


Functional Mechanism of Bone Marrow-Derived Mesenchymal Stem Cells in the Treatment of Animal Models with Alzheimer's Disease: Inhibition of Neuroinflammation

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Abstract: The transplantation of bone marrow-derived mesenchymal stem cells (BMMSCs) alleviates neuropathology and improves cognitive deficits in animal models with Alzheimer's disease. However, the underlying mechanisms remain to be determined. Available data demonstrate transplanted BMMSCs can inhibit neuroinflammation, which may be related to microglial M1/M2 polarization and is regulated by the secretion of autocrine and paracrine cytokines. BMMSCs also mitigate A β plaques and Tau tangles in the brain, which may be associated with the recruitment of peripheral blood monocytes and the subsequent comprehensive effects. The therapeutic effects of stem cells involve potential mechanisms such as immunomodulation, apoptosis, and proliferation. BMMSC-mediated functional reconstruction through dynamic remodeling develops a novel balance. Herein, present review recapitulates the molecular basis of BMMSC-assisted biological processes and summarizes the possible mechanisms related to the interaction between BMMSCs and microglia. The transplanted BMMSCs can suppress neuroinflammation that plays a key role in the pathogenesis of Alzheimer's disease.

Keywords: Alzheimer's disease, bone marrow-derived mesenchymal stem cells, microglia, immunomodulation, apoptosis

Highlights

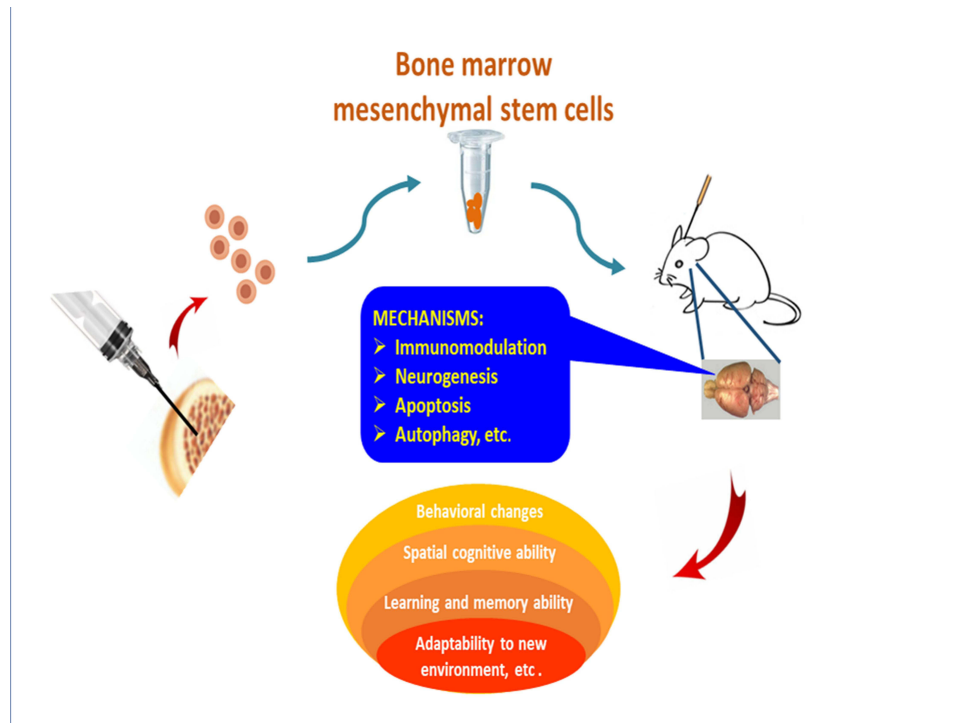
1. Alzheimer's disease is characterized by the accumulation of aberrant amyloid-beta (A β) peptides and Tau aggregates in pathological tissues.
2. Neuroinflammation plays an important role in the pathogenesis of Alzheimer's disease, which can be alleviated by the transplantation of bone marrow-derived mesenchymal stem cells (BMMSCs).
3. The functional activity of transplanted stem cells establishes a new balance through dynamic reconstruction, which lays a theoretical foundation for stem cell therapy.

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder.¹⁻³ Clinical manifestations are characterized by memory decline and cognitive deficits, but symptoms may be varied due to the location and severity of neuropathology. Pathological features are reflected by the extracellular deposition of amyloid-beta (A β) peptides, neurofibrillary tangles, microglia-driven inflammation, and neuron loss in various areas, such as

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Graphical abstract



hippocampus and temporal lobe. Neuronal death is caused by different mechanisms, mainly due to apoptosis/necroptosis/necrosis induced by aberrant A β plaques, neurofibrillary Tau tangles, and inflammatory cytokines. Meanwhile, neuronal apoptosis plays an important role in the development of AD, especially in the early stage. The apoptosis cascade may be initiated through intrinsic and extrinsic pathways (Figure 1). The disturbance of intracellular homeostasis triggers intrinsic pathway, leading to apoptotic cell death. The intrinsic pathway can be further divided into mitochondrial failure because of abnormal energy metabolism and/or oxidative stress, and endoplasmic reticulum (ER) stress due to hyperphosphorylated aggregates of the microtubule-associated protein Tau in neurofibrillary tangles.⁴⁻⁶ The extrinsic pathway is activated by the aberrant A β proteins of brain plaques. Inflammatory cytokines, such as IL-6, IL-1 β , and TNF- α from microglia can cause neuronal apoptosis through the mediation of membrane receptors.⁷⁻⁹ Accumulated A β plaques and Tau tangles are hallmarks in the pathogenesis of AD, which are correlated with neuronal degeneration and cognitive impairment in patients with AD. In terms of treatment, there is no cure for Alzheimer's disease. Owing to uncertain pathomechanism, most treatments are symptom-related or exploratory.

