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ABOUT COVER

Editorial Board Member of *World Journal of Stem Cells*, Dr. Yong-Can Huang received his Bachelor's and Master's degrees from Sichuan University (China) in 2007 and 2010, respectively; in 2015, he obtained his PhD from the University of Hong Kong. Currently, he is Associate Professor at Peking University Shenzhen Hospital in Shenzhen (China). His major research interests include bone marrow- and placenta-derived stem cells for musculoskeletal regeneration, and intervertebral disc transplantation. Dr. Huang is member of the International Society of Orthopaedic Surgery and Traumatology, the International Chinese Musculoskeletal Research Society, and the Tissue Engineering and Regenerative Medicine International Society. (L-Editor: Filipodia)

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Mesenchymal stem cell-derived small extracellular vesicles in the treatment of human diseases: Progress and prospect

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Abstract

Mesenchymal stem cells (MSCs) are self-renewing, multipotent cells that could differentiate into multiple tissues. MSC-based therapy has become an attractive and promising strategy for treating human diseases through immune regulation and tissue repair. However, accumulating data have indicated that MSC-based therapeutic effects are mainly attributed to the properties of the MSC-sourced secretome, especially small extracellular vesicles (sEVs). sEVs are signaling vehicles in intercellular communication in normal or pathological conditions. sEVs contain natural contents, such as proteins, mRNA, and microRNAs, and transfer these functional contents to adjacent cells or distant cells through the circulatory system. MSC-sEVs have drawn much attention as attractive agents for treating multiple diseases. The properties of MSC-sEVs include stability in circulation, good biocompatibility, and low toxicity and immunogenicity. Moreover, emerging evidence has shown that MSC-sEVs have equal or even better treatment efficacies than MSCs in many kinds of disease. This review summarizes the current research efforts on the use of MSC-sEVs in the treatment of human diseases and the existing challenges in their application from lab to clinical practice that need to be considered.

Key Words: Mesenchymal stem cells; Small extracellular vesicles; Exosomes; Human diseases; Therapeutics; Prospects

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Core Tip: Mesenchymal stem cell-derived small extracellular vesicles (MSC-sEVs) have drawn much attention as attractive agents for treating multiple diseases. The properties of MSC-sEVs include low immunogenicity and increased stability in circulation. Moreover, emerging evidence has shown that MSC-sEVs have equal or even better treatment efficacies than MSCs in many kinds of disease.

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INTRODUCTION

Mesenchymal stem cells (MSCs) are self-renewing cells that can differentiate into multiple tissues, including muscle and fat cells, and connective tissues^[1]. MSC-based therapy could regulate immune reaction and promote tissue regeneration, and has become a promising and important strategy for treating diseases. However, MSC-based cell therapy is limited because of its safety. Some studies showed that MSCs may cause tumorigenesis^[2] or abnormal differentiation after ectopic engraftment^[3]. In addition, MSCs might aggregate to form pulmonary emboli or infarctions, and thus result in infusional toxicity in patients^[4]. Accumulating data have indicated that MSC derived secretome, which consists of soluble components and encapsulated extracellular vesicles (EVs), could contribute to most MSC- base effects^[5-7].

EVs are small membrane vesicles composed of a phospholipid bilayer that are released by all kind of cell types. EVs influence recipient cell functions by exchanging components between cells. There are proteins, nucleic acids, and lipids in EVs. EVs are recognized as signaling vehicles in intercellular communication under normal or pathological states. At present, according to their biogenesis, EVs can be classified into three main categories, exosomes, microvesicles, and apoptotic bodies, each with specific characteristics (Table 1).

