellular amyloid plaques and paired helical filaments are observed at a late stage.[82] Transgenic models are useful in evaluating Aβ proteopathy, but not models of sporadic AD as they poorly mirror the pathogenesis of the human disease. In addition, AD-like animal models can also be established by other methods, such as intraperitoneal injection of D-galactose, direct injection of scopolamine to impair cholinergic neurons, gamma knife-mediated hippocampal damage, and so forth.[89–92] Interestingly, Aβ produced in the liver is able to induce neurodegeneration as well, which is another potential cause of Alzheimer's disease.[93] Therefore, understanding the advantages and limitations of AD-like models will help select a suitable model that better approximates to human sporadic AD.[82] Since very successful results in

animal models may reflect only limited aspects of human AD pathology, the track record of success in AD clinical trials is very poor.[88,94]

3.3 | To optimize stem cell types

Stem cell therapy can improve cognitive deficits as demonstrated by different AD-like animal models.[11,42] So far, there are no conclusions regarding the comparison of therapeutic efficacy using different stem cells. In fact, every cell type has its weaknesses or limitations. For instance, ESCs and hUCB-MSCs have ethical and immunogenic issues. Autologous NSCs from brain biopsy may front onto unacceptable attitude and technical challenge. Relatively, BM-MSCs seem to have certain advantages, but they are still complicated by various problems, such as heterogeneity, low viability, and poor homing to lesion area. According to available data, the therapeutic efficiency of stem cells is altered due to (i) viability and heterogeneity, (ii) preconditioning, and (iii) gene manipulation.

The passage number of cultured MSCs has a significant impact on the pluripotency. Mouse BM-MSCs can maintain functional morphology and multipotent state in the 4th generation.[95,96] The expression of CD29, CD44, and CD90 on the membrane of rat BM-MSCs is gradually increased with passage numbers, reaching the peak after 5-6 generations.[97,98] It is generally believed that the BM-MSCs before 7 passages have high viability and are suitable for stem cell therapy.

The viability of MSCs may be enhanced through preconditioning, genetic modification, and culture system. Stem cells preconditioned with dimethyloxalylglycine can enhance the therapeutic efficiency of Aβ-induced animal models.[73] Other preconditioning methods, such as hypoxia, lipopolysaccharide (LPS), inflammatory cytokines, vitamin E, electromagnetic stimulation, and low-level lasers, can also improve the viability and immunomodulatory effect of stem cells.[79,99]

Mesenchymal stem cells can be modified through gene manipulation to enhance therapeutic efficiency. When BM-MSCs overexpressing VEGF are transplanted into APP/PS1 mice, the accumulation of amyloid deposits is reduced, which can significantly improve AD cognitive impairment in the middle and late stages of AD in mice.[70] The transplantation of MSCs expressing antisnese-miR-937 lowers the deposition of Aβ proteins, stimulates the secretion of BDNF, and improves behavioral deficits as demonstrated by social recognition test and plus-maze discriminative avoidance task in APP/PS1 mice.[74]

3.4 | To optimize delivery methods

As mentioned above, common methods for stem cell delivery include intravenous, intrahippocampal, intracerebroventricular, and intranasal. Each method has different advantages and weaknesses. Sometimes, the delivery method is a key factor in determining the therapeutic efficacy of transplanted stem cells. For example, it is necessary to repeatedly transplant the stem cells to achieve a satisfactory result. It has been demonstrated that repeated transplantation is more effective than single treatment regimen in the rat model.[81,100] In the clinical trial NCT03117738, autologous adipose tissue derived MSCs (AdMSCs) will be intravenously transfused 9 times at 2-week intervals. In clinical application, it is impractical for patients to receive multiple injections through the intrahippocampal or intracerebroventricular method.

4 | PROSPECTIVE AND CHALLENGE

4.1 | The biosafety of stem cells

The transplanted stem cells can alter their phenotype and function after being implanted in different tissues. Early study has discovered that the transplantation of ESCs can induce teratoma formation in vivo. Moreover, tumorigenesis has been reported from autologous important as its effectiveness. Interestingly, stem cell-derived exosomes (SC-Exos) act as cell-free mediators for the intercellular information exchange.[29,76,101] The intracerebroventricular injection of SC- Exos can reduce Aβ plaques and tau tangles to improve cognitive function in transgenic APP/PS1 mice.[101] The therapeutic advantages of stem cells and SC-Exos will be determined through parallel comparative studies in the future.

4.2 | The standardization of stem cell culture

Whatever the tissue origin of stem cells, the specification of passage numbers represents an important parameter before being able to take advantage of stem cells with greater safety. So far, there is no standardized protocol for stem cell culture. For example, some studies have transplanted BM-MSCs at passages 1-2, but other studies have used BM-MSCs at passages 4-6 or passages 7-10.[63,102] This may explain why therapeutic effects are so inconsistent. In addition to the type of stem cells, therapeutic efficiency is also affected by other factors, such as cell concentration, the species of recipients, and delivery methods. Thus, it is imperative to standardize the protocol for stem cell therapy.

4.3 | Further evaluation of stem cell delivery

Common delivery methods in preclinical studies include stereotactic injection in the brain and intravenous injection in the peripheral vein. Stereotactic injection in the brain is a traumatic procedure, generally a single treatment. Its clinical application and therapeutic effect are thus limited. Multiple injections through peripheral veins can also improve the cognitive ability of AD-like models to a certain extent, but the optimization of this method needs further evaluation. Recently, nasal administration has been utilized to deliver stem cells, which can alleviate the cognitive impairment in AD-like mice.[58] However, this is a new alternative method whose effectiveness and stability have to be determined by future study.

4.4 | The prospects of stem cell therapy

Autologous stem cells are the most-used cell type owing to easy isolation and intravenous transplantation, without immunogenic and ethical issues.[103] Still, there are some problems that need to be resolved, such as long-term safety, optimum cell source and delivery procedure, the response of donor cells to the AD-pathogenic microenvironment, and the mechanisms of action (Figure 3). Nevertheless, stem cells have been employed in the treatment of AD-like animal models for decades, and the accumulation of a large amount of research data has laid the foundation for the clinical trial of AD. Predictably, stem cell therapy will become a good candidate for the treatment of AD and other neurological diseases.

5 | SUMMARY

Stem cell therapy for AD carries enormous promise, but it remains under development. Now, preclinical studies demonstrate proof of concept and reveal the underlying therapeutic mechanisms. Stem cell therapy has been tested in clinical trials. The accumulation of research data has laid the foundation for the future clinical treatment of AD patients. Perhaps the synergy of different methods can be employed in therapeutic strategy that involves cell modification, gene manipulation, and pharmacological intervention. Regarding the efficacy of stem cell therapy in AD patients, more time will be needed to draw conclusions.

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CONFLICT OF INTEREST

Authors of this review are editorial board members of AMEM, but were excluded from the peer-review process and all editorial decisions related to the publication of this article.

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