Presently, its drug intervention involves the adjustment of neurotransmitter release.^{10,11} There are two types of medicines, including (i) cholinesterase inhibitors (i.e., donepezil and galantamine). They may improve neuropsychiatric agitation or depression; (ii) memantine, an uncompetitive NMDA antagonist. It can ameliorate memory and awareness in moderate or severe patients with AD. Non-pharmacological therapies are also supplemented for the improvement of patients' life quality, including health diet, regular exercise, and special care. Nowadays, the exact etiology of AD remains unknown. Extracellular A β deposits and intracellular hyperphosphorylated Tau tangles are typical changes in the pathogenesis of AD.^{3,12} These pathophysiological characteristics are highlighted by neuroinflammation. Inflammation is an essential mechanism to induce hippocampal neuron apoptosis and synaptic deficits, leading to cognitive impairment and memory decline.^{13,14}

Alzheimer's Disease and Stem Cell Therapy

Stem cell therapy as a novel strategy has been explored in the treatment of animal models with Alzheimer's disease (Figure 2). According to the tissue sources of stem cells,

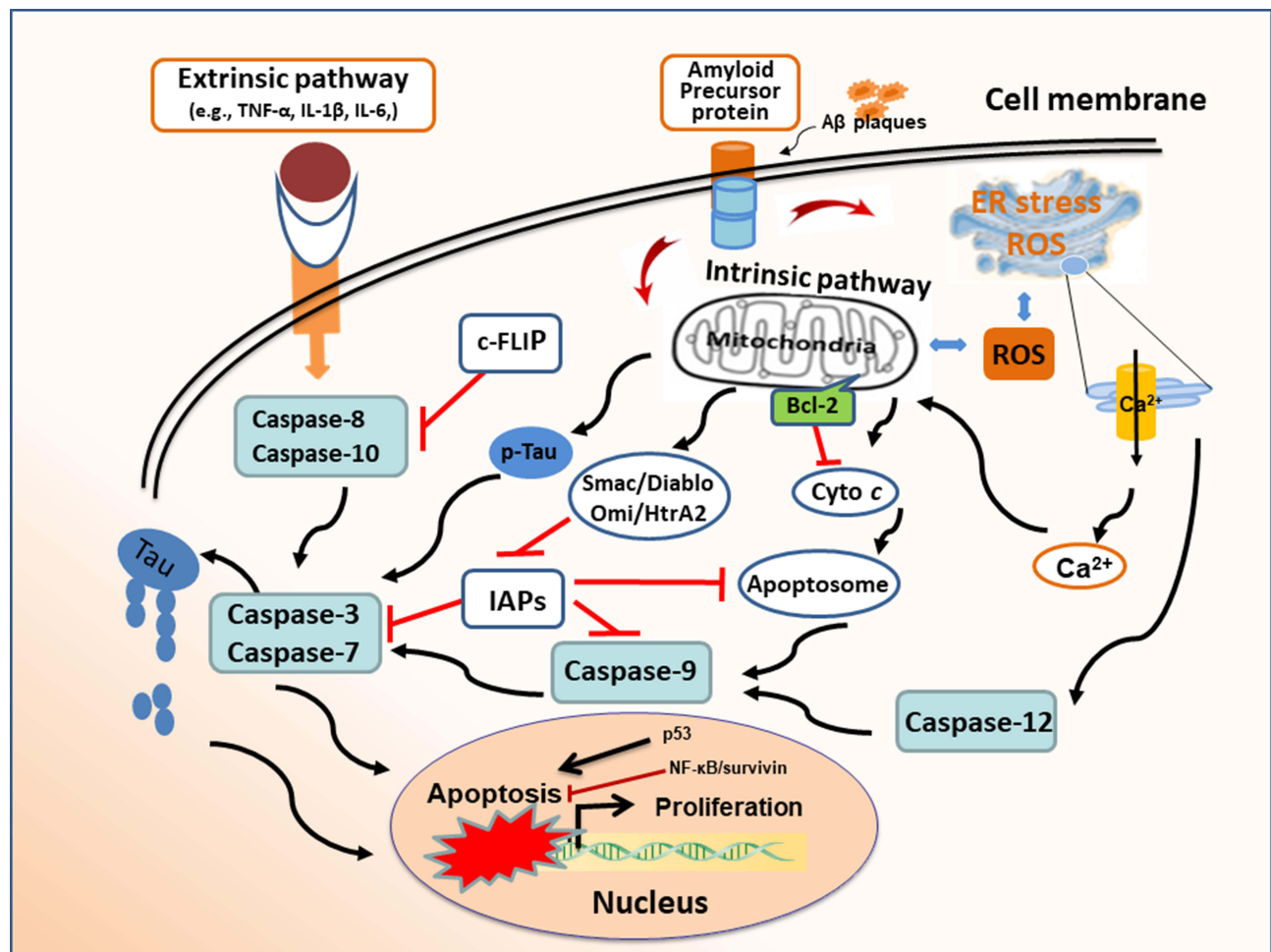


Figure 1 Apoptosis mechanism in Alzheimer's disease. Extracellular A β proteins and inflammatory cytokines (eg, TNF- α , IL-1 β) can cause neuronal apoptosis through membrane receptors. The interruption of intracellular homeostasis induces apoptosis via intrinsic pathway as evidenced by oxidative stress and the hyperphosphorylated aggregates of microtubule-associated protein Tau in neurofibrillary tangles. The release of cytochrome c leads to apoptosome formation, which results in caspase activation and subsequent apoptosis. Pro-survival Bcl-2 proteins block the mitochondrial pathway of apoptosis. Endoplasmic reticulum (ER) stress induces apoptosis by initiating calcium-signaling and caspase activation. Inhibitors of apoptosis proteins (IAPs) regulate apoptosis by binding and inhibiting caspases. Mitochondrial Smac/Diablo and Omi/HtrA2 can bind to IAPs to facilitate caspase activation and apoptosis.

