



Mesenchymal stem cell-derived exosomes: Shaping the next era of Alzheimer's disease treatment

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Abstract

Alzheimer's disease (AD) is a multifaceted neurodegenerative disease for which effective disease-modifying therapies are lacking. Mesenchymal stem cell-derived exosomes (MSC-Exos) have emerged as a promising therapeutic approach due to their unique biological functions and favorable biocompatibility. This review systematically explores the mechanism of action of MSC-Exos in AD therapy, including the removal of β -amyloid *via* the delivery of degradative enzymes, modulation of neuroinflammation, and promotion of neural regeneration. Meanwhile, this paper summarizes recent advances in preclinical and clinical studies, and analyzes the challenges in production standardization, safety assessment, and long-term efficacy validation of exosome therapies. Finally, several innovative strategies are proposed to enhance the therapeutic potential of MSC-Exos, including exosome functionalization and targeting optimization, gene editing techniques. This aims to promote the translation of exosomes from basic research to clinical application.

Key Words: Alzheimer's disease; Mesenchymal stem cells; Exosomes; Precision medicine; Cell-free therapy

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Core Tip: Mesenchymal stem cell-derived exosomes represent a promising therapeutic modality for Alzheimer's disease, owing to their biological functions and biocompatibility. Mesenchymal stem cell-derived exosomes facilitate the clearance of β -amyloid by carrying degradative enzymes, modulate neuroinflammation, and promote neurorestoration. While pre-clinical and clinical data are encouraging, challenges such as production standardization, safety, and long-term efficacy remain. Strategies like exosome functionalization, targeting optimization, gene editing, and synthetic exosomes may enhance therapeutic potential and accelerate clinical translation.

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INTRODUCTION

Alzheimer's disease (AD) is a prevalent and progressive neurodegenerative disease characterized by significant memory impairment, cognitive dysfunction, and behavioral disturbances. With the acceleration of global population aging, the prevalence of AD is on a significant rise, and the number of patients is projected to exceed 150 million by 2050, posing a critical global public health challenge[1]. Currently available first-line treatments, such as acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, provide temporary symptomatic relief and modest improvements in cognitive function, without altering the pathological process of the disease[2]. In particular, under the concept of "symptomatic relief", therapeutic efficacy exhibits substantial interindividual variability, influenced by factors such as drug mechanism, genetic background, and disease progression[2,3]. Compounding the challenge, the pathology of AD involves multiple interacting pathways, including β -amyloid (A β) plaques deposition, highly phosphorylated tau protein-mediated neurofibrillary tangles (NFTs), and neuroinflammation driven by microglia activation, all of which synergistically cause loss of synaptic plasticity, neuronal degeneration, and brain parenchymal atrophy, ultimately leading to irreversible neurological damage[4,5]. However, existing drugs target only a single pathological component and lack the ability to intervene in a holistic manner[6,7]. Therefore, there is an urgent need for novel therapeutic strategies that can target the multifactorial nature of AD and promote repair of damaged neural functions. Developing interventions that fundamentally address the pathogenesis of AD has become a central focus of current research.

Mesenchymal stem cells (MSC) and their derived exosomes have garnered significant attention in recent years as an innovative therapeutic strategy. MSC are considered promising candidates for the treatment of neurodegenerative diseases due to their potent immunomodulatory, neuroprotective, and regenerative abilities[8]. However, MSC therapy is associated with several limitations, including immune rejection after cell transplantation, low cell survival, tumor risk, and unstable therapeutic effects[9]. To overcome these challenges, MSC derived exosomes (MSC-Exos), as a natural carrier for intercellular communication, offer new ideas for the treatment of AD[8-10]. Compared to MSCs, MSC-Exos has superior biosafety, stronger blood-brain barrier penetration efficiency and lower immunogenicity[11]. Existing preclinical studies have confirmed that MSC-Exos can demonstrate the pathological process of AD at multiple levels, particularly by clearing A β plaques, attenuating neuroinflammation, modulating tau protein pathology and promoting neural repair, thereby contributing to functional improvement[7,12-14]. In addition, the ability of MSC-Exos to strongly penetrate the blood-brain barrier expands their potential for clinical application[11]. This review summarizes current evidence supporting the use of MSC-Exos in AD therapy. In addition, this review highlights the challenges to the clinical translation of exosome therapies and discusses strategies to enhance their function and targeting.

MSC-EXOS BIOGENESIS

MSC-Exos are extracellular vesicles with a single-membrane structure, typically ranging from 30 to 150 nm in diameter. They naturally carry bioactive components, such as proteins, nucleic acids [mRNAs, microRNAs (miRNAs), long noncoding RNAs, circular RNAs] and lipids of matricellular origin. These molecules are involved in intercellular communication and play an important role in neurological disorders therapy[15]. For example, MSC secretes neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor, which support neuronal survival, neurogenesis, and synaptic plasticity[16,17]. In addition, specific miRNAs such as miR-21, miR-22, and others have been widely discussed in AD, and they show therapeutic potential for treating AD by targeting a great variety of multiple pathologic mechanisms in AD, including A β clearance, immunoinflammation, and neuroprotection[18-21].

