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Review Article

Potential Roles of Exosomes in Aging and Age-Related Diseases

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Abstract
Objectives: To review exosomes in aging and age-associated diseases.
Design: A review study.
Participants: Aged animals.
Interventions: Exosome treatment.
Outcome measures: The occurrence of age-associated diseases, aging skin, cognition, and cardiac dysfunction.
Results: Exosomes are secreted by various cell types and comprise proteins, lipids, functional messenger RNAs, cytokines, growth factors, different noncoding RNA, micro-RNAs, and other bioactive substances. These nanoparticles are implicated in several physiological processes, including intercellular communication, cell migration, angiogenesis, and anti-tumor immunity, and have gained major interest in regenerative medicine. Furthermore, several studies have demonstrated the potential roles of exosomes in age-associated diseases such as aging skin, cognition, Alzheimer's disease (AD), Parkinson's disease (PD), and osteoarthritis (OA).
Conclusions: We summarized various mechanisms of exosomes in the treatment of age-related diseases, including OA, PD, AD, and aged skin. These vesicles can be of efficient medicinal value for aged-associated disease therapy in preclinical trials. Further clinical trials are needed, but the majority of the literature suggests research directions that may provide new treatment approaches and strategies for clinical application.
Keywords: Aging, Exosome, Neurodegenerative diseases, Brain, Skin, Osteoarthritis

Introduction

As the world population is aging, it is a fascinating topic for researchers around the world. Aging is related to a progressive diminution in the effectiveness of mechanisms that preserve homeostasis of the body and tissues.[1] It is a major risk factor for several diseases such as cardiovascular disease, aging skin, cognition dysfunction, and the like as well as the reduction in the quality of life among elderly people.[2] It is well known that oxidative stress and inflammation are important contributors to aging.[3] At present, there is no effective therapeutic intervention that can lessen age-related diseases and also slow down the aging process. The development of therapies that postpone aging and the progression of age-associated diseases will be the main implication for the betterment of public health.

Exosomes are nanometer-sized membrane-bound extracellular vesicles secreted by different cell types for intercellular communication and can be detected in biological fluids in pathological and physiological contexts.[4] They are found in numerous biological fluids, including serum, saliva, breast milk, serum, cerebrospinal fluid, and the like. Exosomes carry cargo molecules from their cell of origin, including proteins, mRNAs, microRNA, and lipids,[5-7] and are delivered to the surrounding cells or carried to the distal cells. Owing to their active cargo content, they reprogram the recipient cells. Lately, due to their excellent characteristics, they have also been regarded as a suitable delivery vehicle for medicinal products. Furthermore, exosomes have a lipidic bimolecular structure similar to the cell membrane, thereby enabling them to be loaded efficiently with hydrophobic and hydrophilic drugs.[8]

A large body of studies has demonstrated that exosomes play an important role in the treatment of a wide range of diseases including, nerve injury,[9] stroke,[10] neurodegenerative diseases,[4] aging,[11,12] and heart diseases.[13] In addition, evidence has shown that after intravenous injection, exosomes are mostly distributed in vascular-rich organs and organs related to the reticuloendothelial system such as the kidneys, spleen, lungs, and liver.[14] Because of the dysregulation of exosomes in diseases and their role in delivering drugs to target cells, they are of therapeutic interest. This review summarizes the

application and possible mechanism and function of exosomes in aging and some age-related diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), aged skin, and osteoarthritis (OA) and reveals the current and the latest research progress.

Methods

PubMed, Google Scholar, and Scopus databases were searched to recognize publications from peer-reviewed journals using several keywords and their MeSH terms, including, 'aging', 'exosome', 'diseases', 'Alzheimer's disease', 'Parkinson's disease', and 'elderly'. The search was conducted on April 1, 2023, and there was no search filter on publication type. In addition, studies written in English were selected, and reference lists of all relevant publications were manually selected to identify advanced-qualified studies.