Abbreviation: c-FLIP, cellular FLICE-like inhibitory protein.

therapeutic stem cells are approximately classified into autologous and allogenic categories.^{15–17} Autologous stem cells are isolated from brain, fat, dental pulp, and bone marrow. In contrast, allogenic stem cells are obtained from placenta, umbilical cord, or embryonic tissue. Some studies have used iPS-derived stem cells.^{18,19} iPS-derived stem cells are not discussed as an independent tissue source. Comparative studies have been conducted among different tissue sources of stem cells. There are two problems with allogenic stem cells. One is ethical issue and the other is allogeneic immunogenicity. Since these problems cannot be resolved in the short term, allogenic stem cells may be not suitable for the treatment of AD in the near future. In the clinical treatment of patients with AD, the autologous stem cells derived from brain biopsy may front onto unacceptable attitude and

technical challenges. Therefore, the stem cells from autologous bone marrow or fat are preferred. Interestingly, the therapeutic stem cells derived from bone marrow have better results than those isolated from the adipose tissue.^{20,21} BMMSCs have certain advantages as evidenced in pre-clinical studies, but they are still complicated by various problems, such as heterogeneity, low viability, and poor homing into injured tissue.^{22,23} Also, therapeutic efficiency is affected by preconditioning, cell viability, and delivery methods.^{24,25} There are different methods for the transplantation of stem cells. Usually, autologous MSCs are delivered intravenously, intrahippocampally, intracerebroventricularly, or intranasally.^{26,27} The therapeutic effect of transplanted BMMSCs has been verified in several AD-like models, such as APP mice, DAL mice, or scopolamine-

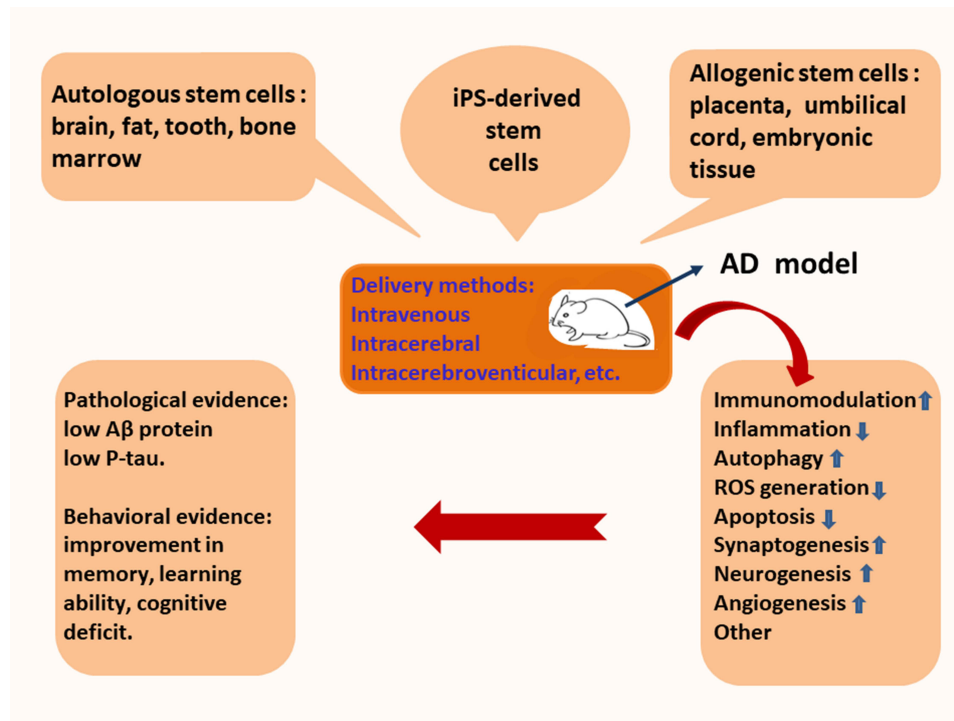


Figure 2 Potential mechanisms of stem cell therapy. The pathological basis of Alzheimer's disease is neuronal death and the impairment of synaptic transmission, which are concomitant with aberrant A β deposits. The transplantation of stem cells derived from bone marrow, adipose tissue, amnion, umbilical cord, or embryonic tissue inhibits neuroinflammation, removes A β proteins, and attenuates Tau pathology in the lesion of AD. The comprehensive effect of different mechanisms alleviates neuropathology and improves cognitive deficits in animal models with Alzheimer's disease.

induced rats.²⁶ A lot of evidence shows that BMSCs can alleviate neuropathology, memory decline, and behavioral deficits. Research data indicate the reduced level of A β plaques is beneficial to both young and aged TASTPM mice.²² Cognitive impairment (i.e., learning ability and spatial memory performance) are improved as demonstrated by Morris water maze test, Y-maze alternation test, plus-maze discriminative avoidance task, social recognition test and open-field evaluation, respectively.^{26,28–30} Moreover, a single transplantation of bone marrow-derived mononuclear cells could obtain a positive result.^{22,31,32} Today, the technical improvement in the preparation of autologous BMSCs provides an assurance for their clinical application.

Autocrine and Paracrine Cytokines

Transplanted stem cells have two essential properties, including (i) self-renewal; (ii) trans-differentiation into tissue-specific cell lineages. Following the transplantation of BMSCs, autocrine and paracrine cytokines are secreted, which are conducive to the adaption of new microenvironment (Figure 3). Nevertheless, cytokine induction and signal transduction are varied due to the

tissue sources (eg, placenta, cord blood, and bone marrow) of mesenchymal stem cells.^{33–35} Those autocrine and paracrine cytokines have special functions as demonstrated in previous studies. In cardiology, the autocrine and paracrine cytokines from transplanted hBMSCs could upregulate the expression of angiogenic factors, such as VEGF-A, HGF, bFGF, Ang1, Ang2, and PDGF-B, which promoted cardiomyogenesis for the repair of myocardial damage.^{35–39} In hepatology, the transplantation of autologous BMSCs improved liver function in patients with acute liver failure. MSCs secreted a mixture of growth factors (eg, PCNA, SDF-1, HGF, VEGF), immunoregulatory factor (eg, IL-10), chemokines, and other constituents.^{40–43} The therapeutic effects of autologous BMSCs could be maintained more than six months. Further long-term effects are still under observation.⁴⁴ Currently, there are no data on stem cell therapy for patients with Alzheimer's disease, although clinical trials using hMSCs has been carried out for the therapeutic purposes.⁴⁵ The favorable effects of BMSCs observed in other organs (eg, heart, liver) should be carefully translated to central nervous system, because the secretion of autocrine and paracrine cytokines can be influenced by local environment. Up to now, most

