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REVIEW

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Advances in mesenchymal stem cell and exosome-based therapies for aging and age-related diseases

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Abstract

Mesenchymal stem/stromal cells (MSCs) and their exosomes (MSC-Exos) have great potential for tissue repair and regenerative medicine, which can improve the symptoms and prognosis of aging-related diseases and potentially slow the aging process through multiple pathways. This comprehensive review summarizes the characterization of MSCs and MSC-Exos from various tissue sources and their applications in treating diseases associated with aging, such as premature ovarian failure (POF), Alzheimer's disease (AD), atherosclerosis (AS), and osteoporosis (OP). MSCs exert therapeutic effects through multiple mechanisms, including differentiation into various cell types, secretion of bioactive molecules, and immune response regulation. MSC-Exos, which contain a diverse array of proteins, miRNAs, and other biomolecules, can deliver MSC-derived bioinformatics to target cells and demonstrate comparable therapeutic benefits to MSCs. This review highlights the signaling pathways and molecular mechanisms underlying the therapeutic efficacy of MSCs and MSC-Exos in age-related diseases, and further discusses the importance of MSC and MSC-Exo tissue source selection for specific disease applications and the potential of combination therapies and preconditioning strategies to enhance their therapeutic outcomes. Despite promising preclinical and clinical results, challenges such as uneven distribution, in vivo environmental maladaptation, apoptosis, and immune responses need to be addressed before widespread clinical application. Future research requires multidisciplinary collaboration to further elucidate the mechanisms of action and develop optimized therapeutic strategies for the prevention and treatment of age-related pathologies using MSCs and MSC-Exos.

Keywords Mesenchymal stem/Stromal cells, Exosomes, Aging-related diseases, Cell therapy

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Introduction

Aging is a complex and multifaceted process that encompasses a decline in the function of tissues and organs in multicellular organisms, often culminating in the onset of chronic diseases. For an extended period, researchers have posited that aging is intrinsically linked to a spectrum of chronic diseases. The likelihood of developing conditions such as diabetes, Alzheimer's disease (AD), premature ovarian failure (POF), cardiovascular disease, osteoporosis (OP), and osteoarthritis(OA) increases [1]. Over the past several decades, significant strides have been made in prolonging the healthy lifespan of model organisms through diverse interventions, including dietary modifications, physical exercise, genetic alterations, and pharmacological treatments (such as metformin, NAD + precursors, rapamycin, etc.) [2]. However, the efficacy of these approaches in mitigating adverse outcomes in patients with age-related diseases remains to be established, and their utility is a subject of ongoing debate. In contemporary biomedical research, stem cell therapy is a pioneering strategy in the fields of tissue engineering and regenerative medicine. Accumulating evidence has highlighted the unique properties and therapeutic potential of MSCs and their secreted exosomes, suggesting their promising role in the management of aging and frailty-related diseases. Studies have revealed that MSCs derived from different tissues exhibit distinct biological attributes that dictate their clinical applications. Moreover, the composition, bioactivity, and secretion of exosomes by MSCs can differ depending on their tissue origin. Therefore, it is particularly important to explore the clinical applications of different MSC sources and their exosomes in age-related diseases. In this review, we delineate the characterization of MSCs and MSC-Exos, highlighting the potential mechanisms and therapeutic applications of MSCs and their exosomes in the treatment of diseases associated with aging.

Aging in general

Population aging is a major problem facing the world today, with the number of people aged 60 years and over expected to double worldwide by 2050. Aging is an intricate biological phenomenon characterized by the progressive deterioration of an organism's structure and function over time. Unraveling the molecular mechanisms underlying aging from the cellular to organismal level has emerged as a critical area of scientific inquiry, as aging is a pivotal risk factor for numerous chronic diseases. Insights into the molecular basis of aging can pave the way for strategies aimed at delaying the aging process, enhancing age-related phenotypes, and fostering healthier and longer lifespans. Recently, López-Otín et al. [3] provided a comprehensive and updated analysis of aging mechanisms, delineating 12 hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of protein homeostasis, macroautophagy dysfunction, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and ecological dyshomeostasis. They elucidated the primary, integrative, and antagonistic phases of aging and highlighted the interconnected nature of these hallmarks. Given the multifaceted and individualized nature of aging, the development of biomarkers capable of quantifying molecular impairments associated with aging and declining clinical function is critical. The concept of biomarkers for aging has been introduced in the scientific literature to identify and evaluate interventions that promote human longevity. The effectiveness of anti-aging intervention strategies was evaluated using these markers. Mahdi Moqri and co-workers [4] have categorized aging biomarkers into three broad domains: molecular, physiological, and digital. Molecular biomarkers include omics data and specific molecules; physiological biomarkers encompass functional performance and physical attributes; and digital biomarkers are gathered using wearable and non-wearable technologies. Researchers have validated these biomarkers, demonstrating their utility and potential significance in aging research, and have charted a course for future investigations and applications of such biomarkers.

Basic characteristics of MSCs and MSC-exosomes

MSCs originate from the mesodermal layer and are characterized by their multipotent nature and ability to self-renew and differentiate into various cell types. Initially discovered in the bone marrow, MSCs have since been identified in a plethora of tissues, including the umbilical cord, adipose tissue, umbilical cord blood, dental pulp, placenta, amniotic membrane, perivascular tissue, synovial membrane, and others. In 2006, the International Society for Cellular Therapy (ISCT) established minimum criteria for defining human MSCs. These criteria include the plastic adherence of MSCs and the expression of specific surface markers: positivity for cluster of differentiation 73(CD73), CD90, and CD105, and negativity for CD14, CD19, CD34, CD45, and human leukocyte antigen-DR (HLA-DR). Functionally, MSCs can differentiate into mesodermal derivatives, such as bone, cartilage, adipose, tendon, and connective tissue cells [5]. Their homing ability, facilitated by the high expression of CD44, CXC chemokine receptor type 4(CXCR4), and CXCR7, enables them to navigate damaged tissues, where they exert anti-inflammatory and reparative effects [6]. Additionally, the low expression of major histocompatibility complex class I (MHC-I) antigens and the absence of MHC-II antigens under normal conditions confer low immunogenicity, lack of tumorigenic risk, and

address ethical concerns, underscoring their strong economic value [7]. The primary mode of action of MSCs is through paracrine signaling, involving the secretion of a diverse array of cytokines and soluble factors, including microvesicles, exosomes (with a diameter of 30–150 nm), and apoptotic bodies, which collectively promote anti-inflammatory, antifibrotic, antioxidative, immunomodulatory, angiogenic, tissue regenerative, and repair processes [8]. Among them, MSC-Exos are instrumental in intercellular communication, transferring genetic material and functional proteins from MSCs to target cells, thereby influencing their behavior. The ExoCarta Exosome database contains over 9,000 proteins and 3,400 RNAs associated with exosomes. Notably, some studies suggest that exosomes released by MSCs may serve as an alternative to MSC-based treatments, reducing adverse reactions and eliminating the risk of pulmonary embolism associated with cell administration, thereby playing a significant role in various injury and disease models [9]. As shown in (Fig. 1). MSCs and exosomes exert anti-aging effects through various pathways and mechanisms, such as anti-apoptosis, oxidative stress, and promotion of autophagy, and could be used as innovative therapeutic approaches for preventing or even reversing aging-related diseases.