The biogenesis of MSC-Exos mainly involves endosomal sorting complex required for transport (ESCRT) machinery mechanisms and lipid-mediated pathways[8,22,23]. Its biogenesis begins with the cell internalizing external material through endocytosis, forming early sorting endosomes. As the early sorting endosomes matures, the endosomal boundary membrane buds inward to generate intraluminal vesicles (ILV). ILV formation is mainly regulated by the ESCRT. This machinery complex is mainly composed of complexes ESCRT-0, ESCRT-I, ESCRT-II and ESCRT-III and ILV-forming proteins such as vacuolar protein sorting 4, ALG-2-interacting protein X, and tumor susceptibility 101, each of

which performs distinct roles in cargo recognition, membrane deformation, and vesicle segregation[22]. ESCRT-0 is mainly responsible for recognizing ubiquitinated cargoes, whereas ESCRT-I/II/III mediates membrane bending and invagination. The vacuolar protein sorting 4 complex ensures vesicle cleavage and ESCRT component recycling[22,23]. Another pathway for exosome biogenesis is a lipid based ESCRT-independent mechanism responsible, which involves lipids such as sphingolipids (SLs), phosphatidic acid, and cholesterol, ceramides (Cers), as well as the family of four-transmembrane structural domain proteins[22,24,25]. The lipid mediation mechanism was first described by Trajkovic *et al*[25], who emphasized that exosome biosynthesis occurs in the membrane domains enriched in SLs. To be specific, SLs are hydrolyzed to Cers by neutral sphingomyelinase, a key enzyme in lipid metabolism, leading to the formation of Cer-rich microdomains. These microdomains coalesce into larger membrane platforms, promoting inward vesicle outgrowth[26,27]. In addition, lipid components such as Cers, SL and cholesterol also mediate the sorting of specific cargoes (RNA and other molecules) into vesicles[25,28]. Specific cytoplasmic molecules are encapsulated into the lumen and accumulate in the late endosomes, resulting in the formation of multivesicular bodies. Some multivesicular bodies fuse with the plasma membrane and release their contents as exosomes into the extracellular space, while others fuse with autophagosomes or are translocated to lysosomes[8,29,30]. The released exosomes carry various biomolecules which can interact with recipient cells locally or at a distance, thereby influencing their physiological activities[22]. In this regard, MSC-Exos are considered to be the best cell-free candidate to promote repair processes by activating positive responses in the brain microenvironment through intercellular communication, showing promising prospects especially in the treatment of neurodegenerative diseases.

MSC-EXOS: MULTIDIMENSIONAL REPAIR OF AD

Typical pathologic features of AD include A β deposition, abnormal phosphorylation of tau proteins to form NFTs, loss of synaptic plasticity, and widespread neuroinflammation. Although A β has long been recognized as a main causative factor of AD, recent evidence suggests that disease onset and progression result from the interplay of multiple biological processes, involving protein aggregation imbalances, immune dysfunction, and metabolic disorders, among others (Figure 1)[31-33]. These findings underscore the necessity of approaching AD from a systems biology perspective, focusing on the integration of complex molecular networks involved in disease pathogenesis. Exosomes, as carriers of intercellular communication, are increasingly being recognized for their significant roles in the pathological progression and treatment of AD. MSC-Exos are enriched with a variety of bioactive molecules that can modulate AD-related processes through cell-to-cell messaging. These include A β clearance, modulation of neuroinflammation, promotion of neuroregeneration, and targeted delivery across the blood-brain barrier (Table 1). Thus, MSC-Exos are expected to serve as an innovative therapeutic tool that provides integrated interventions for multiple pathologies of AD.

AD pathogenesis: A time-dependent multicascade chain of events

AD is a progressively worsening neurodegenerative disease marked by a time-dependent, multistep pathological cascade. The disease course involves a gradual deterioration from early molecular imbalances to late neural network breakdown[34,35]. The different pathological factors in the course of AD reinforce each other in a vicious cycle, ultimately leading to widespread degeneration of the brain and loss of cognitive function[35-37].