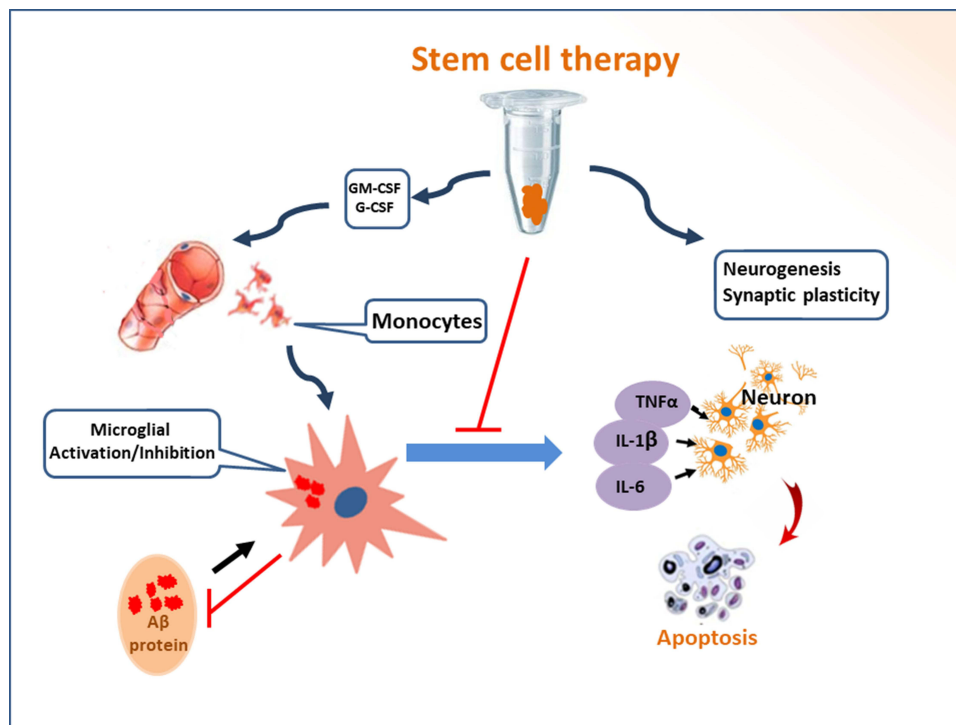


Figure 3 Stem cell therapy induces the inhibition of neuroinflammation and recruitment of peripheral blood monocytes. The transplantation of stem cells leads to the secretion of the autocrine and paracrine factors, which recruits peripheral blood monocytes into the lesion of Alzheimer's disease. The activated monocytes can accelerate the elimination of aberrant A β proteins. Recruited monocytes may facilitate microglial M1/M2 polarization. Neuroinflammation can be inhibited by transplanted stem cells. Immunoregulation participates in functional reconstruction through dynamic remodeling.

studies on the transplantation of BMMSCs belong to preliminary stage. The comprehensive effects of autocrine and paracrine cytokines are under investigation.

The types of autocrine and paracrine factors are classified as follows: (i) pro-inflammatory cytokines such as IL-1 β , IL-6, IL-8 and TNF- α ;^{46,47} (ii) fibrosis-related cytokines FGF, bFGF, TIMP-1, and TIMP-2;^{34,48} (iii) chemokines CXCL-12, CXCL-10, CCL5 and so forth;^{36,48,49} (iv) leucocyte chemoattractant factors CINC-1, G-CSF, SCF, GM-CSF or IL-3;⁵⁰ (v) transcription factors, such as GATA-4, Nkx2.5, and MEF2C;⁵¹ (vi) growth factors HGF and IGF-1;^{23,36} (vii) anti-inflammatory cytokines such as IL-4, IL-10 and IL-11;^{46,52,53} (viii) other active factors, including Ang-1, Ang-2, PDGF-B, MCP-1, VEGF-A, and OPG.^{36,54} Gene analysis has proved that certain cytokines such as MIF (GIF, DER6), IL-8 (CXCL8), Serpin E1 (PAI-1), GRO α (CXCL1) and IL-6, can be secreted by the most types of stem cells.³³ MCP-1, however, is produced in the MSCs from bone marrow and amnion.^{33,55} CXCL-12 (SDF-1) is only expressed in BMMSCs.^{33,56} There are significant differences in the expression levels of autocrine and paracrine factors, which have been tested in APP/PS1 transgenic mice or

rat model following the transplantation of BMMSCs.^{23,47,49,57} Now, certain cytokine profiles mediated by transplanted BMMSCs have been clarified, but the overall spectrum and their respective patterns still need to be investigated. For instance, the proteomics of BMMSC-mediated cytokines was characterized by the predominant hybridization signal for IL-6 and the moderate elevation signals for IL-8, TIMP-2, MCP-1, VEGF and OPG.⁵⁴

The types and levels of autocrine and paracrine cytokines are regulated by various factors, including (i) age. The constitutive secretion of IL-6 in human bone marrow is positively correlated with age.⁴⁶ The basal secretion of immunoreactive IL-6 and IL-11 is increased when the cell culture time is extended. Moreover, the secretion of IL-6 and IL-11 can be stimulated by IL-1 β in a dose-dependent manner;^{46,58} (ii) gender. The cytokines secreted by human bone marrow are modulated by estrogen status. Women receiving estrogen replacement therapy show a low secretion of IL-6 and IL-11 as compared with those of age-matched controls;^{46,59} (iii) injection site and delivery method. When MSCs are injected into APP/PS1 mice via the tail vein, there are no significant changes in the