MSCs from different sources for treating age-related diseases

In recent years, the anti-aging effects of MSCs have been extensively studied. The anti-aging mechanisms of MSCs can be divided into three categories. (1) Promote cell repair and regeneration: MSCs can differentiate into various cell types to replace damaged or aging cells and repair tissue functions. (2) Regulation of

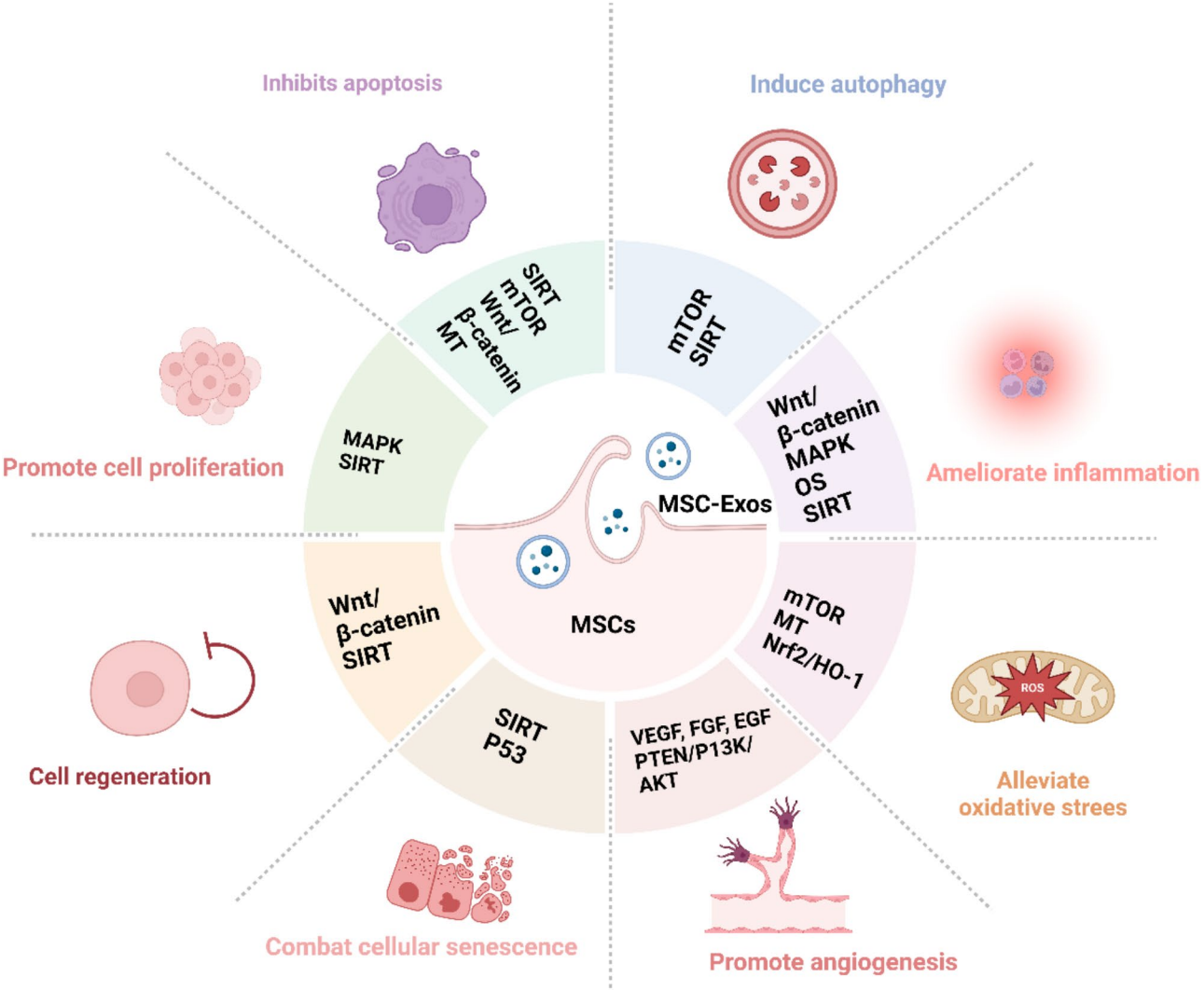

Fig. 1 Anti-aging mechanism of mesenchymal stem cells (MSCs) and their derived exosomes (MSC-Exos). OS: Oxidative stress; MT: Mitochondrial transfer; VEGF: Vascular endothelial growth factor; FGF: fibroblast growth factor; EGF: Epidermal growth factor. Created using BioRender.com

immune response: MSCs can regulate the immune system, immune response, reduce inflammation, and delay the aging process. (3) Secretion of bioactive molecules: MSCs can secrete a variety of bioactive molecules, such as growth factors and cytokines, which can stimulate cell health and delay aging (Table 1). Studies have demonstrated that infusing young stem cells into aging mice enhances their lifespan and longevity. In addition, transplanted MSCs can promote the repair of damaged tissues by differentiating into various tissue cells, expressing antioxidant enzymes to remove free radicals, and carrying the Bmi-1 gene to inhibit molecules associated with aging, which delays the aging process in Bmi-1 deficient mice [10]. Therefore, MSC have great potential to delay the aging process and treat age-related diseases. In the future, we will explore the mechanisms and applications of MSCs in the treatment of age-related diseases.

Premature ovarian failure

POF is a condition in which a woman's ovaries decline before the age of 40, leading to a drop in estrogen levels, which can lead to a host of health problems. MSCs have made significant progress in the treatment of POF, offering new hope for the treatment of this disease that plagues women. Numerous experiments have demonstrated that MSCs are effective in treating POF by increasing follicle numbers, improving hormone levels, reducing granulosa cell (GC) apoptosis, and promoting angiogenesis. MSCs significantly promote the recovery of ovarian function in various ways, such as by enhancing ovarian function by regulating the AMPK/NR4A1 signaling axis, TGF-β1/Smad3 signaling pathway [11], Wnt/β-catenin and Hippo signaling pathways [12]. MSCs can also reduce apoptosis through a mitochondrial mechanism mediated by NR4A1, reduce oxidative stress, and inhibit excessive autophagy in ovarian GCs by regulating the AMPK/mTOR pathway [13, 14]. Additionally, UC-MSCs transfected with miRNA21 further enhanced their therapeutic potential by inhibiting the PTEN/AKT/FOXO3a signaling pathway [15]. Meanwhile, the UC-MSC subpopulation with high LRP1 expression was able to secrete a variety of factors, such as chemokines, cytokines, and growth factors, after transplantation to regulate the extracellular matrix and NAD metabolism of oocytes, as well as the mitochondrial function of GCs, which significantly enhanced the improvement of ovarian function [16]. Autologous AD-MSCs can also improve oocyte quality and fertility in aged mice via mitochondrial transfer [17]. There are three main transplantation methods for MSC treatment of POF: intravenous, ovarian, and abdominal injections. Injection of both UC-MSCs and AD-MSCs improved the function of aging ovaries, and AD-MSCs were superior to UC-MSCs in promoting granulosa cell proliferation, increasing ovarian weight, and promoting angiogenesis. Intravenous injection of UC-MSCs is more effective than intraovarian injection in improving the functional and structural parameters of the ovaries [18]. Moreover, MSCs have been found to be located in the interstitial region of ovarian tissue rather than in follicles, and repair ovarian decay through paracrine mechanisms rather than differentiation into germ cells [19]. Nevertheless, this may not be the only approach, because Yue Ling et al. noted that MSCs injection was more effective than MSC conditional medium in alleviating ovarian injury and restoring ovarian function [20]. These findings provide a solid experimental basis for the use of MSCs in the treatment of ovarian aging.

Because MSCs face a challenging environment of hypoxia and chronic inflammation when transplanted into damaged tissues, preconditioning and combination therapies have also become popular treatment options. Crosslinked hyaluronic acid binds to hUC-MSCs to activate the PI3K-AKT pathway via HGF, promoting follicle survival and enhancing ovarian function [21]. The application of melatonin can enhance the therapeutic effect of autologous AD-MSCs, preserve the ovarian function of POF mice, and play a role through the SIRT6/NF-κB signaling pathway [22]. Drug-free in vitro activation (IVA) technology combined with 3D bioprinting-engineered ovaries significantly improves the retention of AD-MSCs and promotes cell differentiation into vascular endothelial cells, thereby enhancing angiogenesis [23]. In addition, for the first time in a clinical study, engineered MSC were used to treat POF. In this study, human umbilical cord blood mesenchymal stem cells (hUC-MSCs) combined with collagen scaffolds were transplanted into the ovaries of patients to activate the growth of original follicles and improve ovarian function and fertility [24].

At the same time, although there are few clinical trials of MSC treatment for POF, it is worth noting that some clinical studies have reported positive results. A study found that when BM-MSCs were injected into the right ovary of patients with POF, there was a 50% reduction in FSH values and a 30% increase in AMH and estradiol levels at 18 months (NCT02696889). To date, MSC transplantation has mainly been performed by intravenous or intraovarian injection in clinical trials, and there is no consensus on the optimal dose, transplantation route, and timing. Further research is required to confirm this hypothesis.

Alzheimer's disease

Aging is a major risk factor for neurodegenerative diseases. AD is a progressive neurodegenerative disease characterized by neuronal loss and cognitive decline. MSCs have emerged as promising candidates for the treatment of neurodegenerative diseases, including AD.