The initial stages of AD are triggered by abnormal shearing of A β precursor protein (APP), which generates A β ₁₋₄₂ oligomers *via* the β / γ -secretase pathway[38,39]. Gradually, the accumulation of A β exceeds the clearance threshold in the brain. A β activates localized prion protein receptors on neuronal membranes, which further initiates the Fyn kinase signaling pathway. This activation leads to overactivation of N-methyl-D-aspartate receptors and impairs synaptic plasticity, one of the core pathological features of the early stages of AD[40,41]. With the accumulation of A β and the exacerbation of early synaptic damage, AD progresses to a more advanced stage, where the abnormal phosphorylation of tau protein becomes a key feature of this stage[35,42]. A β not only exerts direct neurotoxic effects but also promotes tau hyperphosphorylation at specific localization sites (*e.g.*, Ser199, Ser396, Ser413, Thr205, Tyr18) by activating the pathways, such as CDK5/p25 and glycogen synthase kinase-3 β , and the formation of NFTs[17,43-45]. The abnormal phosphorylation of tau destabilizes the microtubule system, impairs axonal transport, affects the normal transport of substances within the neuron and further exacerbates neuronal function decline[46]. Simultaneously, deposition of A β and tau initiated a neuroinflammatory response, which not only exacerbated the pathological progression of AD, but also formed a secondary linkage mechanism[35,42,47]. A β stimulated the release of inflammatory factors, such as interleukin (IL)-1 β , tumor necrosis factor (TNF)- α and other inflammatory factors, through activation of the Toll-like receptor 4/nuclear factor-kappa B pathway on microglial cells, further exacerbating the neurological damage[38,48,49]. In turn, the phosphorylation of tau proteins exacerbated the inflammatory response by activating nod-like receptor protein 3 (NLRP3) inflammatory vesicles through interaction with high mobility group box-1 protein[50]. Neuroinflammation not only accelerated the accumulation of A β and tau, but also induced oxidative stress through reactive oxygen species (ROS) and reactive nitrogen species released (inducible nitric oxide synthase) by microglia, exacerbating neuronal damage and death[35,48,50]. As the disease progresses, synaptic loss and neuronal death become the main features of advanced AD. At this stage, the toxic effects of A β and tau on neurons intensify, and synaptic disintegration and neural network collapse lead to severe loss of cognitive and memory functions. A β induces atrophy of dendritic spines by binding to postsynaptic density protein-95, whereas phosphorylation of tau proteins further blocks kinesin binding to microtubules, halting presynaptic vesicle transport, thereby affecting neural signaling[46,51,52]. In addition, late AD is accompanied by malignant transformation of glial cells. Astrocytes transform into type A1, accelerating neuronal death, whereas microglia enter a senescent state, losing their scavenging function and secreting senescence-associated secretory phenotype, which

Table 1 Therapeutic properties of mesenchymal stem cell exosomes in Alzheimer's disease

Source	Cargoes	Model	Injection/culture	Machine	Character	Ref.
Wharton's jelly MSCs	Exosomes	FAD human neural cell	Matrigel culture model	NEP	A β degradation	[7]
Bone marrow MSCs	MiR-29c-3p	A β ₁₋₄₂ injected rat	Lateral ventricle injection	Wnt/ β -catenin	A β degradation	[13]
Bone marrow MSCs	GDF-15	A β ₄₂ incubated SH-SY5Y	Gibco	Akt/GSK-3 β / β -catenin	A β degradation	[17]
Human umbilical cord MSCs	Exosomes	APP/PS1 mice	Caudal vein injection	Glial cell polarisation	A β degradation, immune regulation	[61]
Induced pluripotent stem cell derived MSCs	MiR-223-3p	STZ mice	Intracisternal injection	NLRP3/GSDMD	Immune regulation	[75]
Bone marrow MSCs	Exosomes	STZ mice	Lateral ventricle/caudal vein injection	BDNF	Neuroregeneration, immune regulation	[12]
Human bone marrow MSCs	Exosomes	3xTg mice	Intranasal route	Glial cell polarisation	Immune regulation	[70]
Wharton's jelly MSCs	Exosomes	J20 (JAX-006293)	IV	Glial cell polarisation	Immune regulation	[7]
Adipose derived MSCs	MiR-22	APP/PS1 mice	Caudal vein injection	GSDMD	Immune regulation	[19]
MSCs	MiR-223	A β ₁₋₄₀ incubated SH-SY5Y	-	PTEN	Neuroprotection	[18]
Bone marrow MSCs	Exosomes	A β ₁₋₄₂ injected mice	Lateral ventricle injection	-	Neuroregeneration	[14]
Bone marrow MSCs	MiR-21, miR-155, miR-17-5p, miR-126-3p	AlCl ₃ incubated rat	Intraperitoneal injection	PI3K/Akt/mTOR	Neuroregeneration	[20]
Bone marrow MSCs	MiR-146a	APP/PS1 mice, astrocyte	Intracerebroventricular injection/transwell	NF- κ B	Neuroregeneration	[81]
Bone marrow MSCs	MiR-21	APP/PS1 mice	Caudal vein injection	STAT3 NF- κ B	Neuroregeneration	[21]
Human amniotic fluid	Exosomes	A β incubated SH-SY5Y, LSP incubated BV-2	Transwells	Oxidative stress	Neuroprotection	[82]
Bone marrow MSCs	Exosomes	Hippocampal neuronal exposed A β O	Transwells	Oxidative stress	Neuroprotection A β degradation	[83]
Olfactory mucosa MSCs	Exosomes	A β ₁₋₄₂ injected mice	Caudal vein injection	LRP1	Neuroprotection	[84]