expression of IL-10, CCR5, and IFN- γ ;²¹ (iv) the interaction between stem cells and immune cells. The transplanted stem cells can facilitate the shift of microglial M1 to M2 phenotype and thereby decrease the secretion of pro-inflammatory cytokines.^{21,48,60} The polarization of M1/M2 phenotype can even be elicited by the intranasal delivery of BMMSC-derived exosomes, rather than whole-cell transplantation, which also exerts immunomodulatory and neuroprotective effects in the 3xTg model;⁶¹ (vi) the modification of stem cells. The preconditioning MSCs with dimethylxalylglycine enhance the therapeutic efficiency of A β -induced animal models.⁶² Other preconditioning methods, such as hypoxia, LPS, inflammatory cytokines, vitamin E, electromagnetic stimulation and low-level lasers, can also improve the viability and immunomodulatory activity of MSCs.^{25,63} Chemokine receptor CXCR4 is involved in the homing processes to injured tissues.⁶⁴ The expression of CXCR4, CCR2, Nrf2 and HIF-1 α is upregulated in the MSCs, which mediates the rescue of learning and memory function in A β -injected rats.⁶² When anti-apoptotic microRNA Let-7f-5p is used in APP/PS1 transgenic mice, the prolonged survival of BMMSCs can increase the therapeutic effect of BMMSCs.⁶⁵ Paracrine effects are reflected by the secretion of soluble cytokines, such as TGF- β , IL-10, VEGF, BDNF, NGF, and neurotrophin-3 in human MSCs.⁶⁶ In addition, paracrine cytokines are modulated by local blood supply, metabolic activity, and nutrition.

Transplanted BMMSCs Inhibit Neuroinflammation

Transplanted stem cells not only provide cell sources for regeneration but also regulate inflammatory and immune responses.^{67,68} Immunomodulation is an important function of stem cells that play an inhibitive role as neuroinflammation in an active state. Stem cell treatment suppresses neuroinflammation through different mechanisms, including (i) direct roles. Transfused stem cells secrete anti-inflammatory cytokines such as IL-4, IL-10, and IL-11.^{46,52,53} Furthermore, anti-inflammatory IL-11 can activate downstream signaling pathways to regulate neurogenesis;⁶⁹ (ii) indirect roles. Growth factors such as HGF and IGF-1 are upregulated by stem cells.^{23,36} Neurotrophic factors such as BDNF and NGF are also enhanced.^{70,71} All these mediators have indirect effects on the inhibition of neuroinflammation; (iii) microglial M1/M2 polarization. In the classic M1 state, the

expression of CD86 and the release of pro-inflammatory cytokines are increased, including TNF- α , iNOS, IL-1 β , IL-6, IL-12, and IL-23.^{72,73} In contrast, the M2 phenotype can be determined by candidate markers, such as CD206 and Arg1, which has neuroprotective effects by enhancing anti-inflammatory cytokines and growth factors, such as IL-4, IL-10, IGF-1, and TGF- β . The heterogeneity of microglia is discovered through high-throughput single-cell transcriptomics, showing at least nine transcriptional states that are affected by age and pathological conditions.²⁴ The transcriptomic responses of microglia may be used to identify signaling pathways, particularly focusing on pro- and anti-inflammatory signatures.^{74,75} The transplantation of stem cells modifies the resident microglia to trigger M1/M2 polarization.^{76,77} This process prevents M1 microglia from secreting pro-inflammatory cytokines, but stimulates M2 microglia to produce anti-inflammatory cytokines.⁷⁸ A series of comprehensive effects result in the mitigation of neuroinflammation.

In the lesion of AD, microglia are activated by (a) the direct effect of A β peptides; (b) A β protein-caused apoptotic bodies; and (c) paracrine cytokines. Transplanted BMMSCs can mediate microglial M1/M2 polarization through autocrine and paracrine factors, which represses microglial M1 activity and decrease the release of pro-inflammatory cytokines. Microglia reside in the parenchyma of central nervous system in activated or quiescent state. The activated microglia are distributed in the area of A β deposits.^{79–81} After phagocytosis, the morphology of microglia is changed from ramified to amoeboid, which is considered to be in an activated state.⁸² The degree of microglial activation can be measured using frequent markers such as CD68 and IBA-1. For example, hMSC treatment could significantly down-regulate IBA-1 levels in the young and aged brains of APP/PS1 transgenic mice.³² There was a dramatic decline in the panel of cerebral cytokines, such as IFN γ , diverse interleukins (IL-1 β , IL-2, IL-5, IL-6, and IL-12p70), KC/GRO, and TNF- α .³² Even, a single injection of hMSC might reduce levels of IL-1, IL-2, IL-12p70, TNF- α and IFN γ in APP/PS1 mice.^{32,47} The anti-inflammatory role of BMMSCs was also confirmed in the rat model of spinal cord injury.⁸³ BMMSCs could secrete anti-inflammatory factors, such as IL-4, IL-10, and IL-11. When the IL-4 and IL-10 were utilized to treat microglia, they had different effects on proliferation and differentiation, suggesting that the type of microglial activators could change cell fate and affected neuronal damage and repair.^{84,85} Moreover, the

transplanted BMMSCs could elevate the expression of Nrf2 and seladin-1 in A β -injected AD rats as well as aluminium chloride-induced AD rats.^{62,86} The function of Nrf2 was to regulate the levels of antioxidant proteins and protect neurons from oxidative damage.⁵ Seladin-1 inhibited the activation of caspase-3 and mediated neuronal apoptosis, improving neuroprotective effects.⁸⁷ Moreover, MSCs could release mediators to mediate the gene expression in astrocyte cultures, including intermediate filaments (GFAP, vimentin), pro-inflammatory enzymes (iNOS, COX-2), and receptors (TLR4, CD14, mGluR3, mGluR5).⁸⁸ Astrocytes participate in the secretion of inflammatory factors. Previous studies demonstrated BMMSCs could decrease the levels of pro-inflammatory genes (IL-1 β , TNF- α , IL-6) in astrocytes.^{37,88} In the lesion, neurons produce A β peptides and take part in the initiation of inflammatory reaction. Microglia secrete pro-inflammatory as well as anti-inflammatory cytokines, showing an obvious duality. All three types (neurons, astrocytes, and microglia) are implicated in the inflammatory process. There are complicated mechanisms involved in intercellular interactions. Many details need to be clarified by future study. Clearly, the transplanted stem cells inhibit neuroinflammation and regulate the dynamic remodeling of tissue function, which stimulates neurogenesis and synaptogenesis. The therapeutic effects of BMMSCs are highlighted by the alleviation of neuropathology and the improvement of cognitive deficits in different AD-like models.

