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Mesenchymal stem cell exosome therapy: current research status in the treatment of neurodegenerative diseases and the possibility of reversing normal brain aging

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Abstract

With the exacerbation of the aging population trend, a series of neurodegenerative diseases caused by brain aging have become increasingly common, significantly impacting the daily lives of the elderly and imposing heavier burdens on nations and societies. Brain aging is a complex process involving multiple mechanisms, including oxidative stress, apoptosis of damaged neuronal cells, chronic inflammation, and mitochondrial dysfunction, and research into new therapeutic strategies to delay brain aging has gradually become a research focus in recent years. Mesenchymal stem cells (MSCs) have been widely used in cell therapy due to their functions such as antioxidative stress, anti-inflammation, and tissue regeneration. However, accompanying safety issues such as immune rejection, tumor development, and pulmonary embolism cannot be avoided. Studies have shown that using exosome derived from mesenchymal stem cells (MSC-Exo) for the treatment of neurodegenerative diseases is a safe and effective method. It not only has the therapeutic effects of stem cells but also avoids the risks associated with cell therapy. Therefore, exploring new therapeutic strategies to delay normal brain aging from the mechanism of MSC-Exo in the treatment of neurodegenerative diseases is feasible. This review summarizes the characteristics of MSC-Exo and their clinical progress in the treatment of neurodegenerative diseases, aiming to explore the possibility and potential mechanisms of MSC-Exo in reversing brain aging.

Keywords Mesenchymal stem cells, Exosomes, Neurodegenerative diseases, Brain aging

Brain aging is a complex process that occurs at molecular and cellular levels and progresses to changes in organ function. In healthy adults, as they age, brain aging is manifested as a reduction in overall brain volume (brain atrophy), loss of gray and white matter, an increase in the width and depth of sulci, thinning of the cortex, loss of gyri and enlargement of ventricles. In pathological brain aging, it is characterized by neuronal cell atrophy, dendritic degeneration, demyelination, small vessel disease, slowed metabolism, microglial activation, and the formation of white matter lesions, leading to cognitive deficits and decreased motor performance [1]. These manifesta-

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tions involve various factors, from cellular and molecular to genetic levels. In 2013, López-Otín's team proposed nine original hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, loss of proteostasis, deregulated nutrient sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication [2]. However, due to the complexity of aging mechanisms, a single hallmark template cannot explain the multifactorial nature of aging [3]. Consequently, researchers have explored new hallmarks of aging [4]: impaired autophagy [5], dysregulated microbiome, altered mechanical properties, splicing dysregulation, and chronic inflammation [6], integrating them with the original hallmarks for a more comprehensive understanding of aging mechanisms. Currently, many studies are investigating the links between aging phenotypes and characteristic molecules, seeking new strategies to treat brain aging and related neurodegenerative diseases [7]. Some research suggests that aging is a major risk factor for neurodegenerative diseases [8, 9], which, in turn, accelerate aging mechanisms and cause more pronounced changes in brain structure [1]. This raises the hypothesis: could the mechanistic pathways of neurodegenerative diseases be linked to those of natural brain aging, thereby applying strategies for treating neurodegenerative diseases to reverse brain aging?

In the past, cell therapy involving the direct transplantation of mesenchymal stem cells (MSCs) has made significant progress in combating aging-related conditions, including osteoarthritis (OA) associated with physiological aging [10–12], cardiovascular diseases [13, 14], frailty in aging [15, 16], and neurodegenerative diseases [17, 18]. MSC therapies have already carried out clinical trials in various disease fields. However, most MSC therapies have not passed the clinical trials, and only more than 300 clinical trials have been successfully completed. Among them, MSC therapies for only more than ten diseases such as acute myocardial infarction, spinal cord injury, and complex perianal fistulas have been globally approved [19, 20]. Some studies have found significant risks associated with direct transplantation of MSCs, such as significant adverse reactions, clonal chromosomal and genomic instability, and induced thrombus formation [21–23]. Besides the issues of safety risks, the possibility of poor treatment quality and efficiency also needs to be considered. Recent studies suggest that in MSC therapy for neurodegenerative diseases, MSCs primarily promote neurovascular regeneration, alleviate neuroinflammation, and modulate immunity through paracrine effects, thus restoring neural networks and improving cognitive function, mediated by exosome (Exo) [24, 25]. In vitro experiments usually use the conditioned medium or supernatant of MSCs (which contains cytokines such as neurotrophic factors, angiogenic factors, anti-inflammatory factors, and immunomodulatory factors secreted by MSCs) to observe the therapeutic effects of MSCs. The expression levels of relevant immune and inflammatory factors or the situations of cell proliferation, movement, and metabolism can be measured to evaluate their curative effects [26].Therefore, exosomes derived from different mesenchymal stem cells (MSC-Exo), which play a primary role, have gradually become a hot topic as an alternative to MSC therapy. Currently, MSC-Exo have shown enormous therapeutic potential as a safer and more efficient cell-free therapy in various aspects of clinical treatment, including cardiovascular diseases [27, 28], liver diseases [29, 30], kidney diseases [31, 32], lung diseases [33, 34]s, and neurological diseases [35, 36]. This review focuses on the research on the treatment of neurodegenerative diseases by exogenous MSC-Exo and their derivative products. However, at present, most studies tend to explore the mechanisms or treatment strategies of MSC-Exo for the symptoms related to brain aging caused by neurodegenerative diseases, while there are relatively few studies on the role of MSC-Exo in delaying physiological brain aging. Based on the fact that there is a correlation between the occurrence and development mechanisms of neurodegenerative diseases and aging, and MSC-Exo has shown great potential in the treatment of neurodegenerative diseases. Therefore, this paper aims to seek the possible correlative mechanisms for reversing physiological brain aging from the mechanisms of MSC-Exo in treating neurodegenerative diseases and explore the possibility of their realization.