Results

Molecular Mechanisms of Aging and Age-Related Diseases

As fertility reduces and life expectancy rises, the proportion of individuals aged 60 and over increases. According to UNESAS, about 900 million people are aged 60 and over worldwide, and this number will reach 21. 5% of the world population by 2050, and the prevention of aging is a common problem.[15] Aging is known as the most important driving factor for various diseases and finally death. With the dramatic increase in life expectancy in recent decades, age-related diseases such as AD, frontotemporal dementia, cardiovascular diseases, skin diseases, PD, and other diseases have become one of the most serious global public health problems. High generation of reactive oxygen species (ROS), mitochondrial damage, neuroinflammation, telomere shortening, and abnormal homocysteine metabolism are crucial for the aging process and age-associated diseases. According to growing evidence, oxidative stress rises with age due to ROS accumulation and is accompanied by lipids, nucleic acids, proteins DNA, carbohydrates damage, and a decrease in cell repair mechanisms, eventually leading to the impairment of the epigenetic state of the cell [16]. In addition, mitochondrial dysfunction can lead to respiratory chain deficiencies, increased production of ROS, decreased adenosine triphosphate levels, and promoted apoptosis and inflammation, resulting in numerous age-related diseases.[17] With advanced age, the expression of autophagy genes such as ATG5, ATG7, and BECN1 declines, and the stimulation of autophagy increases the healthy lifespan in various model organisms such as rodents and primates.[18] It was found that neurodegenerative diseases are correlated to defects in autophagy and mitochondria. Autophagy is a necessary process to remove abnormal protein aggregates in cells. It also maintains protein balance. Some studies found that autophagy problems happen in the early stages of AD. Autophagy is complicated in the generation and metabolism of β-amyloid (Aβ) and also affects the phosphorylation status and clearance of tau. Therefore, its malfunction causes the progress of AD.[19] Moreover, the overexpression of α-synuclein protein in PD has been thought to impair autophagy.[20]

Exosomes

Exosomes are tiny extracellular vesicles that are 30 to 150 nanometers in diameter and are released from most cells, including mast cells, lymphocytes, neurons, and dendritic, epithelial, and endothelial cells during physiological and pathological conditions.[21,22] Exosomes spread throughout the body and are found in blood, saliva, urine, and breast milk. These vesicles have a fluid lipid bilayer membrane and contain protein, nucleic acid, and lipids and are key regulators of many biological settings.[23] These extracellular vesicles have different sizes. Large exosomes are 90 to 120 nm, and small exosomes are 60 to 80 nm in diameter. In addition, in recent years, a group of non-membrane nanoparticles called exomers has been discovered with a diameter of less than 35 nm.[24] Exosomes in the plasma membrane are secreted into the extracellular environment after binding with multivesicular bodies.[25] Consequently, exosomes join neighboring cells by endocytosis or are degraded via lysosomes.[26,27] Exosomes are involved in multiple biological processes, including cell-to-cell communication, autophagy, lysosomal exocytosis,[25] crosstalk between organs, intercellular signaling, inhibition of apoptosis,[28] cleansing of cell waste products, maintaining cell homeostasis in an optimal level, the modulation of the immune and inflammatory systems, and angiogenesis; moreover, exosomes have the potential to diagnose and prognosis a wide range of diseases.[25,28,29] The use of exosomes in clinical trials has advantages such as stability for a long time, easy internalization, and operation in recipient cells.[28] Exosomes can be stored, they are unlikely to be rejected by the immune system, they have a low risk of forming tumors and clots in blood vessels, and they have no potential for toxicity. Furthermore, it was identified that microRNAs (miRNAs) carried by exosomes activate restorative and protective pathways in recipient cells by inducing genetic instructions[30-32] (Figure 1).

Discussion

Effects of Exosomes on Aging and Age-associated Diseases

Aging

Delayed neurocognitive recovery (dNCR) is a rampant complexity of the central nervous system in aged patients after surgery, leading to cognitive impairment, memory and inattentiveness disturbances, and also increased morbidity and mortality in sufferers in 30 days following operation.[33] Liu et al revealed that exogenous mesenchymal stem cells (MSCs)-exosome downregulates the levels of ROS, malondialdehyde, Fe^{2+}, and P53, whereas it rises glutathione, GPX4, and SLC7A11 levels in dNCR-aged mice.[34] In addition, they found that treatment