Researchers have invented dozens of different names for secreted vesicles. The International Society for EVs (ISEV) updated Minimal Information for Studies of EVs (MISEV) guidelines in 2018^[8] and suggested that authors should pay attention to use of accurate terms for EV subtypes. Based on the physical characteristics of EVs, small EVs (sEVs) have a diameter < 100 nm or < 200 nm. In most of the studies cited in this review, exosomes were defined by the size of particles. Hence, we will here use the term sEVs instead of exosomes as ISEV suggested. MSC derived sEVs (MSC-sEVs) may transfer into special cells, induce appropriate cellular responses, and contribute to the therapeutic potency by regulating angiogenesis, tissue repair, and inflammation reaction^[9-12]. Recent studies have indicated that MSC-sEVs can be used to treat multiple diseases, including cardiovascular diseases^[13], bone damage^[14], cutaneous wounds^[15], and acute lung injury (ALI)^[16]. Furthermore, MSC-sEVs are convenient to preserve in that they are smaller and simpler than MSCs. MSC-sEVs can be stored in mechanical -70 °C freezers without affecting therapeutic efficacy, whereas MSCs are best stored in liquid nitrogen at -196 °C and can be subject to irreversible damage during the freezing or thawing process, which may result in impaired therapeutic properties^[17-19].

This review mainly focuses on summarizing the current progress on the use of MSC-sEVs in the treatment of diseases and discusses the existing challenges in the application of MSC-sEVs from lab to clinical practice.

THERAPEUTIC POTENTIAL IN DIFFERENT DISEASES

MSC-sEVs in treatment of cardiovascular disease

Cardiovascular disease (CVD) seriously threatens the health and living quality of human beings worldwide. Accumulating evidence indicates that MSC-sEVs protect ischemic cardiomyocytes from death, enhance the cardiac repair process, preserve cardiac function, and play an important role in CVD therapy^[20,21].

Table 1 Classification of different types of extracellular vesicles

Characteristic	Exosomes	Microvesicles	Apoptotic bodies
Size (nm)	20-100	50-1000	500-2000
Morphology	Cup/round shaped	Various shapes	Heterogeneous
Sucrose gradient	1.13–1.19 g/mL	1.04–1.07 g/mL	1.16–1.28 g/mL
Biogenesis	Endosomes	Plasma membrane	Plasma membrane, endoplasmic reticulum
Contents	Nucleic acids, cytoplasmic and membrane protein, major histocompatibility complex, lipid	Nucleic acids, cytoplasmic and membrane protein, receptor proteins, lipid	Nuclear fractions, DNA, cell organelles
Biomarkers	Tetraspanins family, actin, flotillin, Hsc70, Hsp 90, Hsp60 and Hsp20, clathrin, integrins	Integrins, selectins, flotillin-2, CD40, ligand, metalloproteinase	Annexin V positivity, phosphatidyl serine

Hsc: Heat shock cognate; Hsp: Heat shock protein; CD: Cluster of differentiation.

MSC-sEVs in myocardial infarction: Acute myocardial infarction can lead to most of cardiovascular deaths. One study found that sEVs derived from hypoxic murine MSCs facilitated ischemic heart repair *via* antiapoptotic miR-125b-5p^[22]. Furthermore, it has been shown that MSC-sEVs have the ability to regulate immune reactions and improve the myocardial microenvironment by reducing tissue inflammation and promoting tissue regeneration. Zhao *et al*^[23] indicated that MSC-sEVs alleviated myocardial ischemia-reperfusion injury in mice by intramyocardial injection. It was mainly because that miR-182 packaged in MSC-sEVs could promote the polarization of M1 macrophages to M2 macrophages^[23]. Wang *et al*^[24] found that endometrium-derived MSC-sEVs could significantly promote the recovery of cardiac function after myocardial infarction. They suggested that miR-21-containing MSC-sEVs improved the cardiac function by increasing the levels of vascular endothelial growth factor (VEGF) and enhancing neovascularization in rat ischemic hearts, and improved the cardiac function after acute myocardial infarction^[24]. Luo *et al*^[25] designed a synthetic MSC (synMSC) in which human MSC secreted factors (containing both soluble factors and sEVs) were packaged into poly(lactic-co-glycolic acid) microparticles with MSC membrane coatings. This exciting synMSC exhibited superior cryostability, and transplantation of synMSCs inhibited cardiac dysfunction after myocardial infarction in mice^[25].