Mesenchymal stem cells and their extracellular vesicles

Mesenchymal stem cells are multipotent stem cells originating from the mesoderm, present in various tissues including bone marrow, umbilical cord blood, adipose tissue, and placenta [37]. Since their first isolation from bone marrow in 1968, MSCs have been extensively studied [38]. Due to their strong multipotency and tissue regenerative properties, MSCs hold significant therapeutic potential in regenerative medicine [39]. Current research suggests that many of the therapeutic functions of MSCs are primarily attributed to the paracrine effects mediated by their derived secretory factors, such as tissue regeneration, antioxidative stress, anti-inflammatory, and antitumor effects [40–42]. These secretory factors are mainly released in the form of extracellular vesicles (Ev), and evidence has shown that MSC-Evs are crucial mediators of MSC efficacy. Using MSC-Evs can replicate the therapeutic potential of the parent cells and persist for a longer time, even if MSCs are rapidly cleared from the body, thereby demonstrating that MSCs' therapeutic effects are mediated through EVs [43, 44]. Additionally, since MSC-Evs cannot self-replicate, they can avoid

a series of adverse reactions associated with direct MSC cell therapy, including immune rejection, secondary infections, vascular embolism, and tumor proliferation [45].

Evs are primarily divided into three subtypes based on particle size: exosomes (30–200 nm), microvesicles (100–1000 nm), and apoptotic bodies (500–2000 nm). This review mainly focuses on exosomes. MSC-Exo have distinct characteristics and functions [46, 47], but their biogenesis pathways are largely similar. These pathways include early endosome (EE), intraluminal vesicle (ILV), late endosome (LE) and multivesicular body (MVB) formation and release (Fig. 1). The paracrine effects of MSCs are mediated through the release of Evs, which are transported via body fluids to distant sites or remain in the microenvironment. These Evs are then absorbed by target cells through ligand-receptor interactions, phagocytosis, or direct fusion with the plasma membrane, thereby participating in the regulation of target cell functions and signal transduction [48, 49]. Exosomes contain various bioactive molecules, such as proteins, RNA, DNA, and lipids [20]. Numerous neuroprotective factors have been identified within exosomes. For example, the endogenous catalase in MSC-Exos provides neuroprotection by reducing oxidative stress [50].

Isolation and characterization of MSC-Exo

Given that Exos contain numerous and complex components, efficient, high-purity, and high-quality separation and enrichment methods are particularly important. It is usually obtained by multi-stage centrifugation of the supernatant of MSC conditioned medium (CM) or by