Transplanted BMMSCs Recruit Peripheral Blood Monocytes

Certain cytokines secreted by transplanted BMMSCs have positive chemotactic effect and can recruit peripheral leukocytes into the lesion, including CCL5, G-CSF, SCF, and GM-CSF. CCL5 derived from BMMSCs can be activated by A β protein to promote microglial migration.⁴⁹ GM-CSF or CSF2 functions as a cytokine to recruit granulocytes and macrophages. SCF is a costimulatory factor, which combines other cytokines to produce a synergistic effect on the proliferation, differentiation, and survival of stem cells. In particular, its synergy with G-CSF has biological and clinical significance.⁸⁹ G-CSF is an endogenous neurohematopoietic factor, which has a strong neuroprotection in vivo and in vitro. The therapeutic effect of G-CSF significantly improved the motor coordination and the exploratory behavior of A β -induced rats.⁹⁰ The

improvement of memory in A β -induced rats and Tg2576 mice was associated with the significant reduction of lipid peroxidation, the inhibition of acetylcholinesterase, and the main increase of antioxidant enzymes.^{90,91} The long-term effect of G-CSF could improve the cognitive function of A β -induced mice and APP/PS1 transgenic mice, which might be through potential mechanisms, such as peripheral blood monocyte recruitment, microglial activation and polarization, neurogenesis, and synaptogenesis.^{77,91–93} The analysis of cytokine expression revealed there was a high secretion of chemoattractive factor CCL5 after BMMSCs were transplanted into the brains of APP/PS1 mice.⁴⁹ The levels of leukocyte-chemoattractant factors are affected by stem cell concentration, inoculation position, delivery method, and survival rate. The differential expression profiles of autocrine and paracrine factors remain to be determined when MSCs are transplanted by different methods, such as intrahippocampal, intracerebroventricular, or intravenous. The expression of leukocyte-chemoattractant factors may be regulated by growth factor, cell cycle, and nutrition state.

Aberrant A β Plaques and Neurofibrillary Tau Tangles

The neurotoxicity of over-produced A β peptides is a critical mechanism in the pathogenesis of AD. The extracellular removal of A β deposits is conducted by microglia, astrocytes, and neurons. So far, no evidence demonstrates that transplanted stem cells can directly eliminate aberrant A β peptides. However, a multitude of high-profile studies support that the transplanted BMMSCs alter microenvironmental homeostasis by facilitating intercellular communication and participating in molecular transfer among neurons, astrocytes, and microglia, which promote the removal of aberrant A β peptides.^{47,94,95} Moreover, the transplanted BMMSCs can recruit peripheral blood monocytes into the lesion through leukocyte chemoattractant factors, such as GM-CSF and SCF. In neurodegenerative tissue, the functional conversion of monocyte/microglia could accelerate the clearance of A β deposits via effective phagocytosis in the A β -injected C57BL/6 mice.⁸² In addition, recruited monocytes might facilitate microglial M1/M2 polarization.^{96,97} Microglia account for 10–15% of the total brain cells. They act as the main cell type in inflammatory response to phagocytose damaged cells and pathogens.^{20,84} Adult microglia are a combined population of residents and migrants into the

brain by myeloid progenitors. Under normal circumstances, there are a few microglia in the ramified or quiescent state. The quiescent microglia move at a speed of 1.5 $\mu\text{m}/\text{min}$, covering 15–30 μm wide territory. Focal brain damage induces a rapid and concerted movement.⁸⁴ As part of the cellular response, microglia secrete cytokines, chemokines, prostaglandins, NO and reactive oxygen species, which take part in immunoregulation. Additionally, the M2 phenotype of microglia is instrumental in the resolution of the inflammatory response by producing anti-inflammatory cytokines such as IL-4 and IL-10.^{85,93} The shift of M2 phenotype reduces cerebral amyloid- β load.^{76,98}

The transplantation of BMMSCs could improve cognitive deficits by alleviating neuropathology in animal models of Alzheimer's disease.²⁶ Potential mechanisms involve (i) the accelerated removal of A β protein. Transplanted BMMSCs secrete chemoattractant factors, such as G-CSF, SCF, and GM-CSF. GM-CSF takes part in the shift of microglial M1/M2 phenotype to facilitate the removal of A β protein,^{76,99} (ii) the alleviation of Tau pathology. Stem cell therapy decreases intercellular Tau hyperphosphorylated aggregates or Tau tangles, which may be related to the secretion of exosomes and the degradation of p-Tau,^{57,101,102} (iii) the mitigation of apoptosis due to the clearance of aberrant proteins and the attenuation of oxidative stress; and (iv) the inhibition of neuroinflammation. Transplanted BMMSCs suppress pro-inflammatory IL-1, IL-2, TNF- α and IFN- γ , and enhance anti-inflammatory IL-4 and IL-10.^{47,52,53} Microglial M1/M2 polarization can be mediated by the recruitment of peripheral blood monocytes, which is an essential mechanism for the functional reconstruction of damaged tissues; (v) synaptogenesis. Transplanted BMMSCs stimulate the production of neurotrophins such as BDNF and NGF.^{62,103} Their functional activities promote synaptic formation and endogenous neural growth. Furthermore, BMMSCs can shape the crosstalk between T cells and microglia to mediate synaptic plasticity in the brain.^{25,104,105}

The Establishment of Novel Balance Mechanism

The transplantation of stem cells alters the pathological state in the brain. A series of characteristic changes are induced, which are regulated by autocrine and paracrine cytokines. The BMMSC-mediated functional reconstruction through

dynamic remodeling tends to establish a new balance (Figure 4). The new balance mechanism is based on multiple signaling pathways.