MSC-sEV therapy plays a multifaceted role in promoting heart regeneration and repair after pathological damage. However, there are some limitations in the application of sEVs for the treatment of myocardial infarction. Direct intramyocardial injection is the commonly used route for sEV delivery, increasing cardiac localization. In contrast, systemic administration *via* intravenous infusion may result in off-target effects in organs other than the heart^[26].

MSC-sEVs in vascular regeneration: Several types of signaling molecules in MSC-sEVs could mediate angiogenesis, such as VEGF and miR-126. Wei *et al*^[27] fabricated MSC-sEV-functionalized vascular grafts and evaluated the vascular regeneration in a rat model of hyperlipidemia. The results indicated that MSC-sEVs could effectively promote the vascular smooth muscle and endothelium regeneration. It was demonstrated that the bioactive molecules within the sEVs, including VEGF, miR-126, and miR-145, may participate in the process of regeneration. Furthermore, MSC-sEVs could induce macrophage polarization from a proinflammatory (M1) phenotype to an anti-inflammatory (M2) phenotype^[27]. At the same time, the microenvironment of original cells also could influence the contents of MSC-sEVs. Du *et al*^[28] indicated that human placenta-derived MSC-sEVs (hp-MSC-sEVs) stimulated by nitrogen oxide could promote human umbilical vein endothelial cell (HUVEC) tube formation. hp-MSC-sEVs could rescue limb function in a mouse model of hind limb ischemia^[28].

MSC-sEVs in treatment of neurological diseases

MSC-sEVs in spinal cord injury: Spinal cord injury (SCI) is the most serious complication of spinal injury, and it often causes serious dysfunction of the limb below the injured segment. SCI will not only cause serious physical and psychological harm to the patient, but also cause a huge economic burden on the entire society. To date,

the treatment of SCI remains a huge challenge for clinicians^[29]. MSCs have been widely used in the treatment of nerve injury, but their effects are not obvious, mainly because MSCs are often trapped in the pulmonary vascular bed, and the mechanism of how MSCs work is still unclear^[30].

MSC-sEVs reduce pathological changes after SCI and improve motor function, blood flow, and hypoxia. In addition, MSC-sEVs improve the ability of the endothelium to modulate blood flow, maintain the blood spinal cord barrier, eliminate edema, downregulate the expression of matrix metalloproteinase 2, Bax, hypoxia inducible factor-1 (HIF-1 α), and Aquaporin-4, and upregulate the level of bcl-2, and decrease cell apoptosis^[29]. Riazifar *et al*^[31] showed that MSC-sEVs protect nerves, reduce inflammation, and promote angiogenesis in a mouse model of autoimmune encephalomyelitis (EAE)-induced SCI. MSC-sEVs stimulated by interferon γ (IFN- γ) reduce the clinical score of EAE mice, alleviate demyelination, inhibit neuroinflammation, and increase the number of Treg cells in the spinal cord^[31]. Zhou *et al*^[32] have found that miR-21-5p is one of the most abundant microRNAs (miRNAs) in MSC-sEVs, and miR-21-5p/FasL axis is recognized as a potential mechanism to improve motor function and inhibit apoptosis in MSC-sEVs for SCI^[32]. Totally, these results demonstrate that MSC-sEVs inhibit neuroinflammation and promote nerve regeneration in SCI.

MSC-sEVs in brain injury: Hypoxic ischemia (HI) is closely related to mortality in preterm infants. MSC-sEVs have neuroprotective potential in treating hypoxic-ischemic injury. Systemic administration of MSC-sEVs rather than intact MSCs promotes the recovery of brain function in preterm infants after hypoxic ischemia and prevents structural damage^[33]. MiR-133b was reported to be the foremost mechanism involved in the enhancement of brain recovery in brain injury. MSCs rebalance miR-133b expression in ischemic brain tissue. It was observed that the ischemic environment leads to abundant expression of miR-133b in MSC-sEVs, and therefore, neuronal growth was enhanced by inhibiting the expression of Ras homolog family member A^[34].