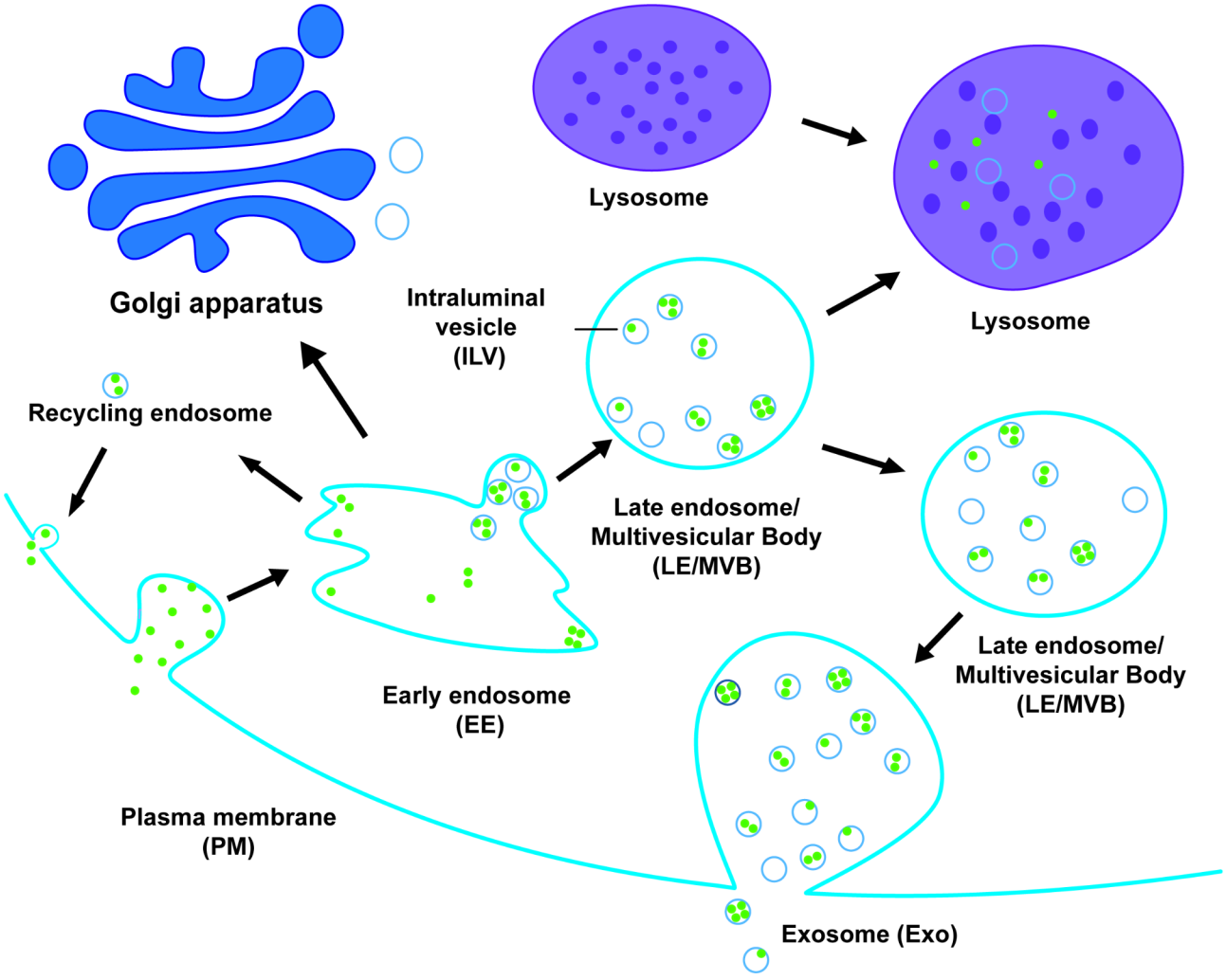

Fig. 1 The biogenesis of exosomes begins with the entry of molecular cargo into the cell, followed by initial sorting in early endosomes. Early endosomes, originating from plasma membrane budding, primarily function in classifying endocytosed cargo: recyclable cargo is returned to the Golgi apparatus or plasma membrane, while non-recyclable cargo progresses to late endosomes. During this process, membrane structures invaginate into the lumen, forming intraluminal vesicles (ILVs) that encapsulate cargo, giving late endosomes a multivesicular body (MVB) morphology. Ultimately, MVBs can either fuse with the plasma membrane to release ILVs as exosomes or fuse with lysosomes, leading to cargo degradation.

directly using a kit for separation. At present, a variety of conditioned media have emerged on the market and are used for MSC-Exo culture separation and clinical transformation of derivative products. Currently, the recognized methods for exosome isolation include differential ultracentrifugation, density gradient ultracentrifugation, ultrafiltration, size exclusion chromatography, antibody affinity capture, precipitation, and microfluidic separation. The most commonly used methods for exosome purification are ultracentrifugation (both differential and density gradient ultracentrifugation). Each of these separation techniques has its advantages and disadvantages, and the appropriate method can be selected based on specific needs and practical conditions [46, 51]. In recent years, many commercial kits for exosome isolation have been introduced. Compared to traditional separation techniques, these kits are less time-consuming, offer higher compatibility and yield, and can be used for various exosome isolation purposes [52].

Based on the physicochemical properties of Exo, characterization is mainly performed using techniques such as mass spectrometry (MS), dynamic light scattering (DLS), nanoparticle tracking analysis (NTA), transmission electron microscopy (TEM), tunable resistive pulse sensing (TRPS), flow cytometry (FCM), atomic force microscopy (AFM), confocal microscopy, Western blotting, and enzyme-linked immunosorbent assay (ELISA) to assess the size, morphology, and protein enrichment of the isolated Exo [53–55]. Exo can be secreted by various cell types, with markers such as CD63, CD9, and CD81. However, MSC-Exo exhibit heterogeneity, with characteristic markers including CD29, CD73, CD90, CD44, and CD105 [56, 57]. Different sources of MSC-Exos show slight variations in component and surface marker expression, but almost all human MSC-Exo contain CD44 and CD105, while CD90 is highly expressed in various mesenchymal stem cells (Fig. 2). Hematopoietic markers CD34 and CD45 have not been detected [46, 51].

The biological characteristics of MSC-Exo

Exosomes are extracellular vesicles with an average diameter of approximately 100 nm and a density of 1.13–1.19 g/mL, characterized by a lipid bilayer membrane structure. The lipid bilayer membrane encapsulates the contents of Exo, protecting them from degradation, and