MSC: Mesenchymal stem cell; FAD: Familial Alzheimer's disease; NEP: Neprilysin; A β : B-amyloid; GDF-15: Growth differentiation factor-15; Akt: Protein kinase B; GSK-3 β : Glycogen synthase kinase-3 β ; APP: B-amyloid precursor protein; STZ: Streptozotocin; NLRP3: Nod-like receptor protein 3; GSDMD: Gasdermin D; BDNF: Brain-derived neurotrophic factor; 3xTg: Triple-transgenic; IV: Intravenous injection; PTEN: Phosphatase and tensin homolog; PI3K: Phosphatidylinositol-3-kinase; mTOR: Mammalian target of rapamycin; STAT3: Signal transducer and activator of transcription 3; NF- κ B: Nuclear factor-kappa B; A β O: Soluble oligomers of the amyloid- β peptide; LRP1: Low-density lipoprotein receptor-related protein 1.

further enhances the local inflammatory response[53-56]. These mutated and dysregulated glial cells significantly contribute to the deterioration of AD[53,55]. Eventually, with the combined effects of A β , tau, neuroinflammation, and oxidative stress, the neural network of AD suffers from severe dysfunction, leading to wide spread brain atrophy and cognitive decline, and ultimately, the terminal stage of the disease. The entire pathological process is mutually reinforcing through positive feedback mechanisms, which propel the disease from early molecular imbalance to late neurological collapse.

Potential of MSC-Exos in AD

A β degradation: A β plaques are composed of A β peptides, which undergo an aggregation process that results in the formation of toxic soluble oligomers and insoluble fibrous material, eventually being deposited as plaques[4,39,42]. In healthy brains, A β production and clearance remain balanced; however, impaired clearance disrupts this equilibrium, leading to A β accumulation, synaptic dysfunction, neuronal damage, and neurodegeneration. Enhancing the clearance of