Traumatic brain injury (TBI) is a common injury in neurosurgery worldwide. There are no effective medications to reduce TBI mortality and improve functional recovery. Cell therapy, including MSCs, has shown promise for TBI. However, relatively few MSCs can be injected intracranially. Intra-arterial injection of MSCs may cause cerebral ischemia. Intravenous injection can cause the distribution of MSCs throughout the body. Recent studies have indicated that MSC-sEVs reduce cognitive impairment in TBI mouse models. sEVs may be safer, and do not induce microvascular embolism. This may open up new clinical applications for TBI intervention^[30].

MSC-sEVs in neurodegenerative diseases: Alzheimer's disease (AD) is a kind of neurodegenerative disease resulting from progressive neuronal death in the hippocampus and cerebral cortex. The accumulation of β -amyloid peptide (A β) can cause neuroinflammation, which in turn leads to memory impairment and AD^[35]. In recent years, cell therapy has become a potential treatment for AD. Injection of MSCs can reduce the accumulation of A β and alleviate the inflammation in a mouse model^[36]. MSC-sEVs reduce neuroinflammation and promote nerve regeneration by clearing A β . Neprilysin (NEP) is the most important metalloendopeptidase related to A β proteolysis. MSC-sEVs contained enzymatically active NEP that prompts the possibility of reducing A β accumulation^[37].

Parkinson's disease (PD) is a motor dysfunction caused by the decrease of dopaminergic neurons in the midbrain. Researchers found that injection of the human bone marrow-derived MSC (hBMSC) secretome have neuroprotective effects in a rat model of PD. Granulocyte colony-stimulating factor and hBMSC combination therapy has beneficial effects on a PD model. Proteomic analysis showed that hBMSC-sEVs but not hBMSC transplantation have positive effects^[38,39]. Sadan *et al*^[40] utilized engineered MSCs producing and secreting high levels of factors such as brain-derived neurotrophic factor and glial-derived neurotrophic factor. The transplantation inhibited dopamine depletion to 72% in the contralateral striatum, which provided a treatment strategy for PD using-modified MSC-sEVs^[40].

MSC-sEVs in treatment of orthopedic diseases

MSC-sEVs in fractures: Accidents, sports injuries, and other reasons lead to many fractures each day in the world. Bone tissue engineering has emerged as an attractive strategy for fracture repair. This method involves the combination of cells and bioactive factors with bone substitutes to enhance their capacity of osteogenesis and angiogenesis^[41]. Liu *et al*^[42] found that hypoxia-treated MSC-sEVs have a therapeutic

role in fracture healing. MSC-sEVs under hypoxia exert their proangiogenic effect by transporting exosomal miR-126 to endothelial cells in an extracellular regulated protein kinases (ERK) pathway-dependent manner^[42]. Liang *et al*^[43] found that MSC-sEV transplantation improved bone regeneration in rats. Phosphatase and tensin homolog deleted on chromosome ten (PTEN) is known as a tumor suppressing gene. Lack of PTEN will lead to the formation of new blood vessels. MSC-sEVs could downregulate PTEN and promote angiogenesis. In addition, dimethylxaloylglycine-stimulated human bone marrow MSC-sEVs promote bone regeneration through angiogenesis^[43].

MSC-sEVs in cartilage regeneration: MSCs have the potential to regenerate cartilage in animal and preclinical studies^[44]. Direct action of MSC-sEVs on chondrocytes triggers a series of positive responses from chondrocytes. CD73 carried by MSC-sEVs regulates the adenosine-activated AKT and ERK signaling pathways, promotes the proliferation and migration of chondrocytes, and inhibits apoptosis. MSC-sEVs promote the expression of chondrocyte genes (collagen and proteoglycan) and inhibit the expression of cartilage matrix metabolism and inflammation markers such as inducible nitric oxide synthase^[45].