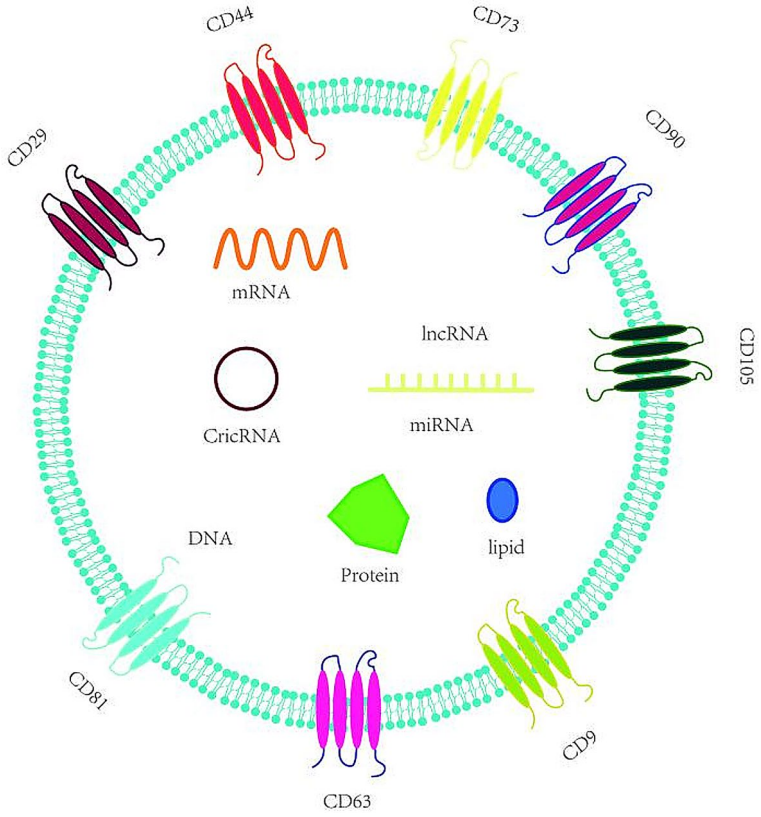

Fig. 2 Components and characterization of MSC-Exo. Exosomes have intrinsic markers such as CD63, CD9, and CD81. MSC-Exo possess characteristic markers including CD29, CD73, CD90, CD44, and CD105, with CD44 and CD105 being present in nearly all human MSC-Exo. Exosomes are a subset of the parent cell encapsulated by a lipid bilayer, containing specific bioactive molecules derived from the parent cell, such as proteins, RNA (mRNA, miRNA, long non-coding RNA, circular RNA), DNA, lipids, and other molecular components

its small size allows it to traverse biological barriers [58, 59]. Under the microscope, Exo exhibits a classic cup-shaped structure, while under transmission electron microscopy, it appears spherical in solution [60]. Exosomes are considered a subset of parent cells, carrying specific biologically active molecules derived from the parent cells, whose content and composition depend on the parent cells. However, due to sorting mechanisms, there are significant differences in the content of RNA between Exo and parent cells [60, 61]. These complex biologically active molecules loaded in Exo include proteins, mRNA, miRNA, long non-coding RNA, circular RNA, DNA, lipids, and other molecules (Fig. 2). Exo serves as functional carriers, transferring and releasing these biologically active molecules to participate in intercellular communication and genetic information exchange [62, 63]. Different specific cargoes (functional proteins or mRNA) exert different functions in various diseases and have certain therapeutic effects [64] (Table 1). For example, MSC-Exo alleviate bronchopulmonary dysplasia by releasing the immunomodulatory protein TSG-6 [65]; MSC-Exo, with high C-C motif chemokine receptor-2 (CCR2) expression, acts as a "decoy" by binding C-C motif chemokine ligand 2 (CCL2) to reduce its bioavailability, thereby inhibiting the recruitment and activation of peripheral monocytes/macrophages and alleviating renal ischemia-reperfusion injury in mice.[66]; Adipose-derived stem cells (ASCs) promote angiogenesis by secreting exosomes carrying miR-31 to endothelial cells [67]. Exo originating from Bone Marrow Mesenchymal Stem Cells (BMMSCs) are enriched with Integrin α5 (Itgα5), Neuropilin-1 (NRP1), and associated microRNAs, potentially modulating the synaptic vesicle cycle signaling pathways in AD and thus holding therapeutic promise [68]. Exosomes derived from human umbilical cord mesenchymal stem cells (hUC-MSCs) may modulate the synaptic vesicle cycle signaling pathway associated with AD by targeting protein complex 2 subunit alpha 1 (AP2A1) and adaptor-related protein complex 2 subunit beta 1 (AP2B1), showcasing their therapeutic potential [69]. Exosomes derived from MSCs of different sources have slightly different characteristics and play different essential functions. Therefore, their applications in clinical treatment of neurodegenerative diseases also vary [46, 64].

Table 1 Different cargos found in MSC-Exo and the diseases to be treated

Organ	Disease or process	Cargo
Heart	Myocardial infarction	miR-125b [70]
	Myocardial ischemia	miR-182 [71]
		miRNA-210 [72]
Brain	Alzheimer's disease	miR-146a [73]
		miR-29c-3p [74]
		miR-29b [75]
		AP2A1 and AP2B1 [69]
	Stroke	miR-17-92 [76]
		miR-210 [77]
		enkephalin [78]
	Neurological deficit	miR-214 [79]
Lung	COVID-19	miR-258 [80]
	Bronchopulmonary dysplasia	TSG-6 [65]
Kidney	Ischemia/Reperfusion - Induced Kidney Injury	CCR2 [66]
Liver	Experimental Autoimmune Hepatitis	miR-223 [81]
Uterus	Endometrial cancer	miR-499[82]

Abundant research has demonstrated that MSC-Exo possess characteristics derived from both MSCs and Exo themselves, including low toxicity, low immunogenicity, low tumorigenicity, long-term circulation, biodegradability, sustained release, tumor homing, tissue-specific homing, high permeability, biocompatibility, biological stability, encapsulation of endogenous biologically active molecules, and the ability to cross the blood-brain barrier (BBB) [51, 83, 84]. These properties lay the foundation for the clinical treatment of various systemic diseases with MSC-Exo and further expand their therapeutic potential. Compared to MSC cell therapy, nanoscale-sized Exo can avoid entrapment in the pulmonary capillary bed, reducing loss and risk, and after reaching the target organ, they are lodged in the small capillaries with high efficiency [85, 86]. Meanwhile, in comparison with MSC, MSC-Exo are unable to differentiate and express potentially immunogenic differentiation antigens. They possess lower biocompatibility and immunogenicity, and it is also safer to carry out modifications on them [20]. Furthermore, reducing their immunogenicity and biocompatibility has become a modification strategy, typically achieved through changes in culture conditions, engineering, selective packaging, pre-processing, etc [85]. Given the safety, circulatory stability, and targeting capability of MSC-Exo, they can serve as natural carriers for delivering drugs to treat neurological diseases. However, to meet the requirements of precision medicine, it is necessary to functionalize MSC-Exo, for example, by modifying the surface proteins of Exo or directly modifying parent cells to enhance their targeting and homing abilities, increase the half-life in circulation, and maximize the targeting of drugs to lesions [87, 88]. Through the engineering of exosomes to increase their cargo capacity for specific molecules, the delivery efficiency for therapeutics is thereby enhanced [89, 90]. Additionally, Exo engineering technology is also a direction for expanding their clinical applications, achieved by optimizing separation and acquisition methods or directly engineering artificial Exo to achieve large-scale production while ensuring safety and efficacy [84, 91]. Throughout this process, the pursuit of developing more efficient and accessible characterization