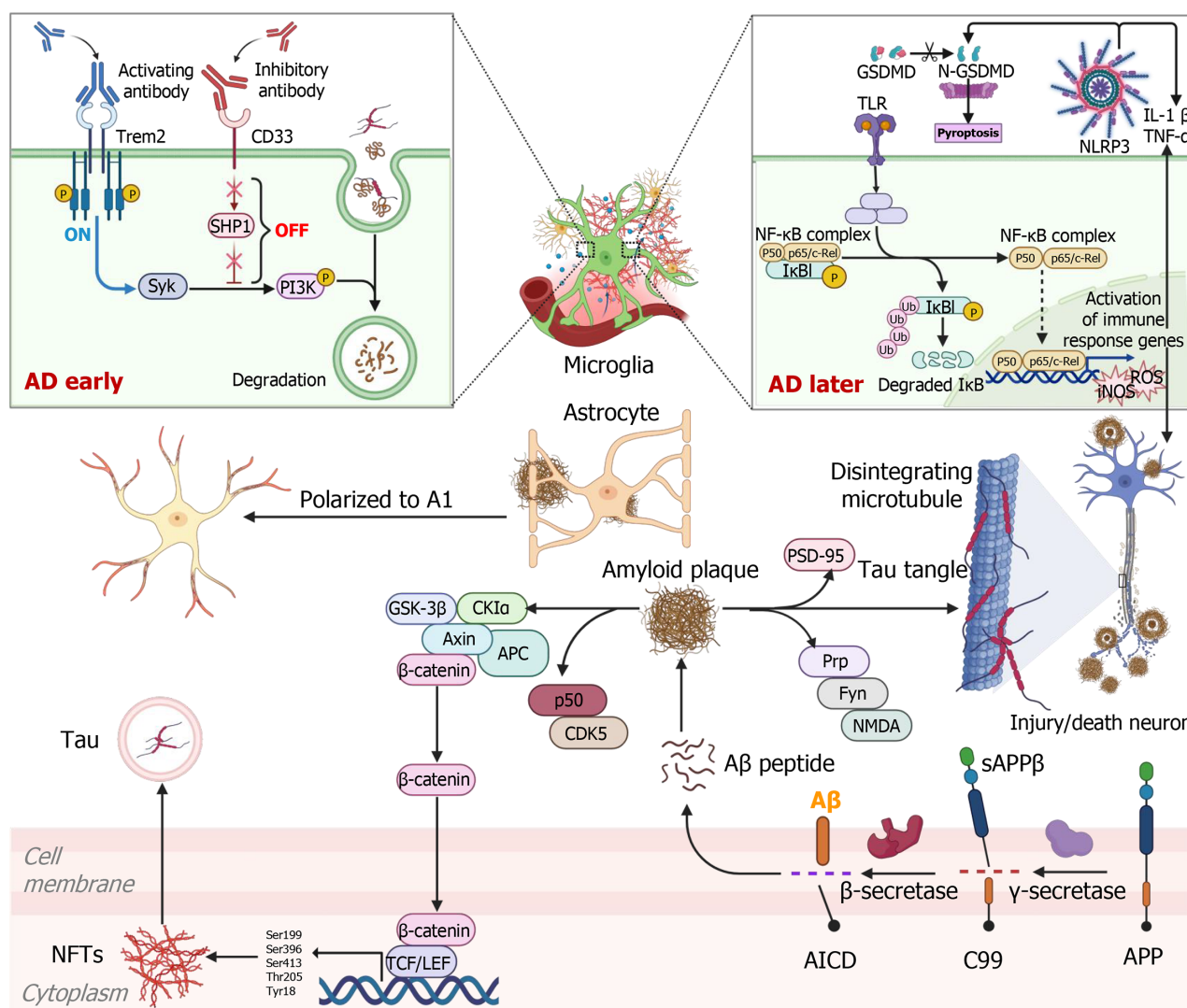


Figure 1 Alzheimer's disease pathogenesis. A combination of A β , tau proteins, neuroinflammation, and oxidative stress, the neural network in Alzheimer's disease suffers severe dysfunction, leading to widespread brain atrophy and cognitive decline. Figure was created with BioRender (Supplementary material). Trem2: Triggering receptor expressed on myeloid cells 2; Syk: Spleen tyrosine kinase; SHP1: Src homology region 2 domain containing phosphatase-1; PI3K: Phosphatidylinositol-3-kinase; GSDMD: Gasdermin D; N-GSDMD: N-terminal gasdermin D; TLR: Toll-like receptor; NLRP3: Nod-like receptor protein 3; IL-1 β : Interleukin-1 β ; TNF- α : Tumor necrosis factor α ; NF- κ B: Nuclear factor-kappa B; I κ B: Inhibitor of nuclear factor kappa B; ROS: Reactive oxygen species; iNOS: Inducible nitric oxide synthase; PSD-95: Postsynaptic density protein-95; GSK-3 β : Glycogen synthase kinase 3 beta; CK1 α : Casein kinase I alpha; APC: Antigen-presenting cell; Prp: Prion protein; NMDA: N-methyl-D-aspartate; A β : B-amyloid; sAPP β : Soluble amyloid precursor proteins; AICD: Amyloid precursor protein intracellular domain; APP: Amyloid precursor protein; NFTs: Neurofibrillary tangles; TCF: T-cell factor; LEF: Lymphoid enhancer-binding factor; AD: Alzheimer's disease.

pathogenic proteins has been shown to be beneficial in treating AD[57]. In the degradative clearance system, extracellular A β can be degraded by proteases such as neprilysin (NEP), matrix metalloproteinases and glutamate carboxypeptidase II, insulin degrading enzymes (IDE) and zinc metalloproteinases[58,59]. NEPs expression and function are significantly reduced in AD patients. In 2000, researchers observed that brain-derived NEP could degrade disease-causing A β_{1-42} peptides in the hippocampus of rats injected with radiolabeled synthetic A β_{1-42} [60]. Interestingly, Chen *et al*[7] observed the expression of NEP-specific enzymatic activity on the membrane of MSC-Exos. They further co-cultured familial AD neuronal cells with MSC-Exos and found that they could reduce A β levels, along with restoration of BDNF exon IV and Homer genes (related to neuronal memory and synaptic plasticity)[7]. Bone marrow MSC-Exos (BMMSC-Exos) miR-29c-3p treatment effectively inhibited A β formation and deposition, increased the expression of NEP and IDE, and promoted soluble A β_{1-42} degradation, thereby significantly improving cognitive behavior in AD rats[13]. Further, the downstream mechanism by which miR-29c-3p alleviates AD is associated with targeting APP cleaving enzyme 1 (BACE1), an APP cleavage enzyme. BMMSC-Exos inhibit BACE1 expression and activate the Wnt/ β -catenin pathway by carrying miR-29c-3p into neurons, reducing A β production and deposition, ultimately leading to reduced inflammation and neuronal apoptosis[13]. Additionally, *in vitro* experiments revealed that BMMSC-Exos containing growth differentiation factor-15 also upregulated NEP and IDE through activation of the protein kinase B (Akt)/glycogen synthase kinase-3 β / β -catenin pathway, which degraded the A β_{42} protein to attenuate SH-SY5Y cell injury. *In vivo*, M2 microglia have likewise been noted to increase IDE and NEP expression[17]. One study found that human umbilical cord MSC-Exos treatment

significantly enhanced the expression of IDE and NEP in AD mice by alternatively activating microglia, thereby reducing A β deposition and soluble A β levels[61]. In conclusion, the critical role of MSC-Exos in A β degradation highlights their potential in the treatment of AD.