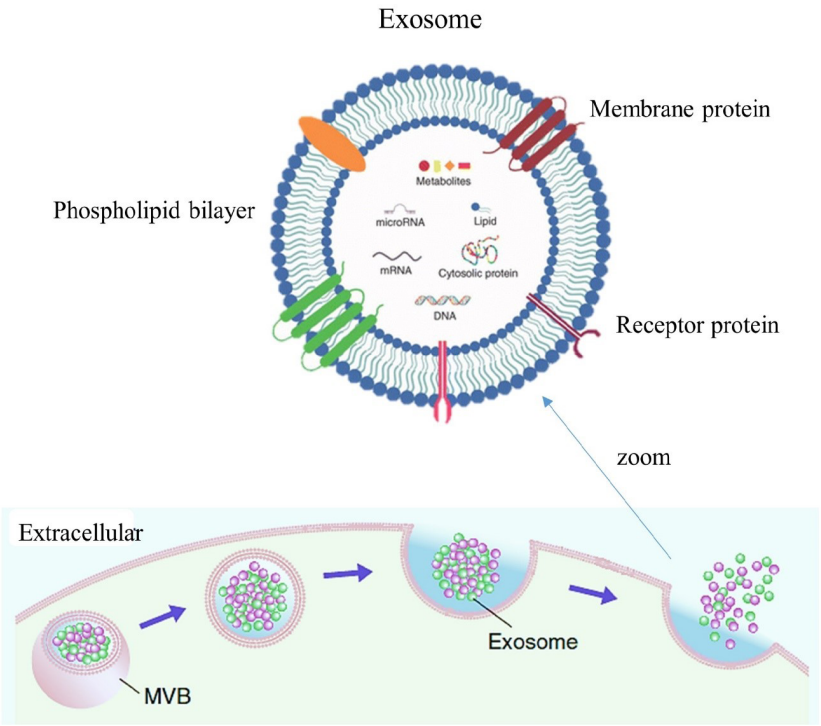

Figure 1. Schematic Figure of Exosome. *Note.* MVBs: Multivesicular bodies. These vesicles are released from MVBs in the vesicle trafficking process

with exosomes derived from MSCs ameliorates cognitive dysfunction by inhibiting ferroptosis in the hippocampus of dNCR-aged animals by activating the Sirt1/Nrf2/HO-1 signaling pathway. The mentioned effects of MSCs-exosome on dNCR-aged animals were prevented by the selective Sirt1 inhibitor.[34]

The previous reports suggested that long non-coding RNA (lncRNA) metastasis-associated lung adenocarcinoma transcript (MALAT1) regulates cell cycle and inflammation, and its expression is reduced with age.[35] Furthermore, umbilical cord MSC-derived exosomes attenuate age-induced heart dysfunction via an exosome/lncRNA MALAT1/NF-κB/TNF-α signaling pathway.[36]

It was reported that levels of mmu-miR-126-5p and mmu-miR-466c-5p in lungs, liver, and exosomes are downregulated, while levels of mmu-miR-184-3p and mmu-miR-200b-5p raised in exosomes in aged mice compared to young animals. The administration of young exosomes could reverse the mmu-miR-126-5p level in the lungs and liver in old animals.[37] Additionally, treatment with young exosomes could result in a decrease in the level of aging-associated biomarkers such as $p16^{Ink4A}$, MTOR, and IGF1R in the lungs and also in the liver of aged mice. Furthermore, telomerase-related genes (*Men1*, *Mre11a*, *Tep1*, *Terf2*, *Tert*, and *Tnks)* were increased in the liver of aged animals following the injection of young exosomes.[37] It has been shown that telomeres are shortened when telomerase activity in human somatic cells declines with aging, and it was found that the transfection of a telomerase gene to aged animals delays aging and increases longevity.[38]

The intrabursal injection of exosomes derived from human umbilical cord MSCs into old mice revealed their rescuing effects on the age-related reduction in fertility by increasing oocyte generation and improving oocyte quality.[39] Several studies have found that exosomes secreted by MSCs promote neurogenesis in the subventricular zone of the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus and reduce cognitive impairment correlated with stroke, traumatic brain injury, and PD.[40,41] Zhang et al reported that exosomes from young MSCs translocate exosomal miR-136 and reduce apoptotic peptidase activators, thereby enhancing the activity of aged MSCs and increasing myocardial repair function.[42]