techniques to refine the large-scale manufacturing workflow has emerged as a prevalent research approach [92].

Among these properties, the unique property of MSC-Exo to cross the blood-brain barrier and migrate to the brain lesion area provides the possibility for direct treatment of neurological diseases or drug delivery. Regarding the specific mechanism of crossing, existing studies suggest that it may be the brain microvascular endothelial cells (ECs) that internalize and transport Exo across the BBB through endocytosis, only a small portion of exosomes (Exo) cross the blood-brain barrier (BBB) through the paracellular pathway [93](Fig. 3). Although Exo can be uniformly taken up by the brain, the uptake mechanisms of Exo from different sources are diverse and often nonlinear, possibly related to brain-to-blood efflux [94]. Additionally, the complex components in MSC-Exo, such as various proteins, cytokines, and genetic materials, synergistically function through different targeting pathways, which are more efficient compared to single mechanisms [85].

As a treatment tool for clinical precision medicine, the tissue distribution and targeting mechanisms of MSC-Exo are also one of the research focuses. Currently, brain drug delivery methods include intravenous injection, oral administration, stereotactic injection, nasal administration, etc. Different delivery methods have their own advantages and disadvantages in the treatment of brain diseases and also present specific tissue distribution patterns. Most studies use intravenous injection and find that MSC-Exo accumulate most in the heart, liver and spleen [93, 95]. The non-invasive method of intranasal administration allows Exo to bypass the BBB more specifically and effectively deliver to the brain and accumulate in the damaged brain area [96, 97]. However, there are currently no studies directly comparing their biological distribution and efficiency through different administration methods in the same model.

The function and clinical significance of MSC-Exo

Based on the above characteristics, significant progress has been made in research on the treatment of neurodegenerative diseases using MSC-Exo, including studies on mechanistic pathways, analysis of molecular factors, exploration of optimal treatment regimens, gene modification or knockout to alter protein expression, improvement of MSC-Exo packaging, pharmacokinetics, and tissue-specific distribution. MSC-Exo can serve as nanocarriers to deliver drugs or small molecules to improve cognitive deficits in Alzheimer's disease (AD) [98, 99]. MSC-Exo obtained from connective tissues such as bone marrow and adipose tissue can degrade Aβ peptides inside and outside brain cells or directly interact with Aβ to reduce the accumulation of the main pathogenic factor of AD in brain cells, while also exerting neuroprotective

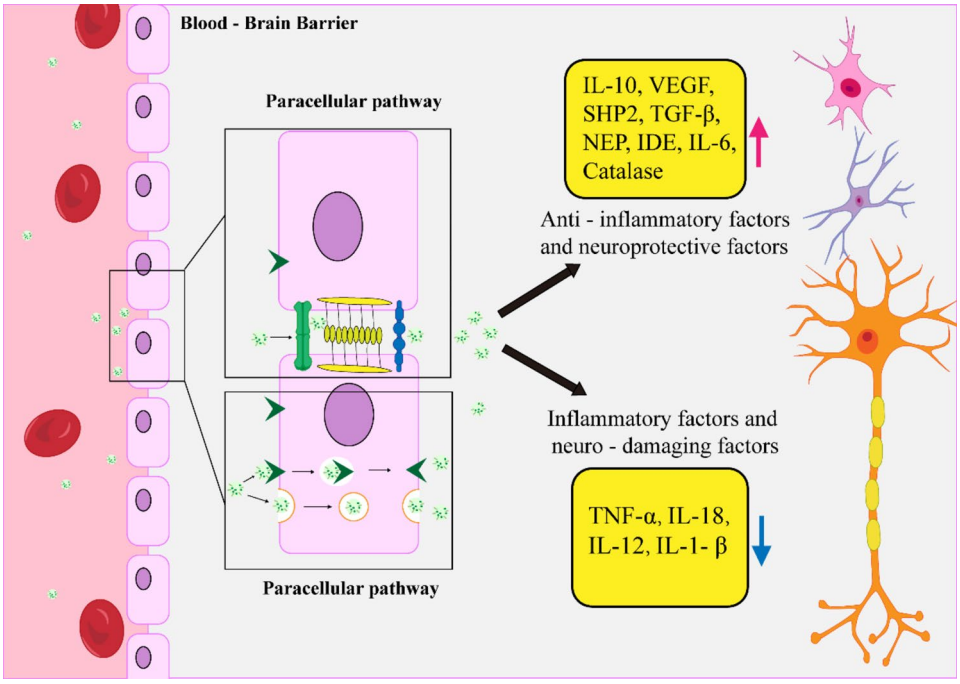

Fig. 3 MSC-Exo cross the blood-brain barrier (BBB) through endocytosis and internalization by brain microvascular endothelial cells (ECs) or via the paracellular pathway. The complex components within MSC-Exo mediate and regulate neuroprotective factors such as pro-inflammatory factors, anti-inflammatory factors, Aβ-degrading enzymes, as well as damaging factors, which target different nerve cells to exert their functions. Consequently, they can reduce Aβ deposition and oxidative stress, regulate neuroinflammatory responses, promote mitochondrial autophagy, and ultimately achieve the effect of treating neurodegenerative diseases

effects [100]. Transferring proteins or genetic materials (such as miRNA) carried by MSC-Exo into neurons to promote neural function recovery can be a potential therapeutic tool for Parkinson's disease (PD) [101].