Immune regulation: Neuroinflammation is a major contributor to the pathogenesis and progression of AD, primarily mediated by glial cells, including microglia and astrocytes[62]. These cells play two roles in the entire pathological process of AD, by acting as the “protector” in the early stage of AD to the “accomplice” later[63,64]. The immunomodulatory role of MSC in disease treatment has been widely discussed, owing to their ability to limit the tissue inflammatory microenvironment through the release of immunomodulatory factors such as prostaglandin E2 (PGE2), growth factors, ILs and nitric oxide[64–66]. It has been proposed that MSC regulation of the immune response is at least partially dependent on the activation of two negative feedback loops, PGE2 and TNF- α stimulating gene 6[67,68]. According to the “loop hypothesis”, MSC suppress inflammation by activating one of these two loops depending on the brain environment. Only when the inflammatory response is activated will microglia be driven toward an M2 anti-inflammatory phenotype[68]. MSC-Exos inherit a wide range of immunomodulatory molecules from their parental MSCs, thereby exerting comparable immunosuppressive effects[69]. Losurdo *et al*[70] demonstrated that MSC-Exos induced the upregulation of cyclooxygenase 2 (associated with increased PGE2) and indoleamine 2,3-dioxygenase when microglia were subjected to pro-inflammatory stimulation with TNF α and interferon γ , thereby driving microglia polarization towards the M2 phenotype *in vitro*. Moreover, they delivered MSC-Exos to 3xTg mice for the first time *via* the nasal route and found that MSC-Exos inhibited microglia activation and increased dendritic spine density, exerting neuroprotective effects in the early stages of AD[70]. *Ex vivo* and *in vivo* studies of human umbilical cord MSC-Exos have demonstrated their capacity to regulate microglial activation in the brain, evidenced by increased transforming growth factor- β and IL-10 expression and decreased IL-1 β and TNF- α levels in both the brain and peripheral blood, thereby attenuating neuroinflammation[61]. Also, hyperactivation of microglia and astrocytes in the hippocampus was suppressed after BMMSC-Exos injection in the lateral ventricle of AD mice, accompanied by a decrease in the expression of IL-1 β , IL-6, and TNF- α [12].

In addition, pyroptosis has become a focus in cellular inflammatory responses research in recent years. In response to noxious stimuli, intracellular and extracellular signals induce the inflammasome in the cytoplasm *via* the caspase pathway, activating caspase-1 to promote the release of inflammatory factors (IL-18, IL-1 β), thereby inducing inflammatory cascade response[71]. Adipose derived MSC-Exos loaded with miR-22 have been shown to enhance neurological function and locomotor ability in AD mice by regulating gasdermin D (GSDMD), down-regulating the expression of cellular focal death-related protein caspase-1 and inflammatory factor NLRP3[19]. Notably, NLRP3 is also an important pathway for the secretion of inflammatory cytokines by reactive microglia. Once NLRP3 is activated, it cleaves caspase-1 and subsequently induces the release of GSDMD (the pyroptosis regulatory protein), which triggers pyroptosis[72]. A previous study found that GSDMD was expressed in A β plaque-associated microglia, further confirming the role of pyroptosis in AD[73]. In AD, in addition to A β -driven M1 polarization of microglia to secrete inflammatory factors, microglial cell pyroptosis also affects their normal clearance function, ultimately contributing to a vicious cycle of A β pathology[73,74]. MSC-Exos have been reported to inhibit cellular pyroptosis and neuroinflammation, reduce A β accumulation, and mitigate neurodegeneration in AD mice *via* miR-223-3p-mediated inhibition of the NLRP3/GSDMD pathway[75].

Neuro restoration: Brain dysfunction in AD arises from reduced synaptic plasticity, altered homeostatic scaling, and disrupted neuronal connectivity[76,77]. The neuroprotective and neuro regenerative effects of MSC-Exo in AD have been well-documented[14]. Wei *et al*[18] found that the establishment of an AD cell model was accompanied by elevated hypoxia-inducible factor-1 α expression and apoptosis, impaired cell migration, and decreased miR-223. When MSC-Exos were introduced into the AD cell co-culture model, internalization occurred in a time-dependent manner, reversing these pathological changes. The increased MSC-Exos miR-223 binds to phosphatase and tensin homolog and initiates its downstream phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway that controls axonal remodeling, cell proliferation and differentiation[18]. These findings suggest that MSC-Exos miR-223 can reduce neuronal apoptosis in AD by interfering with signaling pathways related to neuronal cell cycle. Ebrahim *et al*[20] also demonstrated that BMMSC-Exos enhances synaptic function, reduces astrocyte scarring, and promotes neurogenesis. These beneficial effects are associated with modulation of the PI3K/Akt/mTOR signaling pathway, autophagy, and inhibition of neuroinflammation. Additionally, BMMSC-Exos regulate specific miRNAs to support their therapeutic potential, including miR-17-5p, miR-21, miR-155 and miR-126-3p[20]. Interestingly, enhanced activation of the PI3K/Akt/mTOR signaling cascade has been closely associated with the pathological signaling from A β to tau in AD, which underlies cognitive decline[78]. MSC-Exos regulate miRNAs to improve the pathological process of AD. In this context, MSC-Exos represent a promising option for the treatment of AD.