Cartilage usually needs a long time to regenerate. Local MSC-sEV injection that was conducted weekly increased the pain of patients. Liu *et al*^[46] developed a light-induced imine-crosslinked hydrogel that was easy to use, biocompatible, integrated with cartilage, and functionalized with human induced pluripotent stem derived MSC-sEVs to make cell-free tissue patches for cartilage regeneration. It was found that cell-free tissue patches retain MSC-sEVs *in vitro* and actively regulate chondrocytes and bone marrow stem cells. In addition, cell-free tissue patches could be combined with natural cartilage matrix and promote the deposition of cells at the site of cartilage defects, ultimately promoting the repair of cartilage defects^[46].

MSC-sEVs in osteoarthritis: Osteoarthritis (OA) is a common degenerative disease caused by obesity, labor injury, and old age. The mechanism of osteoarthritis is complex and involves multiple processes and tissues. Autologous chondrocytes represent an important cell type in cartilage, which can provide a safe and effective solution. However, the inherent disadvantages are limited availability during *in vitro* expansion, dedifferentiation, and loss of function. MSC-based therapy represents a new and promising treatment strategy for OA in recent years. It is reported that cartilage in joints could be protected from degeneration by intra-articular injection of bone marrow MSCs, which could delay the development of OA. In addition, several clinical trials have shown that MSC-based treatment is a well-tolerated cell-based therapy by reducing inflammation of OA^[47].

Human embryonic stem cell-induced MSC (ESC-MSC) derived exosomes increase the expression of collagen type II (the main component of the cartilage matrix) in the cartilage matrix and decrease the expression of ADAMTS5 (a disintegrin and metalloprotease with thrombospondin-like repeat family of enzymes)^[48]. MSC-sEVs have some particular effects, such as promoting angiogenesis and inhibiting cell apoptosis and oxidative stress, which can help rescue of OA. MSC-sEVs promote the proliferation and migration of chondrocytes^[49]. Some miRNAs in MSC-sEVs can exert a therapeutic effect against OA through their regulatory role in proliferation and cartilage formation. For example, miR-92a in MSC-sEVs can alleviate OA by upregulating chondrocyte proliferation and matrix synthesis through the PI3K/AKT/mTOR pathway. *In vivo*, enhanced cartilage regeneration and prevention of OA were demonstrated in rats that were treated with miR-140-5p-transported MSC-sEVs^[47].

MSC-sEVs in treatment of lung diseases

MSC-sEVs in acute respiratory distress syndrome: The clinical manifestations of acute respiratory distress syndrome (ARDS) are progressive hypoxemia and respiratory distress. The clinical features include injury of alveolar epithelial and capillary endothelial cells, leading to diffuse pulmonary interstitial and alveolar edema. However, there is still no specific therapy for ARDS^[50]. MSC therapy has the ability to regulate immunity and inflammation, and prevent lung injury caused by infection and regeneration through differentiation or paracrine mechanisms^[51]. There is increasing evidence that stem cell-derived conditioned medium and/or extracellular vesicles may be convincing alternatives^[52]. Zhu *et al*^[53] found that MSC-sEVs have a therapeutic effect on endotoxin-induced ALI, partly attributed to the expression of keratinocyte growth factor mRNA in the injured alveoli^[53]. Khatri *et al*^[54] showed that transfer of RNA from EVs to epithelial cells is the primary cause of the anti-influenza

property of MSC-sEVs. In a swine influenza virus model, intratracheal injection of MSC-sEV_s significantly reduced the release of virus in nasal swabs from infected pigs at 12 h after infection, inhibited replication of influenza virus, and downregulated virus associated pro-inflammatory cytokines. Histopathological results showed that MSC-sEVs could reduce the lung injury of pigs caused by influenza virus^[54]. Stone *et al*^[55] found that sEVs derived from MSCs reduce lung inflammation and injury after ischemia-reperfusion and promote *ex vivo* lung perfusion-mediated donor lung repair. The therapeutic effect of MSC-sEVs is partly mediated by reducing the anti-inflammatory mechanism of immune cell activation and protecting the integrity of the endothelial barrier to prevent pulmonary edema^[55].