Most research results have demonstrated the favorable therapeutic benefits of MSC-Exo and significant post-modification effects [102]. Mechanistic studies on treating AD suggest that MSCs block the damage to neurons caused by soluble amyloid-β oligomers (AβOs) by releasing Exo that upregulate levels of IL-6, IL-10, and VEGF, while releasing catalase to alleviate oxidative stress and protect neurons [103]. A fundamental pathological feature of AD is mitochondrial dysfunction, and dysfunctional mitochondrial autophagy further exacerbates AD by accumulating AβOs. Engineered MSC-Exo with high expression of tyrosine phosphatase-2 (SHP2), can promote mitochondrial autophagy, thereby blocking this critical mechanism of AD [104]. It has been proposed that in the process of AD, the integrity of the BBB is disrupted, which may be a prerequisite for MSCs to enter the brain and exert therapeutic effects [105]. However, under normal intact BBB conditions, MSCs do not directly contact neurons but can still be efficacious, possibly due to MSC paracrine effects and the internalization mechanism of brain microvascular endothelial cells (BMECs), whereby MSCs secrete Exo that can be internalized by BMECs [103] (Fig. 3). This internalization process occurs in both healthy and inflammatory BBB models but only results in specific targeting and long-term accumulation of MSC-Exo, particularly in diseased non-healthy BBB states, such as in brain inflammation pathological areas [93, 106]. Therefore, MSC-Exo can traverse the BBB of normal aging brains, laying the groundwork for studying the reversal of normal brain aging using MSC-Exo.

Studies have tracked the distribution of MSC-Exo in various models of neurodegenerative diseases and found that MSC-Exo migrate to inflammatory pathological brain areas and are specifically taken up by neurons, demonstrating the specific targeting homing ability of MSC-Exo, which provides the possibility of loading and delivering targeted drugs to brain lesion areas [106]. Meanwhile, there are studies on modifying MSC-Exo to improve their targeting homing ability. For example, exosomes derived from MSCs pre-treated with iron oxide nanoparticles (IONP) form magnetic nanovesicles (MNV). These can be magnetically guided to ischemic brain regions under an external magnetic field, and they carry a large amount of therapeutic growth factors produced by IONP stimulation. Compared to natural MSC-Exo, they exhibit higher targeting specificity and more significant efficacy [107]. Coupling the cyclic peptide (Arg-Gly-Asp-D-Tyr-Lys) [c(RGDyK)] to the exosome surface allows high-affinity binding to reactive brain vascular endothelial cells containing c(RGDyK) and integrin αvβ3, thereby targeting migration to the ischemic brain region [77]. One characteristic of MSC-Exo is their ability to encapsulate and deliver endogenous bioactive molecules. They contain various miRNAs and cytokines. Inducing the overexpression of one or more miRNAs and targeting their delivery to supplement key miRNAs lacking in diseases has become a current research hotspot. In the treatment of neurodegenerative diseases, overexpressing miR-188-3p in exosomes derived from adipose-derived stem cells (ADSC) targets NALP3 and CDK5 to inhibit autophagy and inflammation in PD model mice [108]. Intravenously infusing Interferon-γ (IFNγ) stimulated MSC-Exo (IFNγ-Exo) into experimental autoimmune encephalomyelitis (EAE) mouse models can reduce neuroinflammation and demyelination by decreasing pro-inflammatory factors, thereby improving the neurological dysfunction of EAE [85].

In terms of the treatment course, considering the relatively short half-life of MSC-Exo, most studies have adopted multiple intravenous injections at the affected sites [109]. The Exo complex after specific packaging has enhanced retention and targeting properties, is less likely to be cleared prematurely, and can reduce the number of injections [110, 111]. In the research on the treatment of Exo from miR-17-92 transfected MSCs in the mouse model of stroke, the researchers adopted the single tail vein injection method. The results indicated that Exo treatment could significantly promote the recovery of neurological function after stroke, and the efficacy of Exo transfected with miR-17-92 was even more remarkable [76]. In a few studies that have entered clinical trials, an ongoing research on the treatment of Alzheimer's disease with different doses of MSC-Exo adopts the method of multiple intranasal administrations for 12 consecutive weeks [51]. Therefore, there is currently no unified conclusion regarding the dosage, administration method, and treatment course of MSC-Exo. It may still be necessary to conduct further exploration based on different disease models, target organs, administration methods, experimental methods, and differences in Exo products. Some researchers have conducted investigations on this and suggested making judgments based on treatment effects rather than direct quantitative comparisons [112].

In conclusion, the research on cell-free therapy using MSC-Exo in neurodegenerative diseases has become a current hotspot, demonstrating remarkable potential. Therefore, MSC-Exo also have great potential in alleviating debilitation and delaying the aging process by reducing oxidative stress, mitochondrial damage, cell apoptosis, and inflammatory responses, while releasing active substances such as neuroprotective factors [113, 114].