Table 1 Exploitations of MSCs in aging-related diseases

Disease	Source	Animal model	Precondition	Route Dosage/cells	In vitro model	Follow-up period	Effects	Ref.
weakness	mAM-MSC	*Bmi-1*$^{-/-}$ mouse model		IP 1×10^7		21 days	AM-MSC transplantation improved the premature aging phenotype in Bmi-1-deficient mice	[10]
POF	hUC-MSC	CDDP induced POF rat model		IV			AMPK/NR4A1 signaling pathway is involved in the recovery of ovarian function and tissue fibrosis	[11]
POF	rBM-MSC	Y Radiation-induced POF rat model		IV 2×106		2 weeks	BM-MSCs upregulate the expression of FOXO1, GDF-9, and Fst genes, downregulate TGF-β, and simultaneously epigenetically upregulate the Wnt/β-catenin and Hippo signaling pathways.	[12]
POF	hUC-MSC	CDDP induced POF rat model		IV 1×10^6	TIC	1 week	hUC-MSCs improve ovarian function in POF rats by regulating NR4A1-mediated mitochondrial mechanisms to inhibit TICs apoptosis	[13]
POF	hUC-MSC	CTX induced POF rat model		IV 1×10^6	GCs	28 days	hUC-MSCs can alleviate the over-autophagy of ovarian GCs through paracrine VEGFA, regulate the PI3K/AKT/mTOR signaling pathway, and thus improve the ovarian function of POF	[14]
POF	hUC-MSC	ZP3 induced POF mouse model	Transfer MicroRNA 21	IV 1×10^6		1 week	miR-21 can improve the recovery of ovarian function in UC-MSCs transplanted POF mice, possibly by inhibiting the PTEN/AKT/FOXO3a signaling pathway and up-regulating the circulation of CD8 + CD28-T cells	[15]
POF	hUC-MSC	Naturally aged mice / CTX induced POF mouse model	LRP1 high subset MSCs	OV 1×10^6	GCs	3 Weeks	UC-MSCs with high LRP1 subgroup can improve oocyte quality in aged mice mainly through DNA damage pathway, extracellular matrix related signaling and cell metabolism regulation	[16]
POF	hUCMSC/ hAD-MSC	Naturally aged mouse model		OV 3.5×10^5		3 Weeks	AD-MSCs had better effect on improving ovarian function than UC-MSCs	[18]
POF	hBM-MSC	CTX induced POF mouse model		OV 5×10^5		4 weeks	Intrarenal transplantation of hBM-MSCs may be a safe stem cell-based therapy	[19]
POF	hUC-MSC	VCD induced POF mouse model/ Naturally aged mouse model	hyaluronic acid and hypoxia	OV 1×10^5		14 days	Hyaluronic acid is an excellent cellular scaffold for improving the efficiency of UC-MSCs in the treatment of ovarian senescence under physiological and pathological conditions	[21]
POF	mAD-MSC	CTX induced POF mouse model	MT	OV 1×10^6		1 week	MT enhances the therapeutic effect of AD-MSCs, and SIRT6/NF-κB signaling pathway may be a potential therapeutic mechanism for AD-MSCs to treat POF	[22]
POF	hAD-MSC	CTX-induced POF rat model	3D bioprinted engineered ovaries	Back sides 1×10^7		4 weeks	3D bio-printed engineered ovaries composed of drug-free IVA and hAD-MSCs improve hAD-MSCs retention and revascularization in grafts	[23]
POF	hUC-MSC	Naturally aged mice	Collagen scaffold	MI 5×10^6		1year	Collagen /UC-MSCs transplantation may provide an effective treatment for POF	[24]
AD	hUC-MSC	5XFAD mice		coculture	Neural stem cell		hUC-MSCs induce neurogenesis through activin A	[25]
AD	hUC-MSC	SAMP8 mice		IP 5×10^6		8 weeks	HGF mediated HUC-MSC-induced functional recovery of AD model improved	[28]

Table 1 (continued)

Disease	Source	Animal model	Precondition	Route Dosage/ cells	In vitro model	Follow-up period	Effects	Ref.
AD	rBM-MSC	AlCl3 induced rat model		IV 1×10^6		1 month	BM-MSCs have neuroprotective potential, capable of enhancing autophagy and inhibiting proteopathy, while also promoting neurogenesis to replace damaged neurons	[29]
AD	hUC-MSC	APP/PS1 transgenic AD mouse model	MG53 protein	IV 1×10^6		28 Days	MG53 can restore the vitality of aging hUC-MSCs by activating Nrf2 signaling pathway, and combine with hUC-MSCs to treat AD	[31]
AD	hUC-MSC	APP/PS1 transgenic AD mouse model	Resveratrol	IV 1×10^6		2 months	hUC-MSCs and resveratrol have cumulative effects on neurotrophic factor secretion, neurogenesis, nerve cell survival and apoptosis, and SIRT1 signaling in the hippocampus of AD mice	[32]
AD	rAD-MSC	Intrahippocampal infusion of Aβ induces AD in a rat model	DMF	hippocampus			Pretreatment of AD-MSCs with DMF improves therapeutic efficacy	[33]
AS	Rabbit AD-MSC	high-fat diet constructed AS rabbit model		IV 6×10^6		3 months	Allograft AD-MSCs can be transported to atherosclerotic aortic plaque and inhibit ox-LDL uptake, inflammatory response and endothelial injury	[34]
AS	mAD-MSC	high-fat diet constructed AS rat model		IV 5×10^6		3 weeks	AD-MSC transplantation can inhibit vascular inflammation and endothelial dysfunction by inhibiting the NF-κB pathway in AS rats.	[35]
AS	mAD-MSC	D-gal induces transgenic FVB mouse model	NapFF-NO	NA 2×10^7		1 month	NapFF-NO hydrogel significantly improved the therapeutic effect of AD-MSCs on myocardial infarction by increasing cell implantation and paracrine effect of angiogenesis.	[37]
AS	hAM-MSC	high-fat diet-induced as mouse model		IV 5×10^5		10 weeks	hAM-MSC treatment can effectively reduce immune response	[38]
OP	mBM-MSC	OVX induced OP mouse model		IV 1×106		4 weeks	BM-MSCs can induce T cell apoptosis	[40]
OP	hDP-MSC	OVX induced OP rat model		IV 1×10^6		2 months	DP-MSCs demonstrate the best therapeutic efficacy in treating OVX-induced OP compared to AD-MSCs, UC-MSCs, and AM-MSCs	[41]
OP	hDP-MSC	OVX induced OP mouse model		IV 2×10^6		56 days	hDP-MSCs-produced CD39 regulates the balance between osteoclasts and osteoblasts in OP through the Wnt/β-catenin signaling pathway	[42]

Table 1 (continued)

Disease	Source	Animal model	Precondition	Route Dosage/ cells	In vitro model	Follow-up period	Effects	Ref.
Aging skin	hUC-MSC	Skin aging model of nude mice		SC 2×10^6	HDFs		hUC-MSCs provide new insights into the anti-aging efficacy and paracrine mechanisms of the skin	[43]
Aging skin	hAD-MSC			Coculture	HDFs/ HaCaTs		AD-MSCs combat skin photoaging in vitro by activating dermal fibroblast proliferation, antioxidant effect, and matrix metalloproteinases reduction	[44]

hUC-MSC: human umbilical cord-derived mesenchymal stem cells; mUCMSCs: mouse umbilical cord-derived mesenchymal stem cells; hAD-MSC: human adipose-derived mesenchymal stem cells; mAD-MSC: mouse adipose-derived mesenchymal stem cells; rAD-MSC: rat adipose-derived mesenchymal stem cells; hBM-MSC: human bone marrow-derived mesenchymal stem cells; mBM-MSC: mouse bone marrow-derived mesenchymal stem cells; rBM-MSC: rat bone marrow-derived mesenchymal stem cells; hAM-MSCs: human amniotic membrane-derived mesenchymal stem cells; mAM-MSCs: mouse amniotic membrane-derived mesenchymal stem cells; hDP-MSCs: human dental pulp-derived Mesenchymal Stem Cells;

POF: Premature Ovarian Failure; AD: Alzheimer's Disease; AS; atherosclerosis; OP: osteoporosis; CTX: cyclophosphamide; CDDP: Cisplatin; OVX: Oophorectomy; SC: subcutaneous injection; IV: Intravenous Injections; IM: Intramuscular injection; OV: Ovarian Injection; IP: Intraperitoneal injection; VCD: 4-vinylcyclohexene diepoxide; HDFs: Human dermal fibroblasts; TEC: Thymus epithelial cells; TIC: Theca interstitial cells; GCs: Granulosa cells; MT; Melatonin; DMF: Dimethyl fumarate; HDFs: Human dermal fibroblasts; NA: Not Applicable