- (a) Cytokine signaling. After stem cell therapy, non-specialized BMMSCs have the potential for self-renewal and differentiation, accompanied by the secretion of autocrine and paracrine cytokines. For instance, G-CSF recruits peripheral blood monocytes and exerts neuroprotective effect.^{89,91,100} The low expression of seladin-1 and nestin in aluminium-induced AD rats is reversed by transplanted BMMSCs via PI3K/Akt and ERK1/2 signaling pathways.⁸⁶ An increased level of BDNF and total antioxidant capacity are revealed in the hippocampus of A β -injected rats following the transplantation of MSCs.⁶² Of note, the pathophysiological role of autocrine and paracrine factors is a double-edged sword. Some cytokines may be harmful to neurons at certain stages. The therapeutic effects of stem cells are associated with functional construction through new balance mechanism, which involve multi-level signaling crosstalk, including inflammation, peripheral blood monocyte recruitment, and microglial M1/M2 polarization.
- (b) Removal of A β peptides and plaques. The transplantation of BMMSCs inhibits neuroinflammation. However, the transplanted BMMSCs can also recruit peripheral blood monocytes into the lesion and further activate them. Activated monocytes exert neuroprotective effect by eliminating A β proteins.⁴⁹ It seems to be a contradictory, but this does happen. Functional cytokines such as CCL5, G-CSF and GM-CSF play a crucial role in the recruitment of peripheral blood monocytes. These monocytes are then activated by extracellular A β proteins, which accelerate A β clearance as demonstrated in APP/PS1 mice.^{81,106} The enhanced phagocytosis of aberrant proteins attenuates cortical and hippocampal A β deposits, thereby improving memory and cognitive deficits. Similar result has also been observed in the A β -injected AD mice.⁸²
- (c) The alleviation of Tau tangles. As compared with the age-matched control brains, AD patients have numerous A β plaques and Tau tangles observed in different regions, such as hippocampus, temporal and parietal lobes.^{107,108} Neurofibrillary tangles are

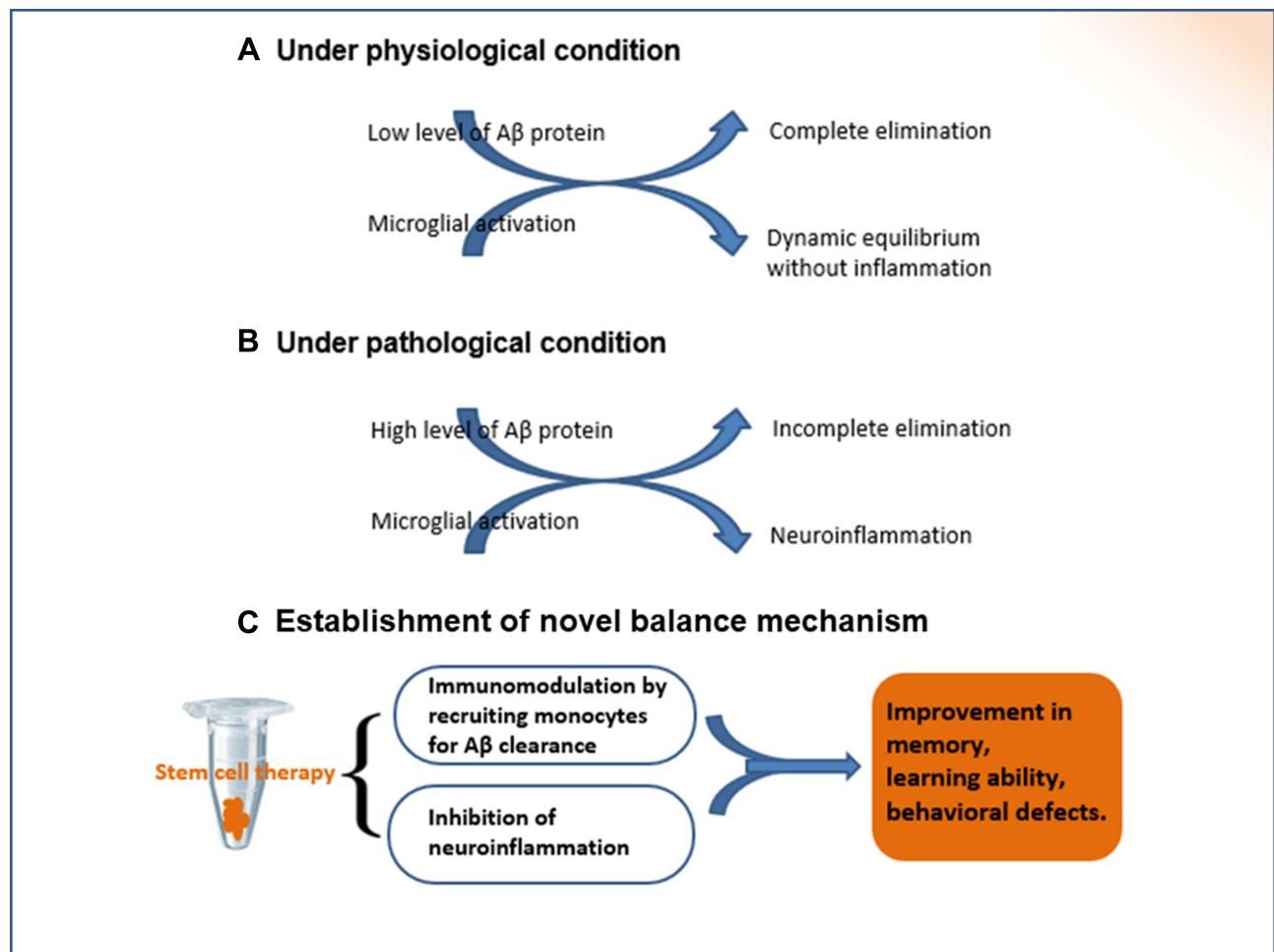


Figure 4 The establishment of new balance mechanism. Under physiological conditions, there is a dynamic equilibrium between the production and elimination of A β peptides. If the intrinsic homeostasis is altered, the excessive accumulation of extracellular A β proteins results in pathological changes, as shown in the pathogenesis of Alzheimer's disease. Autocrine and paracrine cytokines are secreted subsequent to the transplantation of BMMSCs, which regulate inflammatory/immune processes. The transplantation of stem cells is key regulator for the establishment of new balance mechanism.