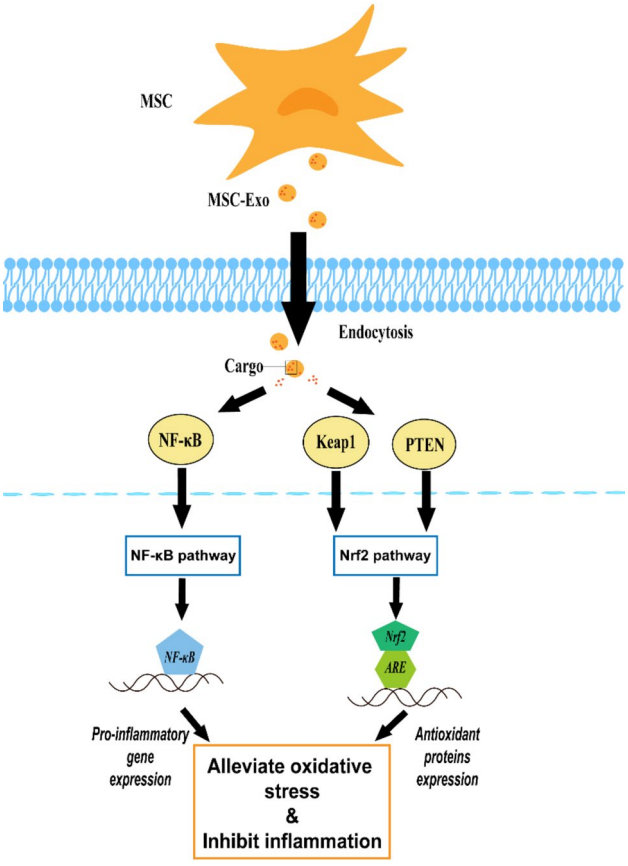

Fig. 4 MSC-Exo carry microRNAs (miRNAs), inflammatory factors and antioxidant factors. By activating the Nrf2 (up-regulation and nuclear translocation of Nrf2) and NF-κB (activation and translocation of NF-κB) signaling pathways, they enhance the anti-inflammatory and antioxidant capacities, thus playing a role in protecting neurons, delaying aging and treating neurodegenerative diseases

The potential mechanisms of MSC-Exo in neurodegenerative diseases and their association with brain aging

Currently, most research focuses on the therapeutic strategies of MSC-Exo in neurodegenerative diseases and the engineering strategies of MSC-Exo, while there is limited research on reversing normal brain aging with MSC-Exo to extend lifespan and improve quality of life. The studies have shown that EVs isolated from BMMSCs of young mice can reduce the expression of aging markers in naturally aged mice and Ercc1-deficient premature aging mice when administered via intraperitoneal injection, thereby prolonging the healthy lifespan of both naturally aged and premature aging mice. Similarly, EVs derived from human embryonic stem cell-derived mesenchymal stem cells (hESC-MSCs) also exhibit the same function. Meanwhile, the study found that aging can lead to MSC dysfunction, and Ev derived from young MSCs can reverse cellular aging and improve MSC functions, which provides a new idea for the selection of MSC sources [115]. This validates the potential of MSC-Exo in reversing aging, but it focuses on overall survival rates and aging markers rather than changes in brain aging and specific markers. Therefore, it is worth exploring the correlation and potential mechanisms of reversing natural brain aging with MSC-Exo based on the extensive research on MSC-Exo therapy for neurodegenerative diseases. Furthermore, another research strategy is to explore the mechanisms or methods of neuroprotection by MSC-Exo in neurodegenerative disease models. In the treatment of neurodegenerative diseases associated with astrocyte changes, MSC-Exo improves reactive astrogliosis, alleviates neuroinflammatory responses, regulates abnormal calcium signal transduction and mitochondrial dysfunction, and further restores learning and memory impairments caused by neuronal damage. It is suggested that the Nrf2 and NF-κB signaling pathway may be a potential mechanism of action [116]. Nrf2 is one of the key pathways in aging and neurodegenerative diseases, and it is also one of the targeted targets for the treatment of neurodegenerative diseases and the delay of aging based on antioxidant stress and neuroinflammation [117]. MSC-Exo is endowed with miRNA, inflammatory factors, and antioxidant factors. By activating the Nrf2 and NF-κB signaling pathway, it augments the anti-inflammatory and antioxidant capacities(Fig. 4), thereby playing crucial roles in protecting neurons, retarding aging, and treating neurodegenerative diseases [118, 119]. Additionally, microglia polarization induced by MSC-Exo from an inflammatory M1 phenotype to an immunosuppressive M2 phenotype leads to increased expression of related Aβ-degrading enzymes [such as neprilysin (NEP) and insulin-degrading enzyme (IDE)] and anti-inflammatory cytokines (such as IL-10 and TGF-β), and decreased expression of inflammatory cytokines (such as TNF-α, IL-18, IL-6, IL-12, IL-1β), thereby reducing inflammation and Aβ deposition [120]. In neurodegenerative diseases with vascular changes, MSC-Exo can promote angiogenesis [121, 122]. In summary, the mechanisms of neuroprotection by MSC-Exo can be summarized as inhibiting pathological processes and promoting regeneration. The former includes reducing damaged neurons, anti-apoptosis, immunomodulation, and reducing oxidative stress, while the latter includes promoting neurovascular regeneration and restoring the integrity of BBB, thereby improving motor, learning, and memory impairments caused by neurodegeneration [45, 123]. Combined with the research on aging mechanisms mentioned earlier, it can be observed that there is a high degree of overlap and correlation between the mechanisms of aging and the neuroprotective mechanisms of MSC-Exo in neurodegenerative disease models, indicating the enormous potential of applying MSC-Exo to reverse brain aging, but further research is still needed for validation.