MSC-sEVs in pulmonary fibrosis: Pulmonary fibrosis is a serious consequence of changes in normal lung tissue structure and loss of function. Mansouri *et al*^[56] examined the therapeutic effect of human bone marrow MSC-sEVs in a bleomycin induced pulmonary fibrosis model and explored the mechanism. They found that MSC-sEVs effectively prevent or reverse bleomycin-induced pulmonary fibrosis through systematic regulation of the monocyte phenotype^[56]. MSC-sEVs are profitable in ALI and lung fibrosis. Shentu *et al*^[57] demonstrated that MSC-sEVs but not fibroblast sEVs (fsEVs) inhibit transforming growth factor (TGF- β 1) induced myofibroblast differentiation or idiopathic pulmonary fibrosis lung fibroblasts. Compared with fsEVs, MSC-sEVs showed a time and dose-dependent increase in cell uptake. Downregulating Thy-1 (CD90) or blocking Thy-1-integrin interactions reduced MSC-sEVs uptake and prevented the inhibition of myofibroblast differentiation^[57].

MSC-sEVs in pulmonary hypertension: Pulmonary hypertension (PAH) is defined as an average resting pulmonary arterial pressure of ≥ 25 mmHg^[58]. PAH is often a progressive and ultimately fatal disease. Adipose-derived mesenchymal stem cells (ADMSCs) and ADMSC-derived sEVs (ADMSC-sEVs) have protective effects in PAH. ADMSCs increased the proliferation of monocrotaline pyrrole (MCTP)-treated human pulmonary artery endothelial cells (HPAECs) through coculture of ADMSCs and MCTP-treated HPAECs. The expression of bone morphogenetic protein receptor 2 (BMPR2) in HPAECs and PAH mice was inhibited by miR-191 in ADMSCs and ADMSC-sEVs^[58]. Hogan *et al*^[59] found that MSC-sEVs recovered the mitochondrial dysfunction that is associated with PAH. MSC-sEVs improve energy balance and ameliorate O₂ consumption, which plays a role in enhancing mitochondrial function in pulmonary arterial hypertension^[59]. Lung morphology, pulmonary fibrosis, right ventricular (RV) hypertrophy, right ventricular systolic pressure, RV/body weight ratio (RV:BW), and pulmonary vascular remodeling can be significantly improved by MSC-sEVs derived from either human bone marrow or the umbilical cord Wharton's jelly^[60].

MSC-sEVs in bronchial dysplasia: Bronchopulmonary dysplasia (BPD) is a chronic lung disease that appears during infancy with high morbidity in premature infants. Premature babies with conditions such as respiratory distress syndrome are at an increased risk of developing BPD. Despite improvements in clinical treatment, the incidence of BPD has not decreased. MSC-sEVs significantly increase the tubular network of HUVECs, partly through a VEGF-mediated mechanism. Daily intraperitoneal injection of MSC-sEVs increases the number and size of pulmonary vessels by promoting angiogenesis^[61]. The therapeutic effect of MSC-sEVs was blocked by tumor necrosis factor (TNF)-stimulated gene-6 (TSG-6) gene knockout in MSCs or injection of TSG-neutralizing antibody in BPD mice. The levels of the proinflammatory cytokines such as interleukin-6 (IL-6), TNF- α , and IL-1 in peripheral blood and TSG-6-treated BPD mice were decreased, suggesting their regulatory role in lung injury^[62]. The effect of MSC-sEVs on the pulmonary macrophage phenotype is the basis of their therapeutic effect by regulating hyperoxia (HYRX, 75% O₂)-induced bronchopulmonary dysplasia. Early intervention and slowing the early inflammatory phase induced by HYRX are critical in maintaining normal lung development^[63].