By activating microglia, they can improve the deposition of Aβ plaques in the hippocampus and neocortex, reduce necrotic apoptosis and neuronal damage, and alleviate neuropathological defects in AD. MSCs primarily play a role in paracrine mechanisms. For example, UC-MSCs release activin A to promote nerve cell differentiation and axonal growth [25] and can transfer mitochondria to neural stem cells to protect them from the neurotoxicity of cisplatin treatment [26]. Mitochondrial dysfunction plays an important role in the pathogenesis of AD, and mitochondrial transfer via tunnel nanotubes (TNT) is an interesting mechanism. Two nasal administrations of cisplatin-induced mice with mitochondria isolated from MSCs restored executive function, work, and spatial memory. Mitochondria derived from MSCs may have higher antioxidant activity, helping to lower free radical levels and thus reduce oxidative stress in neurons [27]. Jia et al. revealed that the core functional factor secreted by UC-MSCs, hepatocyte growth factor (HGF), regulates tau protein phosphorylation through the cMet-AKT-GSK3β pathway and reverses neuronal dendrite loss, thereby enhancing synaptic plasticity in the hippocampus and promoting cognitive recovery [28]. By secreting various cytokines, such as IL-10 and TGF-β, BM-MSCs activate autophagy-related signaling pathways, such as the PI3K/Akt/mTOR pathway. They also directly interact with neurons to release SDF-1 and activate neuronal autophagy [29], which can regulate M1/M2 polarization of microglia and inhibit neuroinflammation. Abozaid et al. first proposed a neuroprotective mechanism for BM-MSCs. They believed that BM-MSCs improved neurogenesis by upregulating SIRT1 gene and protein levels, downregulating miR-134 expression, and inhibiting GSK3β activity, which promoted neurite growth and synaptic loss [30]. Although these mechanisms show promise for AD treatment, their exact mechanisms of action require further investigation. Co-culture and preconditioning of MSCs are also suitable for AD treatment. UC-MSCs pretreated with the Mitsugumin53 protein (MG53) enhanced the therapeutic effect in AD mice. The MG53 protein can also activate the Nrf2 signaling pathway in AD mice and synergistically enhance the therapeutic effect of UC-MSCs [31]. Resveratrol, as a SIRT1 (sirtuin family member) activator, can bind to UC-MSCs to regulate the expression of SIRT1, PCNA, p53, AC-p53, p21, and p16 in the hippocampus. This combination treatment was more effective in neuroprotection in AD mice than any single treatment [32]. Melatonin-and dimethylfumaric acid-pretreated AD-MSCs enhanced their therapeutic efficacy in AD brain tissue [33].

Over the past few years, several clinical trials have evaluated the use of MSCs in clinical studies of AD. In the United States, a study of 33 patients with AD explored intravenous BM-MSCs, which were safe to treat but did not significantly improve cognitive performance [NCT02600130]. Another 21-patient trial using AD-MSCs was limited by its small sample size [NCT03117738]. A Korean study attempted intracerebroventricular infusion of UCB-MSCs in 46 patients, and its safety was confirmed; however, its efficacy remains unclear [NCT02054208]. More trials are currently underway or planned, including those involving different sources of MSCs and different injection modes. Although most clinical trials have demonstrated the safety of MSC therapy, its efficacy remains unclear.

Atherosclerosis

AS is a chronic inflammatory disease that mainly manifests as lipid deposition, inflammation, fibrous tissue proliferation, and calcification in the inner layer of the arterial wall, eventually leading to thickening of the blood vessel wall and narrowing of the vascular lumen.

Transplantation of AD-MSCs inhibited the formation of atherosclerotic plaques and lowered blood lipids and attenuated plaque formation in the early stages of AS by inhibiting oxidized LDL uptake, apoptosis, inflammatory responses, repairing impaired endothelial damage, and promoting macrophage polarization toward anti-inflammatory phenotypes [34]. After AD-MSC transplantation, AD-MSCs inhibited the expression of the NF-κB signaling pathway, thereby reducing vessel wall inflammation and ameliorating endothelial dysfunction [35]. Kaiming Liu et al. also found that BM-MSCs could transfer mitochondria between human umbilical vein endothelial cells via TNT structure [36], which protects endothelial cells from apoptosis and repairs damaged vascular endothelial cells. Therefore, mitochondrial transfer of MSCs may be a good therapeutic strategy for the treatment of cardiovascular diseases. Additionally, in a combination therapy study, co-transplantation of NapFF-NO hydrogel with AD-MSCs enhanced the secretion of angiogenic factors VEGF and SDF-1α by AD-MSCs, which significantly improved therapeutic efficacy [37]. Injecting AM-MSCs into the tail vein of mice with AS can also reduce the accumulation of macrophages, inhibit aortic inflammation, and regulate the levels of TNF-α, IL-10, and other cytokines through the NF-κB pathway, thereby participating in AS treatment [38].

In clinical trials, a retrospective analysis of 78 patients with atherosclerosis treated with AD-MSC found that HDL, LDL, and RLP-cholesterol levels significantly improved. The study also confirmed that autologous reinfusion is safe and effective and can be used as an adjuvant treatment for AS [39].

Osteoporosis

OP is one of the most prevalent bone diseases worldwide and affects the elderly, particularly postmenopausal females. As the balance of bone remodeling is disrupted, bone mass is reduced, and the microstructure of bone tissue is degraded, leading to an increased risk of OP. Marrow cavities and intravenous transplantation are common methods of MSC therapy for OP. As early as 2002, it was demonstrated that the injection of allogeneic BM-MSCs into the marrow cavity could prevent OP. Subsequent studies have validated this finding in various animal models of OP, including rats, rabbits, and goats. This was demonstrated by significant increases in bone density, trabecular volume, trabecular number, trabecular thickness, percentage of trabecular area, and trabecular spacing, as well as increased serum levels of osteogenic markers, such as calcium, alkaline phosphatase, and osteocalcin. Sui BD et al. [40] also discovered that BM-MSC transplantation led to a decrease in TNF-α levels and T cell apoptosis. This suggests that BM-MSCs may play a crucial role in OP treatment through their immunosuppressive function of inducing T-cell apoptosis. Dental pulp-derived mesenchymal stem cells (DP-MSCs) have been demonstrated to possess a stronger osteogenic capacity than BM-MSCs. The invasiveness of BM-MSCs limits their clinical applications. Chuncai Li and others found that DP-MSCs have the best efficacy in treating ovariectomy-induced OP compared to AD-MSC, UC-MSC, and AM-MSC, mainly through paracrine and immunomodulatory mechanisms, including regulating Th17/Treg cell balance and macrophage polarization, and affecting bone metabolism-related cytokine levels [41]. At the mechanistic level, Wu et al. demonstrated that DP-MSCs produce CD39, which regulates the balance between osteoclasts and osteoblasts in OP through the Wnt/β-catenin signaling pathway [42].

To date, clinical trials on MSC transplantation for OP have focused on using autologous cells. A phase I uncontrolled, open-label clinical trial of intravenous infusion of autologous fucosylated BM-MSCs for the treatment of patients with established OP was conducted at the Clinico Virgen de la Arrixaca Hospital in Spain; however, no results have been reported [NCT02566655].

Skin aging

Skin aging is one of the most intuitive manifestations of aging, and in skin aging research, MSCs have been found to be effective in combating it. By promoting epidermal stem cell proliferation, collagen synthesis, and angiogenesis, MSCs reduce the production of matrix metalloproteinases while inhibiting collagen degradation and oxidative stress, demonstrating their ability to combat skin aging. This echoes the findings of Li et al., who demonstrated in a skin aging model that UC-MSCs upregulate collagen-1 (Col-1) and vascular endothelial growth factor (VEGF) expression by reversing superoxide dismutase (SOD) and malondialdehyde (MDA) levels. In addition to reversing the aging of human dermal fibroblasts (HDFs) through autophagy-mediated parasecretory mechanisms, anti-aging effects can be achieved [43]. Similarly, ultraviolet radiation is a key factor in skin aging, and AD-MSCs have been found to activate the proliferation of HDFs, regulate collagen synthesis, reduce the pro-reduction of matrix metalloproteinases, and protect HDFs from UV-induced oxidative stress, thus delaying skin aging [44]. Studies have shown that mitochondria can repair UV-irradiated cells and mitochondrial damage [45], and that MSC can shift cells from pro-inflammatory to immunomodulatory via mitochondrial transfer [46]. Therefore, this method may be a promising approach for treating skin aging. In the past five years, there have been significant advances in skin aging research, particularly in the exploration of the effects of stem cell secretions on skin regeneration and rejuvenation.