Summary and Outlook

MSC-Exo, as a cell-free therapy alternative to MSCs, has shown great potential in neurodegenerative diseases, not only possessing the functions of parent cells but also avoiding the risks associated with MSC cell therapy. The multiple neuroprotective mechanisms of MSC-Exo hold promising prospects for reversing brain aging, offering hope for prolonging lifespan, delaying aging, improving inconvenience caused by neurodegeneration, and enhancing the quality of life for the elderly, further providing significant benefits to society in alleviating population aging.

Although the therapeutic effects of MSC-Exo in neurodegenerative diseases and even normal aging models have been validated, most studies are still at the stage of animal experiments, with many limitations and uncertainties in clinical trials. The treatment duration and follow-up period in most studies are not long. Depending on the size of the experimental animals and the type of diseases, the follow-up period of most preclinical trials usually ranges from one week to one month. There are also studies with a follow-up period of less than one week or as long as one year [53]. Only a few studies have entered clinical trials and proved its safety. However, the limitation of this study lies in the relatively small sample size [124]. Meanwhile, before the large-scale production or clinical translation of MSC-Exo, there are also no small challenges.

Firstly, there is a lack of standardized protocols and quality control regarding the characterization, quantity, size, purity, content, and drug delivery of MSC-Exo treatment. Variability may exist during large-scale production, leading to batch differences and non-reproducibility. Some researchers have successively proposed methods for the large-scale production of MSC and MSC-Exo that comply with GMP. The standardized protocols and corresponding supervision mechanisms will also be increasingly improved [125]. Before Exo - therapy is approved, a series of rapid, strict, and cost - effective methods can also be used for its quality control. Especially during large - scale production, these methods can serve as an alternative to animal testing and include fingerprint identification detection, potency determination, mechanism testing, and safety testing [126, 127]. Secondly, there is still a deficiency in the large - scale isolation and target - tracking of MSC-Exo. However, more and more markers are emerging, and many researchers and institutions are working on the development of high - yield and high - performance Exo isolation methods or reagent kits [125]. Finally, the issue of safety is an inescapable key point in clinical trials. During the treatment process, repeated administrations are required to determine the optimal clinical dose and treatment course, and it must be ensured that there are no biotoxicity and other risks in this process. However, relevant studies on MSC-Exo therapy have indicated that its short-term safety is good, and no safety risks such as tumorigenicity, immunogenicity, and gene mutations related to the parental cells (MSC) have been found yet [12, 128].

In addition, many studies have currently proven the short-term safety of MSC-Exo therapy, but there are relatively few studies and discussions on long-term safety and ethical issues [127]. Of course, it is a necessary process for researchers to conduct risk assessments, including short-term risks and long-term risks, namely the immune responses caused by allogeneic infusion and multiple injections, as well as the potential risks of epigenetic modifications to the host cells due to long-term use [126]. Therefore, if MSC-Exo is to truly become a safer and more efficient clinical diagnosis and treatment tool, it still requires in-depth research by expert researchers in this field over a long period of time to identify and solve many potential problems.

Abbreviations

MSC	Mesenchymal stem cell
Exo	Exosome
OA	Osteoarthritis
EV	Extracellular vesicle
EE	Early endosome
ILV	Intraluminal vesicle
LE	Late endosome
MVB	Multivesicular body
MS	Mass spectrometry
DLS	Dynamic light scattering
NTA	Nanoparticle tracking analysis
TEM	Transmission electron microscopy
TRPS	Tunable resistive pulse sensing
FCM	Flow cytometry
AFM	Atomic force microscopy
ELISA	Enzyme-linked immunosorbent assay
CM	Conditioned medium
CCR2	C-C motif chemokine receptor-2
CCL2	C-C motif chemokine ligand 2
ASCs	Adipose-derived stem cells
BMMSCs	Bone Marrow Mesenchymal Stem Cells
Itgα5	Integrin α5
NRP1	Neuropilin-1
AP2A1	Protein complex 2 subunit alpha 1
AP2B1	Adaptor-related protein complex 2 subunit beta 1
BBB	Blood–brain barrier
ECs	Endothelial cells
AD	Alzheimer's disease
PD	Parkinson's disease
AβOs	Amyloid-β oligomers
SHP2	Tyrosine phosphatase-2
BMECs	Brain microvascular endothelial cells
IONP	Iron oxide nanoparticles
MNV	Magnetic nanovesicles
c(RGDyK)	Arg-Gly-Asp-D-Tyr-Lys
ADSC	Adipose-derived stem cells
IFNγ	Interferon-γ
EAE	Experimental autoimmune encephalomyelitis
hESC-MSCs	Human embryonic stem cell-derived mesenchymal stem cells
NEP	Neprilysin
IDE	Insulin-degrading enzyme

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Author contributions
ZGH conceived and Conceptualization, supervision, writing—review and editing. LQ designed the search strategy and conducted the literature search. QJL investigated, drafted the manuscript, prepared the tables and figures — original draft. All authors reviewed the manuscript.

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Data availability
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Declarations

Conflict of interest
There is no conflict of interest in this article.

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