MSC-sEVs in treatment of liver diseases

MSC-sEVs has produced profitable effects in various animal models of hepatic disease, such as acute liver injury and liver fibrosis^[64]. Tan *et al*^[65] demonstrated that MSC-sEVs can protect the liver from toxic injury by activating proliferation and regeneration^[65]. Yan *et al*^[66] demonstrated that glutathione peroxidase 1 (GPX1) derived from human umbilical MSC-sEVs can detoxicate carbon tetrachloride (CCl₄) and H₂O₂, and alleviate oxidative stress and apoptosis. Silencing GPX1 in hucMSCs reduced the antioxidant and anti-apoptotic abilities of hucMSCs-sEVs, and decreased the hepatoprotective effect of hucMSCs-sEVs *in vitro* and *in vivo*^[66]. Li *et al*^[67] showed that human umbilical

cord MSC-sEVs suppressed liver fibrosis through inhibition of epithelial mesenchymal transition and collagen deposition in a CCl₄-induced liver injury mouse model. The potential mechanism is related to decreasing TGF- β 1, the phosphorylation of Smad2, and the expression of collagen types I and III^[67]. MiR-122 target genes were found to participate in hepatic stellate cell (HSC) proliferation and collagen maturation. MiR-122 modification increased the therapeutic efficacy of AMSCs on CCl₄ induced liver fibrosis by inhibiting HSC activation and alleviating collagen sedimentation. Therefore, delivery of miR-122 through exosome mediated communication is a promising strategy for the treatment of liver fibrosis^[68].

MSC-sEVs in treatment of skin diseases

Extensive burns and trauma could lead to skin damage and result in acute or chronic wounds^[69]. In recent years, MSCs have been used in wound healing and regeneration, increasing angiogenesis, resolving wound inflammation, favorably improving extracellular matrix (ECM) remodeling, and promoting skin tissue regeneration^[70]. Recently, MSC-sEVs have gained much attention in the field of skin repairing.

There are three overlapping stages during wound healing, including the inflammation, proliferation, and remodeling^[71]. MSC-sEVs possess effective anti-inflammatory properties and promote the macrophages toward M2 phenotype which is beneficial for wound healing^[72]. MSC-sEVs are enriched in angiogenesis associated miRNAs and proteins^[73,74]. Liang *et al*^[75] indicated that miR-125a, which was enriched in ADMSC-sEVs, could improve endothelial cell angiogenesis by upregulating the levels of the angiogenic inhibitor^[75]. One study revealed that sEVs from hypoxia-treated human ADMSCs could significantly promote angiogenesis by upregulating VEGF-R/VEGF^[76]. The migration of fibroblasts could be regulated by MSC-sEVs^[15,77]. ECM reconstruction plays an important role in the process of wound healing. Zhang *et al*^[78] found that human induced pluripotent stem cell-derived MSC-derived sEVs (hiPSC-MSC-sEVs) were beneficial for cutaneous wound healing in a rat model by improving collagen synthesis and angiogenesis^[78]. In a word, MSC-sEVs play a vital role in wound healing.

THERAPEUTIC CONSIDERATIONS AND PROSPECTS

As described above, the future of MSC-derived sEV therapy has great potential. However, there are some challenges from lab to clinical practice that need to be considered.

Standard methods for separation and purification of MSC-sEVs

The guidelines of MISEV 2018 provide recommendations in six major areas: (1) Nomenclature; (2) Collection and preprocessing of fluids for EV extraction; (3) EV preparation and concentration; (4) EV characterization; (5) Functional studies; and (6) Reporting^[8].

In the clinical setting, it is very important that MSC-sEV preparations are manufactured reproducibly^[79]. To date, there is no perfect technology to separate EVs for either clinical or basic research. The conventional and most widely used method to isolate EVs is differential centrifugation^[8,80]. Although ultrafiltration concentrates conditioned medium into a sucrose cushion after ultracentrifugation^[81-83], this method cannot produce highly pure EVs. Moreover, ultracentrifugation may result in sEV aggregation and poor resuspension^[84]. Precipitation with polyethylene glycol or other polymers is a reproducible and scalable way to enrich EVs, which has been used in EV-based clinical trials^[85,86]. However, because of abundant coprecipitates, this kind of method cannot produce pure EVs. Recently, tangential flow filtration and size exclusion chromatography have gained increasing attention. These size-based fractionation methods are adopted as highly scalable and GMP-compatible technologies. Compared with legacy methods, these methods could produce more comparable, superior purity, and functional EVs at the same time^[85,87]. Finally, these methods should also be standardized to ensure the purity, reproducibility, and maintenance of EV functional properties.