Aged Skin

The number and proliferation of dermal fibroblasts alter with age which diminishes collagen synthesis and repair, and the existing skin matrix degradation by matrix-degrading enzymes accelerates, decreasing the regenerative capacity of skin.[43] Aging results in slowed wound healing,[44] which is a dynamic biological process that requires the interaction of different cell types and cellular activities (e.g., differentiation, migration, and proliferation) and the synthesis of extracellular matrix proteins.[45,46] Age-associated defects in the repair wound are related to decreased myofibroblasts and extracellular matrix deposition dysfunction.[46] MSC exosomes have numerous therapeutic effects on the skin. A study demonstrated that exosomes transfer miR-125b from young into aged fibroblasts and promote the migration and transition of the fibroblast to thwart aging via the

inhibition of sirtuin 7.[47] Oh et al mentioned that exosomes derived from human iPSCs improve skin aging caused by UVB irradiation by accelerating the proliferation and migration of human dermal fibroblasts (HDFs), the inhibition of overexpression matrix metalloproteinases -1/3, and also the restoration of expression of the collagen type I in old HDFs.[48] Chernoff conducted a pilot study on 40 patients with aging skin. This study has demonstrated that human placental mesenchymal-derived exosomes could improve the tone, quality, and clarity of skin and also reduce wrinkles, pores, pigment, and oiliness compared to the control group.[49] Moreover, there were no allergic and hypersensitivity reactions or adverse events in all groups.[49]

Alzheimer's Disease

AD is characterized by cognitive impairments, the loss of memory, and personality changes taking place with advancing age.[50] AD is neuropathologically defined by the accumulation of extracellular senile Aβ plaques and intracellular neurofibrillary tangles, consisting of hyperphosphorylated tau proteins.[51] Several studies showed that exosomes derived from stem cells have therapeutic effects in AD. It was found that exosomes derived from human umbilical cord-derived MSCs attenuate neuroinflammation and boost the degradation of Aβ.[52] Moreover, the intravenous injection of MSC-exosomes with neprilysin and insulin-degrading enzyme (zinc metallopeptidase) activity decreased the deposition of Aβ plaques in AD transgenic mice.[53] Exosomes isolated from adipose-derived stem cells exerted significant neuroprotective effects on AD mice through decreasing the $A\beta_{1\text{-}42/1\text{-}40}$ ratio, Aβ levels, and neuronal cell apoptosis, as well as increasing neurite outgrowth.[54] Furthermore, combined curcumin and exosomes inhibited tau phosphorylation and activated the GSK-3/AKT signaling pathway, to avoid neuronal death and relieve symptoms.[55]

Parkinson's Disease

PD is a chronic neurodegenerative age-related disorder affecting the motor system in the population aged over 70 years. PD cases broadly fall into two categories: sporadic and familial with the same pathological hallmarks such as the dopaminergic neurons loss in the substantia nigra pars compacta and the inclusions of Lewy bodies and neurites of surviving neurons in the midbrain.[56] A study has shown that exosomes from stem cells derived from the dental pulp of human exfoliated deciduous teeth (SHEDs) inhibit 6-hydroxy dopamine-induced apoptosis in dopaminergic neurons.[57] In addition, the intranasal delivery of exosomes from SHEDS could ameliorate dyskinesia and the loss of dopaminergic neurons and normalize tyrosine hydroxylase expression in the striatum and substantia nigra in PD rats.[58] Furthermore, the intracerebroventricular injection of exosome-mediated delivery of antisense oligonucleotides-4 (one antisense oligonucleotides targeting human α-syn sequence) to the brain of PD mice significantly diminished the expression of α-syn and aggregation, improved locomotor functions, and also ameliorated dopaminergic neuron degeneration.[59]

Osteoarthritis

OA is a common and debilitating age-related joint disease. The pathology of OA is the result of synovial inflammation, cartilage degradation, subchondral bone sclerosis, and osteophyte formation, which are common with human aging. While there are many ways to treat OA, no single treatment has been successful in reversing its progression.[60] Zhang et al proved the ability of MSC exosomes to repair OA. They found that MSC exosomes promoted temporomandibular joint repair and regeneration, suppressed pain, attenuated inflammation, and restored the matrix and overall joint homeostasis.[61] Exosomes derived from bone marrow MSCs can be endocytosed by chondrocytes. These exosomes have been shown to restore chondrocyte proliferation, promote extracellular matrix synthesis, and reduce knee OA pain.[62] Moreover, exosomes from healthy chondrocytes exhibited high biological activity in eliminating mitochondrial dysfunction and restoring the immune response by regulating M2 macrophage infiltration, thereby slowing the progression of the OA.[63] Exosome-derived miRNAs exert potent therapeutic effects on in vitro and in vivo models of OA by promoting proliferation and inhibiting apoptosis.[64] Furthermore, treatment with exosomes attenuated the senescence-related β-galactosidase activity in OA osteoblasts, oxidative stress, and the accumulation of γ H2AX foci, possibly due to the protective effects on mitochondria.[65] The effects of exosomes on age-associated diseases are summarized in Table 1.