MSC-Exos from different sources in the treatment of aging-related diseases

The use of MSC-Exos as nanocarriers for drug delivery has been extensively studied. Exosomes can precisely deliver therapeutic agents to the disease site and improve treatment effectiveness while minimizing side effects. Studies have shown that MSC-Exos can help delay aging by inhibiting the SIRT1 and p53 signaling pathways [47]. Moreover, numerous animal studies have shown that MSC-Exos can be used as a targeted delivery vector for miRNAs to treat age-associated disorders, and that miRNA-carrying exosomes exert biological activity by participating in various signaling pathways, including apoptosis, inflammation, autophagy, and oxidative stress. MSC-Exos improved the aging of cells, tissues, and organs, both in vitro and in vivo (Table 2). Therefore, it is particularly important to explore the mechanisms and applications of exosomes from different MSC sources in the treatment of age-related diseases.

Premature ovarian failure

As an innovative therapeutic approach, MSC-Exos have attracted increasing attention in recent years for the application and mechanistic research of animal models of POF. Studies have shown that MSC-Exos can improve the ovarian tissue microenvironment and promote the recovery of ovarian function through various mechanisms, including immune regulation, enhancement of cell viability, inflammation regulation, reduction of fibrosis, and metabolic signaling pathways. UCMSCs-Exo has been shown to increase hormone secretion, inhibit GC apoptosis, promote follicular development, activate PI3K/Akt signaling pathway, and regulate autophagy [48]. Furthermore, it protects the ovary from damage through the Hippo [49] and Nrf2/GPX4 signaling pathways [50], providing a new therapeutic strategy and theoretical basis for POF treatment. To date, most studies have focused on the therapeutic benefits and mechanisms of MSC-Exos carrying various miRNAs in POF. Studies have shown that miRNAs target and regulate related signaling pathways through multiple mechanisms. For example, miRNA-22-3p from UCMSC-Exos targets KLF6 and ATF4-ATF3-CHOP pathways, and miR-21-5p targets and inhibits PTEN expression [51]. miR-644-5p from BMMSC-Exos targets and regulates p53 expression, and miR-144-5p targets the PTEN/PI3K/AKT axis [52]. These miRNAs have been shown to reduce ovarian GC apoptosis, restore follicle numbers and hormone levels, and improve ovarian function in POF. Recently, Yifan et al. developed a novel exosome-encapsulated microcarrier for POF treatment. This vector uses microfluidic technology to encapsulate exosomes from lipopolysaccharide-pretreated UC-MSCs in methylacrylyl hyaluronate (HAMA) polymer. The carrier exhibits good biocompatibility and strong semipermeability [53]. This study demonstrated that HAMA/MSC-Exos can effectively restore ovarian function in mice, providing new insights into the clinical treatment of POF.

A phase 1 clinical trial currently recruiting involved intraovarian injection of 2 ml (equivalent to 30 million cells) of BMMSC-Exos into the ovaries of 10 patients, and after 1 month, hormone levels and sinus follicle counts, as well as ovarian size and volume, were observed to study their safety and feasibility. The results have not yet been published [NCT06202547].

Alzheimer's disease

Early studies have shown that MSC-Exos enhance cognitive function by modulating microglial activation to reduce neuroinflammation and Aβ deposition, promote neurogenesis, and restore gene expression associated with neuronal memory and synaptic plasticity. However, the specific mechanisms by which exosomes exert their effects have not yet been fully elucidated. Recently, SH-SY5Y cells were treated with Aβ or okadaic acid to establish an in vitro AD model. UCMSC-Exo-overexpressing miR-211-5p inhibitors increased NEP expression (a key molecular factor inhibiting Aβ deposition) and protected SH-S5Y5 cells from Aβ, significantly improving exosome efficacy [54]. MSC-Exos also improved mitochondrial dysfunction and inhibited apoptosis in okadaic acid-treated SH-SY5Y cells via mitochondrial transfer [55]. BMMSC-Exos have been shown to promote autophagy, reduce toxic protein aggregates and neuroinflammation by activating the PI3K/Akt/mTOR pathway [56], and reduce Aβ deposition through the sphingosine kinase/sphingosin-1-phosphate signaling pathway [57]. Additionally, miR-146a delivered by BMMSCs inhibits astrocyte inflammation and promotes synaptic formation [58]. It can also transmit miR-467f and miR-466q to regulate the p38 MAPK pathway and inhibit the microglial pro-inflammatory phenotype [59], thereby improving cognitive function in AD. These studies have identified potential targets for the treatment of neurodegenerative diseases.

To improve the therapeutic effect of MSC-Exos, studies have found that the 3D culture environment can affect the composition of exosomes secreted by UC-MSCs, making them rich in functional molecules related to AD therapy, thereby reducing the production and accumulation of Aβ, inhibiting inflammation and oxidative stress, and improving cognitive function in AD [60]. In addition, hypoxic pretreated ADMSC-Exos have been shown to improve cognitive function in AD. This improvement was achieved by delivering circ-Epc1 and sponging miR-770-3p, resulting in the upregulation of TREM2 expression and promotion of microglial shift from pro-inflammatory M1 to anti-inflammatory M2 polarization

Table 2 Exploitations of MSCs-Exo in aging-related diseases

Disease	Source of Exos	Animal model	Size/nm	model Dosage/cells	In vitro model	Follow-up period	Effects	Ref.
POF	hUC-MSC	CDDP induced POF mouse model	30–200 nm	NA		4 weeks	UCMSC-EVs activate the PI3K/Akt signaling pathway and regulate cellular autophagy, thereby reducing GC death.	[48]
POF	hUC-MSC	CTX induced POF mouse model	50–100 nm	IP 150 μg	GCs	2 weeks	hUCMSCs-Exo promotes ovarian function and proliferation by regulating the Hippo pathway	[49]
POF	hUC-MSC	CDDP induced POF mouse model	30–40nm	IV 125 μg	GCs	72 h	hUCMSCs-Exos-miR-22-3p targets the KLF6 and ATF4-ATF3-CHOP pathways.	[51]
POF	rBM-MSC	CTX induced POF rat model		IP 150 μg		2 weeks	The delivery of BMMSCs-Exo-miR-144-5p may improve rat ovarian function after chemotherapy-induced ovarian failure through the PTEN/PI3K/AKT pathway	[52]
POF	hUC-MSC	CTX induced POF mouse model	160 nm	OV 2×10^6 cells		2 weeks	Hyaluronic acid methacryloyl (HAMA)/MSCs-Exo can effectively restore ovarian function in ovarian failure	[53]
AD	hUC-MSC		50–120 nm	Coculture	SH-SY5Y		Engineered hUCMSC-Exos overexpressing miR-211-5p inhibitors can significantly enhance the efficacy of exosomes	[54]
AD	hUC-MSC			Coculture	SH-SY5Y		MSCs improve mitochondrial function and suppress apoptosis in SH-SY5Y cells via mitochondrial transfer by extracellular vesicles.	[55]
AD	mBM-MSC	APP/PS1 transgenic mouse model	110 nm	IV 50 μg		16 weeks	BMMSCs-Exo reduces Aβ deposition by activating the SphK/S1P signaling pathway	[57]
AD	rBM-MSC			coculture 0.4 μg/ml	Astrocytes	24 h	BM-MSCs improve cognitive impairment in AD model mice by transferring exosomal miR-146a to astrocytes	[58]
AD	hUC-MSC	APP/PS1 Transgenic mouse model	50–150 nm	Hippocampus 50 μg	SH-SY5Y	14 days	3D-HucMSC-Exo has demonstrated enhanced therapeutic effects in improving memory and cognitive deficits in AD mice	[60]
AD	hAD-MSC	APP/PS1 transgenic AD mouse model	80–130 nm	ICV 1×10^9 particles		2 months	Hypoxic preconditioning of ADMSC-Exos improve cognition by delivering circ-Epc1 and promoting M1/M2 polarization of microglia	[61]
AD	hBM-MSC	3xTg-AD mouse model	200 nm	IN 30 μg		21 days	Intranasal administration of cytokine-preconditioned BMMSC-Exos can induce immunomodulatory and neuroprotective effects in AD	[62]
AD	mBM-MSC	STZ induced AD mouse model	50 nm	ICV 0.5 μg		5 days	BMMSCs-Exos can modulate gliocyte activation, neuroinflammation, and BDNF-related neuropathological changes in the hippocampus	[63]
AS	hUC-MSC	High-fat diet Apo −/− mouse model	100 nm	IV 0.5 mg/mL		2 weeks	hUCMSC-Exos-miR-21a-5p promotes macrophage polarization and reduces macrophage infiltration by targeting the KLF6 and ERK1/2 signaling pathways.	[66]
AS	hUC-MSC	High-fat diet Apo −/− mouse model	163.4 nm	IV 80 μg/mL		2 weeks	hUCMSC-Exos-miR-100-5p inhibits the cellular progression and inflammatory response of eosinophils through the FZD5/Wnt/β-catenin pathway	[67]
AS	mBM-MSC	High-fat diet ApoE -/- mouse model	50–150 nm	IV 100 mg		12 weeks	BMMSC-Exos promote the polarization of M2 macrophages in plaques through the miR-let7/HMGA2/NF-κB pathway and inhibits macrophage infiltration in plaques through the miR-let7/IGF2BP1/PTEN pathway	[68]
AS	mBM-MSC	High-fat diet ApoE-/- mouse model	142.5–150.9 nm	IV 150 μg		1 month	It offers the potential of a novel nanodrug delivery platform that can enhance drug delivery efficiency while mitigating adverse reactions in the treatment of AS	[70]