the hyperphosphorylated aggregates of microtubule-associated protein Tau, which are accumulated in neurons of AD. Tau protein can activate caspase-3 activity and cause neuronal apoptosis.^{12,109} Early studies demonstrated that Tau protein could be abated subsequent to the transplantation of BMMSCs.^{57,101} However, the underlying mechanism for reducing Tau aggregates still needs to be investigated. It may be associated with oxidative stress and mitochondrial pathway.^{3,109}

- (d) Apoptosis. Transplanted BMMSCs modulate the apoptosis via direct and indirect pathways. Direct pathway includes immediate effects on apoptotic cascade, such as the inhibition of caspase-3 and the enhancement of survivin expression.^{110,111} Indirect pathway may involve other mediators such as nuclear factor p53 and neuroprotective

cytokines BDNF, NGF, IGF-1, and VEGF.^{112,113}

BMMSCs can decrease A β -induced apoptotic cell death in the primary culture of hippocampal neurons.¹¹⁴ The transplantation of stem cells suppresses apoptosis and contributes to the functional remodeling of synaptic plasticity.^{15,22,26,110,115–117} Apoptosis mechanism also regulates the survival of transplanted BMMSCs in the brain, which affects the therapeutic efficiency of stem cells.⁶⁵

- (e) Oxidative stress. The accumulation of A β peptides induces the production of free radicals, oxidative stress, and lipid peroxidation. The transplanted BMMSCs can mitigate A β deposits and ameliorate A β -induced oxidative stress in A β -injected mice, which improve spatial memory impairment in the hippocampus.^{26,115} Oxidative stress and free radicals in neurons stimulate the release of cytochrome

c and the activation of caspase-9, which induces intrinsic apoptosis in the pathogenesis of Alzheimer's disease. The transfused MSCs alleviate ROS-induced damage and initiate neuroprotective mechanisms via the combined action of neurotrophic factors NGF and BDNF.¹¹²

The functional activities of transplanted stem cells involve distinct mechanisms such as inflammation, immunoregulation, autophagy, apoptosis, angiogenesis, and synaptogenesis. Their comprehensive role changes the pathological state in the hippocampus and establishes a new dynamic balance by integrating various signal pathways. The novel balance in the hippocampal microenvironment is a key mechanism by which transplanted BMMSCs alleviate neuropathology and improve cognitive impairment in animal models with Alzheimer's disease.^{22,26,62,86}

Challenge and Perspective

- (a) Uncertainty. Following the transplantation of BMMSCs, a novel balance is established based on dynamic remodeling, but it is unsure how long the functional state of new balance can be maintained.
- (b) Stem cell parameters. In order to achieve therapeutic effects, it may be necessary to transplant BMMSCs repeatedly. At this moment, relevant parameters on the transplantation of BMMSCs need to be determined, including stem cell concentration, time interval, inoculation position, and delivery method. At present, the most important task is to standardize the protocol for BMMSC administration.
- (c) Biomarkers for surveillance. Currently, monitoring markers (i.e., A β ₄₂, T-Tau and P-Tau, or exosomes in cerebrospinal fluid and/or peripheral bloodstream) need to be optimized for the evaluation of therapeutic effects.
- (d) The integration of various mechanisms. Transplanted BMMSCs have diverse functions such as immunoregulation, anti-apoptosis, neurogenesis, the activation of autophagy, and angiogenesis. Meantime, immunoregulation can interact with different mechanisms, which is a key regulator in the pathogenesis of AD. However, some details need to be elucidated, including inflammation and synaptic remodeling, the interaction between astrocytes and microglia, and inflammation and autophagy.

- (e) Exosomes. During stem cell therapy, stem cells can produce extracellular vesicles or exosomes to communicate with recipient cells. In transgenic APP/PS1 mice, exosome-mediated immunomodulation and neuroprotection are similar to transplanted stem cells.^{94,118} However, there are still many influencing variables. The therapeutic advantages of stem cells and exosomes will be determined through parallel comparative studies in the future.

Summary

The transplantation of BMMSCs can improve memory and cognitive deficits by alleviating neuropathology in animal models with Alzheimer's disease. The underlying mechanisms involve (i) the inhibition of neuroinflammation; (ii) the migration of A β and Tau pathology through immunoregulation; (iii) the attenuation of neuronal apoptosis by reducing oxidative stress and ROS generation; (iv) other effects, such as neurogenesis, synaptic plasticity, autophagy, and angiogenesis. The therapeutic effect of stem cells comes from the integral regulation of different mechanisms. The transplantation of BMMSCs acts as a new balance driver and leads to beneficial improvements in AD-like animals. Stem cell therapy may be prospective for the patients with Alzheimer's disease.

Abbreviation

AD, Alzheimer's disease; BMMSCs, bone marrow-derived mesenchymal stem cells; A β protein, amyloid-beta protein; hBMSCs, human bone marrow stem cells; hMSC, human mesenchymal stem cells; PPAR γ , peroxisome proliferator-activated receptor γ ; RXRs, retinoid X receptors; FGF, fibroblast growth factor; TIMP-1, tissue inhibitor of metalloproteinases-1; TIMP-2, tissue inhibitor of metalloproteinases-2; CINC-1, cytokine-induced neutrophil chemoattractant-1; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; IL-10, interleukin-10; TNF- α , tumor necrosis factor- α ; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; SCF, stem cell factor; IFN- γ , interferon- γ ; Seladin-1, selective Alzheimer's disease indicator-1; Nrf2, nuclear factor erythroid 2-related factor 2; VEGF-A, vascular endothelial growth factor A; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element binding; APP, amyloid precursor protein; GSK-3 β , glycogen synthase kinase-3 β ; SCD-1, stromal cell-derived factor-1 α ; CXCL-12, C-X-C motif chemokine 12; CXCL-10, C-X-C-motif ligand 10;

CCL5, chemokine (C-C motif) ligand 5; Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; AIF, apoptosis-inducing factor; PCNA, proliferating cell nuclear antigen; SDF-1, stromal cell-derived factor 1; HGF, hepatocyte growth factor.

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Disclosure

The authors report no conflicts of interest in this work.

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