Conclusions

Studies suggested the therapeutic potential of exosomes in aging and some of age-related diseases through various molecular mechanisms and pathways. Exosomes play essential roles in intercellular communication between donor and recipient cells by delivering proteins and RNAs. These small extracellular vesicles emerge as a therapeutic agent for regenerative medicine because of their roles in anti-inflammatory outcomes, wound healing, and anti-aging properties. Although there is a growing body of evidence on exosomes in aging and age-related diseases, principally focusing on pathophysiological mechanisms and treatment, most of the studies that yielded such results have been conducted using animal models not human models. Applying exosomes to technical and therapeutic safety issues is a main challenge. Cell culture conditions and storage methods can significantly impact exosome content and function and require the standardization of exosome extraction and storage. Moreover, the content, function, and activity of exosomes depend on the origin of the generating cells. Therefore, it is essential to optimize the source of exosome cells, including comorbidities, age,

Table 1. Exosomes as Therapy Agents in the Treatment of Aged-rated Diseases

Source	Disease Model	Main Findings	References
BM-MSCs	dNCR in aged mice	Amelioration of cognitive dysfunction via suppression ferroptosis and activating SIRT1/Nrf2/HO-1 signaling pathway in dNCR-aged animals	34
UMSCs	Aged	Prevention of aging-induced cardiac dysfunction by releasing novel lncRNA MALAT1 and inhibition of the NF-κB/TNF-α signaling pathway	36
Young fibroblast	Skin wound	Increase abundance of myofibroblasts and improvement of wound healing in old animals	47
iPSCs	Skin wound	Reduction of SA-Gal and MMP-1/3 expression and restoration of expression of collagen type I in old HDFs	48
HPMSC	Aging skin	Decrease wrinkles, pores, pigment, oiliness, and improve evenness of skin and vascularity	49
Blood	Aged mice	Upregulation of telomerase-related genes in the liver and downregulation of $p16^{Ink4A}$, MTOR, and IGF1R in liver or lung of aged mice	37
HucMSC-exos	Aged mice	Activation of the oocyte PI3K/mTOR signaling pathway	39
HucMSC-exos	Aged mice	Cardiac function improvement, reduction of fibrosis, and increase of angiogenesis.	42
hMSC	AD mice	Decreases amyloid plaque deposition.	52
hucMSCs	AD mice	Reduced Aβ deposition through modulating microglial activation.	66
ADSC	AD mice	Decreased β-amyloid pathology and apoptosis of neuronal cells.	54
Endothelial cell	AD mice	Reduced phosphorylation of the Tau protein by the activation the AKT/GSK-3β signaling pathway.	55
Exosomes derived from SHEDs	PD Rat	Suppressed apoptosis in dopaminergic neurons.	57
Evs-derived SHEDs	PD Rat	Improved motor symptoms and normalized expression of tyrosine hydroxylase	58
Exosome-mediated delivery of ASO4	PD mice	Exosomes-ASO4 reduced the degeneration of dopaminergic neurons and α-syn pathology and improved motor function in PD animals.	59
ADSC	OA osteoblast	Downregulated inflammation and oxidative stress	65
BM-MSCs	Rat model of OA	Decreased IL-1β, increased COL2A1 protein, and reduced MMP13 protein in the cartilage tissue.	62

Note. BM-MSCs: Bone marrow mesenchymal stem cells; dNCR: Delayed neurocognitive recovery; UMSCs: Umbilical mesenchymal stem cell; iPSCs: Induced pluripotent stem cells; HDFs: Human dermal fibroblasts; HPMSC: Human placental mesenchymal stem cell; HucMSC-exos: Exosomes derived from human umbilical cord mesenchymal stem cells; Extracellular vesicles derived from human exfoliated deciduous teeth stem cells; ASO4: antisense oligonucleotide-4; ADSC: Adipose-derived stem cells; OA: Osteoarthritis; SHEDs: Stem cells derived from the dental pulp of human exfoliated deciduous teeth; AD: Alzheimer's disease; PD: Parkinson's disease.

and other factors associated with exosome-producing cells. On the other hand, researchers mainly focus on exosome functional aspect, and negative effects are seldom studied. Hence, more investigations into exosome functions will help develop novel strategies for protection against aging and age-related diseases.

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Data availability statement

Not applicable.

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Conflict of interests

The authors declare no conflict of interests.

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