Recent studies have reported that exosomal administration increases the number of newborn neurons in the neurogenesis microenvironment (subventricular zone and dentate gyrus)[79]. One of the mechanisms by which exosomes interact with the neurogenic microenvironment is the transfer of miRNAs to precursor neural precursor cells, which triggers neural remodeling events, neurogenesis, angiogenesis, and synapse formation[80]. One study used bilateral dentate gyrus injections of A β ₁₋₄₂ aggregates to establish an AD mouse model followed by *in situ* administration of MSC-Exos, and found that MSC-Exos were able to stimulate neurogenesis in the subventricular zone and attenuate A β ₁₋₄₂-induced cognitive deficits, and that these effects were similar to those of MSCs[14]. Astrocytes are key cells in synapse formation, and restoring their function may help correct neurogenesis and improve cognitive deficits. BMMSC-Exos therapy promotes synaptogenesis by down-regulating nuclear factor-kappa B expression in astrocytes after transferring miR-146a to astrocytes[81]. The expression level of synaptic proteins can reflect the function of synapses to some extent. Hypoxia preconditioning of BMMSC-Exos miR-21 significantly enhances the expression of synaptic proteins (synapsin 1

and postsynaptic density protein-95), thereby rescuing synaptic dysfunction[21]. In addition, human amniotic fluid endometrial stromal cell derived exosomes blocked the negative effects of elevated oxidative stress induced by microglial and neuronal cell interactions and significantly restored neurotoxicity by efficiently reducing inducible nitric oxide synthase and ROS activity[82]. Another study using a transwell co-culture system of rat hippocampal neurons and BMMSCs found that BMMSCs reduce the expression of ROS in neurons by releasing exosomes containing antioxidant enzymes. This effect may help maintain synaptic integrity in neurons exposed to soluble amyloid- β oligomers[83]. Additionally, olfactory mucosa MSC-Exos exerts neuroprotective effects by regulating glial cell activation and influencing the endoplasmic reticulum stress response potentially *via* the low-density lipoprotein receptor-related protein 1[84].

Notably, it has been reported that a limited number of exosomes reach the brain through the peripheral circulation compared to the liver, kidneys, and other peripheral organs of the body[85]. It has been demonstrated that AD mice treated by injection of BMMSC-Exos through the lateral ventricle, rather than tail vein injection, exhibit significant modulation of hippocampal plasticity by up-regulating BDNF to promote neuronal regeneration, reversing the AD-like behavior induced by streptozotocin injection[12]. Furthermore, Losurdo *et al*[70] achieved the observed effects on microglia activation and neuronal recovery by only two temporally close nasal injections of MSC-Exos. This suggests that intranasal delivery may achieve higher brain concentrations compared to those administered *via* other routes. Controversy still exists regarding the ability of exosomes to reach the brain. Therefore, further studies are needed to optimize delivery strategies and investigate the precise biodistribution of exosomes under different administration routes.

In summary, the cascade of pathological responses triggered by A β and tau, primarily centered on neurons, ultimately leads to dementia[86]. Neuronal networks, astrocytes, microglia, oligodendrocytes, and the vascular system contribute all to a complex cellular phase of AD evolving over decades[86]. MSC-Exos act pleiotropically on A β , inflammation, and regeneration, making them a promising approach for the treatment of AD.

MSC-EXOS FROM BENCH TO BEDSIDE: CHALLENGES AND RESPONSES

Although results from cellular and murine models of AD suggest that MSC therapies are promising in AD, only one clinical trial to date has investigated the safety and efficacy of MSC-Exos in patients with mild to moderate dementia (<http://www.clinicaltrials.gov>, NCT04388982, accessed April 27, 2025). This phase I/II clinical trial used nasal drops to give three doses of adipose derived MSC-Exos (5, 10, and 20 μ g) twice weekly to AD patients, with treatment lasting 12 weeks and follow-up lasting 9 months[87]. No serious adverse events occurred during the 12-week treatment period, and the drug did not cause any significant toxicity to vital organs such as the liver and kidneys, indicating that the MSC-Exos treatment was safe and well-tolerated. Specifically, patients receiving the intermediate dose demonstrated significant improvement in cognitive function after 12 weeks of treatment and the effect was maintained for up to 6 months, suggesting potential long-term benefits. Although no significant changes in A β and tau deposition were observed, hippocampal volume reduction was less observed in the mid-dose group, which was neuroprotective for brain tissue.

Challenges

While MSC-Exos hold substantial therapeutic potential for AD, several major challenges must be addressed before widespread clinical application is feasible[10,87-89].

Production standardization: One of the major challenges to the clinical application of MSC-Exos is the lack of standardized protocols for production, isolation and purification. Although a variety of methods including ultracentrifugation, size-exclusion chromatography, and immunoaffinity capture are widely used, there are limitations inherent in these techniques[10,90]. For example, ultracentrifugation is typically time-consuming with low yields, and contamination with non-exosomal particles such as apoptotic bodies or cellular debris is common[90]. In addition, variation in exosome yield is influenced by numerous factors, including MSC source, culture conditions, and passage number, leading to variability and poor reproducibility[88]. In the future, there is a need to further refine and standardize protocols for the isolation, purification and characterization of MSC-Exos. These protocols must be scalable, reproducible, and adaptable to clinical applications to ensure that exosome production is stable, efficient, and meets regulatory standards. In addition, determining the optimal method for large-scale production is critical, as regulatory agencies demand stringent control over product quality and batch consistency.