Table 2 (continued)

Disease	Source of Exos	Animal model	Size/nm	model Dosage/ cells	In vitro model	Follow-up period	Effects	Ref.
AS	hUC-MSC		200 nm	Coculture	HCAECs		hUCMSC-Exos mimetic nanovesicles successfully alleviated TNF-α-induced inflammation in human coronary artery endothelial cells.	[71]
OP	rAD-MSC	STZ induced OP rat model	40–100 nm	IV 1.6 mg/kg		30 days	ADMSC-Exos alleviates diabetic OP by inhibiting NLRP3 inflammasome activation in osteoclasts	[72]
OP	rAD-MSC	STZ induced OP rat model	50–100 nm	Iv 1.6 mg/kg		12 weeks	miR-146a overexpressed ADMSC-Exos demonstrated enhanced anti-inflammatory effects and more powerful therapeutic effects in osteoclasts	[73]
OP	rAD-MSC		80–200 nm	coculture 50 μg/ml	MC3T3-E1	24 h	ADMSC-Exos alleviate apoptosis and oxidative stress by regulating the Nrf2/HO-1 axis	[74]
OP	mAD-MSC	proteoglycan induced OP mouse model	30–150 nm	IV NA		6 weeks	ADMSC-Exo soverexpressing microRNA-21 can increase bone mineral content and bone mineral density, and reduce the number of osteoclasts	[75]
OP	rBM-MSC	STZ induced OP rat model	120 nm	IV NA	Osteoclast	3 days	Delivery of miR-15b-5p via magnetic nanoparticle-enhanced BMMSC-Exos mitigate diabetic OP by targeting GFAP	[77]
OP	rBM-MSC	STZ induced OP rat model	100 nm	IV 10 mg/kg		1 week	Harnessing GMNP-loaded EVs derived from BMMSCs to target miR-3064-5p through MEG3 overexpression, thereby enhancing osteoblast proliferation and differentiation	[78]
OP	hDP-MSC	Surgically establish bone defects in rats	40–172 nm	Femur 150 μg		10 weeks	DPMSC-Exos decorated on titanium scaffolds also exhibit improved bone tissue regeneration	[80]
Skin aging	hUC-MSC		141 nm	Coculture	HDFs	48 h	Utilizing HCOPs to enhance the anti-aging capabilities of hUCMSC-Exos in skin is a potential strategy	[81]
Skin aging	hUC-MSC		57.5–317.5 nm	Coculture 250 μg/mL	HDFs	4 h	The marine sponge Haliclona sp. Spicules provide a safe and effective method to enhance the skin delivery of MSC-Exo	[82]
Skin aging	hUC-MSC	UV radiation-induced photodamage rat model	40–100 nm	SC 200, 400 and 600 μg		72 h	hUCMSC-Exos may represent a novel potential therapeutic agent for the prevention or treatment of skin photodamage and aging caused by ultraviolet radiation	[83]

hUCMSC: Human umbilical cord derived mesenchymal stem cells; hUCMSCs -Exo: Human umbilical cord derived mesenchymal stem cells derived exosomes; hAD-MSC: Human adipose mesenchymal stem cells; rAD-MSC: Rat adipose mesenchymal stem cells; mAD-MSC: Mouse adipose mesenchymal stem cells; hBM-MSC: Human bone marrow derived mesenchymal stem cells; mBM-MSC: Mouse bone marrow derived mesenchymal stem cells; rBM-MSC: Rat bone marrow derived mesenchymal stem cells; DPMSC-Exo: Dental pulp stem cell-derived exosomes; POF: Premature ovarian failure AD: Alzheimer's disease; AS: Atherosclerosis; OP: osteoporosis; OVX: Ovariectomy; CTX: cyclophosphamide; NOA: Natural ovarian aging; STZ: streptozotocin; IV: Intravenous injection; ICV: Intraventricular injection; IP: Intraperitoneal injection; OV: Ovarian Injection; IM: Intramuscular injection; SC: Subcutaneous injection; IN: Intranasal administration; GCs: Granulosa cells; HUVECs: Human umbilical vein endothelial cells; HDFs: Human dermal fibroblasts; HCOPs: Hydrolyzed collagen oligopeptides; NA: Not Applicable

[61]. These findings provide novel insights into the development of treatment strategies for AD.

Subsequent studies have highlighted various methods for the administration of MSC-Exos. Intranasal administration of BMMSC-Exos elicits immunomodulatory and neuroprotective effects [62], characterized by the inhibition of microglial activation and increased dendritic spine density. Injecting BMMSC-Exos into the lateral ventricle also improved AD-like behavior, possibly by modulating changes in glial cell activation, neuroinflammation, and brain-derived neurotrophic factor (BDNF) levels in the hippocampus [63].

In a Phase I/II clinical trial led by Wang, allogeneic ADMSC-Exos were administered via nasal inhalation to nine patients with AD, confirming the safety and efficacy of this treatment [64].

Atherosclerosis

MSC-Exos offer a promising approach for the treatment of AS by inhibiting the MAPK and NFκB pathways, leading to a reduction in the expression of cell adhesion molecules (CAM) in the vascular wall and macrophage accumulation [65]. MSC-derived EVs contain miRNAs that regulate cellular functions. It has great potential for treating diseases. Researchers have found that UCMSC-Exos-miR-21a-5p promotes M2 polarization of macrophages by targeting KLF6 and inhibiting the ERK1/2 signaling pathway [66]. UCMSC-Exos-miR-100-5p inhibits cellular processes and the inflammatory response

of eosinophils through the FZD5/Wnt/β-catenin pathway, both of which have been shown to reduce atherosclerotic plaque area and inflammation [67]. Similarly, BMMSC-Exos can promote M2 macrophage polarization through the miR-let7/HMGA2/NF-κB signaling pathway and inhibit macrophage infiltration through the miR-let7/IGF2BP1/PTEN pathway, thereby improving the development and progression of atherosclerotic plaques [68]. In a clinical study involving 60 newly diagnosed patients with AS and 60 healthy controls, AS severity was inversely associated with serum miR-26 levels. Treatment of ApoE-knockout AS mice with ADMSC-Exos overexpressing miR-26 improved atherosclerotic symptoms and provided protection against inflammatory factors and lipids [69]. The use of exosomes as nanocarriers for drug delivery has been extensively studied. Recently, a novel drug delivery system for AS has been proposed. This system uses biomimetic platelet membrane-coated BMMSC-Exos to simulate nanovesicles, thereby improving drug delivery efficiency and enhancing its therapeutic impact on AS [70]. Furthermore, UC-MSCs derived nanocarriers successfully reduced TNF-α-induced inflammation in human coronary endothelial cells [71].

Osteoporosis

MSC-Exos have great potential for treating OP. Studies have shown that ADMSC-Exos can effectively alleviate OP by inhibiting the activation of the NLRP3 inflammasome in osteoclasts [72]. In particular, ADMSC-Exos, which overexpress miR-146a, exhibit significant anti-inflammatory and curative properties [73]. Furthermore, ADMSC-Exos overexpressing microRNA-21 also increased bone mineral content and bone mineral density and decreased the number of osteoclasts [74]. These exosomes also reduce apoptosis and oxidative stress by regulating the Nrf2/HO-1 pathway [75]. This shows a good therapeutic potential for the treatment of OP. BMMSC-Exos can also relieve OP by reducing oxidative stress, promoting DNA repair, restoring BM-MSC function, activating the Wnt/β-catenin signaling pathway, and restoring the lipogenic-osteogenic balance [76]. However, the study of MSC-Exos in OP is still in its infancy, and the underlying mechanisms have not been fully elucidated. Recently, magnetic nanoparticles (GMNPs) have emerged as potential drug carriers for various therapeutic applications. GMNPs have been used to enhance the delivery of BMMSCs-Exo-miR-15b-5p to osteoblasts to downregulate GFAP expression, inhibit osteoblast differentiation, and alleviate OP [77]. Current studies on targeted delivery systems include miR-3064-5p, Mir-150-3p, and miR-935 [78], which demonstrate different mechanisms of action and have shown promising effects in alleviating OP symptoms. Additionally, various pretreatment methods have demonstrated significant potential for promoting bone tissue regeneration. Hydrogels loaded with osteogenic induction DPMSC-Exos enhanced bone tissue reconstruction [79], whereas DPMSC-Exos decorated on titanium scaffolds showed better bone tissue regeneration [80].