Safety assessment: While MSC-Exos generally demonstrate excellent biocompatibility and low immunogenicity, comprehensive safety evaluations are essential. Harmful paracrine factors may interfere with the desired therapeutic outcome or even lead to adverse reactions[10,91]. Consequently, rigorous evaluations are necessary to assess off-target effects, long-term toxicity, and the potential for triggering an immune response. In addition to short-term safety, long-term studies are needed to evaluate cumulative effects on organ systems, immune modulation, and systemic health[88,92].

Long-term efficacy verification: While MSC-Exos have shown great potential in preclinical models of neurodegenerative diseases and in short-term efficacy in clinical trials, their long-term efficacy in the clinical setting remains underexplored [39,57,75,87]. Future clinical trials should evaluate whether MSC-Exos can halt or slow disease progression, restore lost cognitive function and prevent further neuronal degeneration over months or years. In addition, the mode of exosome administration, optimal dosage, targeting and functionality can also influence clinical effectiveness[93-95].

Responses

Despite their therapeutic promise, MSC-Exos face several practical limitations, including low targeting efficiency, limited intrinsic functionality, and suboptimal yield[89]. These problems can be addressed by various bioengineering techniques [96,97].

Preprocessing: Many studies have indicated that altering the culture conditions of MSC and pretreating these cells can affect exosome production, activity and metabolic regulatory capacity. Compared with two-dimensional, three-dimensional-cultured human umbilical cord MSC-Exos exhibited significantly higher levels of 195 miRNAs and A β hydrolases, which exerted enhanced therapeutic effects on improving memory and cognitive deficits in AD mice[98]. Compared with the group administered normoxic MSC-Exos, MSC-Exos pretreated in hypoxia effectively increased the level of miR-21 in the brains of AD mice, producing greater improvements in synaptic function[21]. In addition to physical factors, biochemical stimuli such as melatonin, interferon γ , and TNF- α memory exogenous genes can also be introduced into the culture environment to modify and optimize their functions[99-102].

Drug loading: Due to its nanoscale structure and biocompatibility, MSC-Exos are ideal candidates for efficient drug loading[96,103]. Two strategies for drug loading include collection of drug-loaded exosomes after pretreatment of parental cells by using various methods and loading of exogenous drugs into isolated exosomes[104]. The Fe65-engineered HT22 hippocampus neuron cell-derived exosomes loaded with corynoxine-B (autophagy inducer) hijacked signaling and blocked the natural interaction between Fe65 and APP for targeted delivery of exosomes and drug[105]. Jahangard *et al*[106] loaded miR-29 into MSC-Exos to target BACE1 and Bcl-2-interacting mediator of cell death, thereby restoring hippocampal learning function in AD rats.

Surface modification: The surface modification of exosomes by gene manipulation targeting peptides or chemical modification sites can enhance their specific functions. To improve the brain targeting ability of intravenously injected exosomes, the surface of the exosomes can be modified by linking peptides. For example, MSC-Exos conjugated with central nervous system-specific rabies virus glycoprotein peptides demonstrated improved targeting of the cortex and hippocampus in AD mice[94]. Furthermore, MSC-Exos with high tyrosine phosphatase-2 expression improved blood-brain barrier penetration in AD mice[107]. Han *et al*[108] designed engineered exosomes with a light-induced protein delivery system that enables CRISPR-Cas-based epigenome editing in AD.

Artificial exosomes: In recent years, artificial exosomes, based on nanobiotechnology, have emerged to overcome the limitations of natural exosomes. These artificial exosomes are usually obtained by top-down, top-down, bottom-up and biohybridization strategies including extrusion, microfluidics, nitrogen cavitation and sonication to break down cell membranes, yielding higher amounts of exosomes. These biohybrid strategies are proving to be a promising alternative for drug delivery systems[109]. However, artificial exosomes are not yet ready for translation due to challenges in preparation protocols, characterization and biocompatibility. In AD therapy, natural exosomes are still in the initial clinical trial stage, while the emerging field of artificial exosomes remains largely unexplored.

CONCLUSION

In conclusion, MSC-Exos have demonstrated great potential as a novel therapeutic strategy in the treatment of AD. Advances in MSC-Exos in the areas of protein disorders, neuroinflammation, and neurogenesis undoubtedly herald the dawn of a new era in the treatment of neurodegenerative disorders, and may pave the way for clinical applications in AD in the future. While early-stage clinical trials have produced encouraging results, several key challenges remain. These include addressing the heterogeneity of MSC-Exos production and mining, optimizing safety assessments, confirming the efficacy, determining the optimal delivery and dosage, improving their targeting capabilities and functions before clinical translation. Recent advances in pretreatment strategies, drug loading techniques, surface engineering, and the development of synthetic exosomes have improved the targeting specificity and therapeutic potential of MSC-Exos, addressing several key limitations in their clinical translation. Future investigations will focus on optimizing the treatment regimen and exploring the underlying mechanisms.

FOOTNOTES

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