Skin aging

In a study on skin aging, Zhu et al. evaluated the combined anti-aging effects of hydrolyzed collagen oligopeptides (HCOPs) and UCMSC-Exos on senescent skin fibroblasts. This study revealed that the combination of HCOPs and UCMSC-Exos was more effective than either agent alone in promoting cell proliferation and migration, reducing oxidative stress levels, enhancing collagen expression, inhibiting the expression of MMPs and inflammatory factors, and downregulating the expression of aging-related genes, thereby delaying skin aging more effectively [81]. In a study of skin damage and aging caused by ultraviolet radiation, Zhang et al. effectively enhanced the skin permeability of UCMSC-Exos by combining them with marine sponge Haliclona sp. spicules. This approach can alleviate skin inflammation and damage, promote skin cell regeneration, and significantly improve photodamaged skin. However, the mechanisms underlying these effects have not yet been experimentally elucidated [82]. Wu P et al. proposed that the mechanism may be related to the cell protection function of UCMSCs-Exo delivered 14-3-3ζ protein through regulating SIRT1-dependent antioxidant pathways [83].

In the current clinical trial of skin aging, 20 women aged 35–65 years were recruited in Iran and injected with UCBMSC-Exos into the face in a superficial manner. Wrinkles and collagen were assessed after 1–3 months, The study is currently ongoing (unpublished results) [NCT05813379]. (Table 3)

Conclusion

In the preceding sections, we summarized the role of MSCs and MSC-Exos in the treatment of age-related diseases based on different organizational sources. These include POF, AD, OP, AS, and skin aging. In addition, we briefly discuss the underlying mechanisms of these effects. It was found that MSCs and their exosomes primarily treat conditions associated with aging through mechanisms such as OS, the SIRT family, the Wnt/β-catenin signaling pathway, the MAPK signaling pathway, the NF-κB signaling pathway, the Nrf/HO-1 signaling pathway, and the PI3K/AKT/mTOR signaling pathway(Fig. 2).

Additionally, we found that the selection of MSCs and exosomes from different sources was crucial for treating various diseases (Table 4). In preclinical studies, MSCs or MSC-Exos selected for disease treatment typically originate from tissue sources closely related to the organ

Table 3 Clinical trials of MSCs and exosomes for the treatment of aging diseases

Disease Type	Purpose	MSC Type	Migration method	Results	Phases	Enrollment	research status	NCT number
POF	UC-MSCs combined with hormone replacement therapy for POF	UC-MSC	OV	No results published	1/ 2	40	unknown	NCT01742533
POF	Autologous MSCs transplantation for the treatment of POF in women	BM-MSCs	OV	Decrease in serum FSH levels, increase in estrogen and AMH levels, and decrease in menopausal symptoms.	1/ 2	60	unknown	NCT02062931
POF	Autologous MSC transplantation for idiopathic and drug-induced POF	BM-MSC	OV	Decrease in serum FSH levels, increase in estrogen and AMH levels, and decrease in menopausal symptoms.	1/ 2	60	unknown	NCT02043743
POF	MSC therapy for POF	BM-MSC	OV	50% decrease in serum FSH values, 30% increase in serum AMH and E2 values, resumption of menstruation, improvement in estrogen levels to normal range, pregnancy	1/ 2	3	Completed	NCT02696889
POF	AD-MSCs transplantation for POF	AD-MSC	OV	No results published	1	10	Not yet recruiting	NCT06132542
POF	YB-1113 safety and efficacy study for the treatment of POF	UC-MSC	IV	No results published	1	6	Not yet recruiting	NCT05494723
POF	Intraovarian injection of MSC-EVs with idiopathic POF	BMMSC-Exos	OV	No results published	1	10	Recruiting	NCT06202547
AD	Safety and exploratory efficacy study of NEUROSTEM® versus placebo in AD	UCB-MSC	ICV	No results published	1/ 2	46	Completed	NCT02054208
AD	AstroStem for AD	AD-MSC	IV	Conclusions limited by small sample size	1/ 2	21	Completed	NCT03117738
AD	Safety and exploratory efficacy etudy of UCMSCs in AD patients	UCMSCs	IV	No results published	1/ 2	16	unknown	NCT02672306
AD	Lomecel-B infusion versus placebo in patients with AD	BM-MSC	IV	No results published	1	33	Completed	NCT02600130
AD	Intranasal administration of allogeneic ADMSCs-Exos in patients with mild to moderate AD	ADMSCs-Exos	IN	Improvement in cognitive functioning	1/ 2	9	Completed	NCT04388982
AD	HUC-MSC-sEV-001 nasal drops for multiple neurodegenerative diseases	UCMSC-Exos	IN	No results published	1	100	Not yet recruiting	NCT06607900
OP	Injection of autologous fucoidan glycosylated BM-MSC for the treatment of OP	BM-MSC	IV	No results published	1	10	Completed	NCT02566655
OP	Safety of UC-MSC in the treatment of OP	UC-MSC	IV	No results published	1	20	Pause	NCT05152381

Table 3 (continued)

Disease Type	Purpose	MSC Type	Migration method	Results	Phases	Enrollment	research status	NCT number
OP	Evaluation of clinical and bone density improvement after UC-MSC implantation	UC-MSC	NA	No results published	2	5	Recruiting	NCT04501354
AS	Autologous AD-MSC for the treatment of patients with AS	AD-MSC	IV	Improved HDL, LDL, and residual-like particle (RLP) cholesterol levels	A retrospective study	78	Completed	[39]
Skin aging	MSC-Exos in skin rejuvenation	UCBMSC-Exos	Superficial injection	No results published	1/ 2	20	Recruiting	NCT05813379

UC-MSCs: Umbilical cord derived mesenchymal stem cells; AD-MSC: Adipose mesenchymal stem cells; BM-MSC: Bone marrow derived mesenchymal stem cells; UCB-MSC: Umbilical cord blood derived mesenchymal stem cells; POF: Premature ovarian failure AD: Alzheimer's disease; AS: Atherosclerosis; OP: osteoporosis; IV: Intravenous injection; ICV: Intraventricular injection; OV: Ovarian Injection; IN: Intranasal administration; NA: Not Applicable; Data obtained from ClinicalTrials.gov

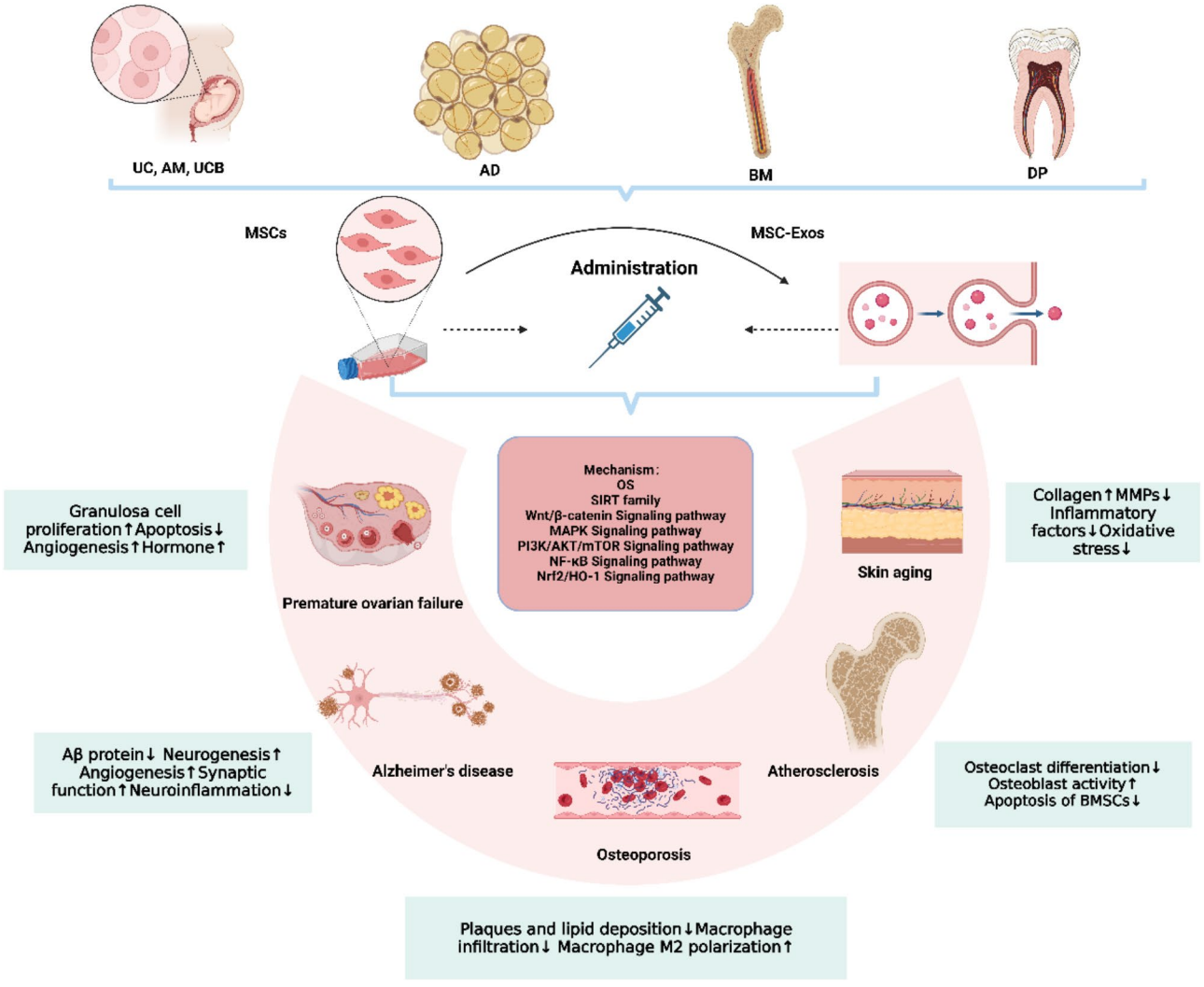

Fig. 2 Mechanism and application of mesenchymal stem cells (MSCs) and their derived exosomes (MSC-Exos) for the treatment of aging diseases. This figure outlines the biochemical mechanisms and signaling pathways by which MSCs and MSC-Exos exert therapeutic effects, especially in aging-related diseases. UC, Umbilical Cord; AM: Amniotic membrane; AD, adipose tissue; BM, bone marrow; DP: Dental pulp; OS: Oxidative stress. MMPs: Matrix metalloproteinases. Created using BioRender.com

Table 4 Advantages and limitations of MSCs from different tissue sources

Source	Method of procurement	Advantages	Disadvantages
BM	Isolated from BM aspirate	λ The most widely studied and experienced in clinical applications λ High differentiation potential, especially osteogenic differentiation	λ Cell quantity and quality decreases with donor age λ Painful and invasive collection process λ Limited proliferative capacity
AD	Isolated from liposuction, lipoplasty or lipectomy materials	λ Relatively easy and less invasive to obtain λ Better proliferation and differentiation ability λ Better immunomodulation than BM-MSC	λ Highly influenced by donor health status λ Differentiation potential may be lower than bone marrow sources λ Higher cellular heterogeneity in adipose tissue
UC	Isolated from the umbilical cord after birth	λ Source-rich, non-invasive λ No ethical controversy λ Higher cell proliferation capacity than AD-MSCs λ Low immunogenicity, suitable for allogeneic transplantation	λ Differentiation potential may be limited
UCB	Isolated from the umbilical cord blood after birth	λ Rich source, no ethical controversy λ Osteogenic differentiation ability λ Low immunogenicity, suitable for allograft	λ Very low MSC content λ No lipogenic potential λ Less osteogenic potential than BM
DP	Isolated from tooth extraction (i.e. wisdom, ectopic or even decayed teeth) or root canal surgery materials	λ Wide range of sources λ High proliferative capacity λ Neurogenic differentiation potential	λ Limited number of cells λ Collection dependent on tooth extraction λ Ectomesenchymal and periodontal tissues affect MSC properties λ Research is in early stages

BM: bone marrow; AD: adipose; UC: Umbilical cord; UCB: Umbilical cord blood; DP: Dental pulp; MSCs: mesenchymal stem cells

affected by the disease. For instance, studies targeting skeletal and spinal-related diseases have tended to use BM-MSCs or BMMSC-Exos. For diseases of the female reproductive system, such as those affecting the uterus, ovaries, and fallopian tubes, UC-MSCs or UCMSC-Exos are the preferred treatment. AD-MSC and ADMSC-Exos are commonly used for scar and anti-aging plastic repair. This selection aimed to enhance the efficacy and specificity of the treatment. However, targeted stem cell therapy is still lacking, and the most appropriate stem cell source and treatment regimen have not been selected on a patient-by-patient basis.

Although the safety and efficacy of different delivery modalities, dosages, and treatment regimens have been demonstrated in clinical studies, the uncertainty of cell fate after cell transplantation remains a concern. For example, the exact distribution and long-term survival of cells in the body remain unclear, and their homing abilities remain a challenge. The potential risks of embolization, impact of dead cells, immunogenicity, and tumorigenic potential need to be closely monitored and evaluated. The field of stem cell therapy still needs to explore the complex mechanisms of action to facilitate the safe and effective application of this technology. Similarly, although MSC-Exo-based therapies are a cutting-edge "cell-free" therapeutic option that uses MSCs to a new level, there are still many hurdles that need to be addressed before they can be utilized in clinical settings. For example, the rapid clearance of MSC-Exos from the body may limit their long-term therapeutic efficacy, and the heterogeneity and stability of MSC-Exos for long-term preservation remains a significant challenge. Advancements in bioengineering and cell-making technologies to engineer exosomes will provide opportunities for more specific applications in highly complex medical fields. Nevertheless, the complexity of exosome composition and the lack of efficient and standardized extraction methods make industrial-scale production difficult.

Therefore, there is still a long way to go before MSCs and MSC-Exos can be clinically applied. Future research requires multidisciplinary collaboration to delve deeper into the mechanisms of action of MSCs and their exosomes in age-related diseases. By addressing the current research challenges, more reliable strategies can be developed for the prevention and treatment of age-related diseases.

Abbreviations

Aβ	β-amyloid
AD-MSCs	Adipose tissue derived mesenchymal stem cells
AD	Alzheimer's disease
ADMSCs-Exo	Adipose mesenchymal stem cells derived exosomes
AM-MSCs	Amniotic membrane derived mesenchymal stem cells
AS	Atherosclerosis
BDNF	Brain-derived neurotrophic factor
BM-MSCs	Bone marrow derived mesenchymal stem cells
BMMSCs-Exo	Bone marrow mesenchymal stem cells derived exosomes
CAM	Cell adhesion molecule
DP-MSCs	Dental pulp derived mesenchymal stem cells
DPMSC-Exo	Dental pulp mesenchymal stem cells derived exosomes
EVs	Extracellular vesicles
FSH	Follicle-stimulating hormone
GCs	Granulosa cells
HAMA	Hyaluronic acid methacryloyl
HDFs	Human dermal fibroblasts
HGF	Hepatocyte growth factor
ISCT	International Society for Cellular Therapy
MAPK	Mitogen-activated protein kinase
MG53	Mitsugumin53 protein
MMPs	Matrix metalloproteinases

MSCs-Exo	Mesenchymal Stem Cells derived exosomes
MSCs	Mesenchymal stem/stromal Cells
NF-κB	Suclear factor κB
NGF	Neurotrophic Factor
OA	Osteoarthritis
OP	Osteoporosis
OS	Oxidative stress
POF	Premature ovarian failure
ROS	Reactive oxygen species
SA-β-gal	Senescence-associated β-galactosidase
SASP	Senescence-associated secretory phenotype
Sirt1	Silent information regulator 1
UC-MSCs	Umbilical cord derived mesenchymal stem cells
UCB-MSCs	Umbilical cord blood derived mesenchymal stem cells
UCMSCs-Exo	Umbilical cord mesenchymal stem cell derived exosomes
VEGF	Vascular endothelial growth factor

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Author contributions
HL drafted the manuscript and the figures. LB edited, revised, and approved the final manuscript.

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Declarations

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Competing interests
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