Characterization and quality control of MSC-sEVs

There are no gold standards for EV identification and analysis currently. MISEV 2018 defined some minimal requirements for identifying EVs^[8]. MSC-sEV preparations must first correspond to the International Society for Cellular Therapy (ISCT) minimal criteria: (1) At least one protein of each category 1 to 3 must be evaluated in any EV

preparation; (2) At least one negative protein marker; (3) Electron or atomic force microscopy; and (4) Single particle analyzers. Moreover, MSC-sEV-specific antigens need to be identified. According to the ISCT minimal criteria, MSC surface antigens, such as CD73, CD90, and CD105, have been found in many published MSC-EV proteomics datasets. In contrast, three non-MSC surface antigens (CD14, CD34, and CD11b) from the ISCT minimal criteria were not found in these datasets^[88].

As a prerequisite for the clinical use of EV agents, quality control criteria must be established that include not only the physicochemical and molecular parameters described above but also functional parameters. Because of the diversity of active constituents, EVs are thought to act in a complex manner, so therapeutic activity cannot be proposed solely through molecular analysis for pharmaceutical characterization. Biological assays should be developed that allow for the prediction of EV functional properties. Moreover, MSC-sEVs have therapeutic potential in many kinds of diseases. We think that the biotherapy activity of MSC-sEVs for specific diseases should be separately tested in qualified biological assays.

Enhancement of therapeutic potential of MSC-sEVs

MSC-derived sEVs are enriched with growth factors, cytokines, lipids, mRNAs, and therapeutic miRNAs. Multiple kinds of stimulation of MSCs, such as biophysical or biochemical methods, as well as cellular reprogramming, have been shown to influence the contents and enhance the therapeutic efficacy of subsequent MSC-sEVs^[89,90].

Multiple different biophysical stimuli have been tested in MSCs, including electric pulsing, low-power laser irradiation, 2D and 3D culture, and magnetic forces^[90]. MSCs are normally cultured on 2D plastic surfaces, which lack the conditions of physiological niche of MSCs. 3D bioreactor culture increases the production of sEVs from MSCs; furthermore, EVs from hMSCs cultured in 3D scaffolds showed better outcomes in a model of traumatic brain injury than those from hMSCs cultured in 2D conditions^[91,92]. Hypoxic conditions (5% O₂) increased the proliferation and viability of MSCs. MSC-sEVs under hypoxic conditions showed increased vascular tube formation compared to that of normoxic MSC-EVs^[93].

Pretreatment of MSCs with cytokines and other biochemical agents has been widely studied. Recent studies revealed that proinflammatory cytokines such as IL-1 β , IL-6, TNF- α , TGF- β , and IFN- γ could enhance the therapeutic efficacy of MSCs effectively^[94,95]. Pre-conditioning of ADMSCs with platelet-derived growth factor stimulated the secretion of EVs with enhanced angiogenic potential^[96].

Immortalized MSCs by genetic modification could continuously produce sEVs, which will improve the batch-to-batch reproducibility of sEVs^[84]. Chen *et al.*^[97] showed that the functionality of MSC-sEVs is preserved after immortalization^[97]. sEVs secreted by GATA-4-overexpressing MSCs improved cardiac function in a myocardial infarction mouse model^[98]. Likewise, sEVs from chemokine (C-X-C motif) receptor 4 (CXCR4)-overexpressing MSCs promoted tube formation of HUVECs and exhibited a cardioprotective effect in a myocardial infarction rat model^[99]. sEVs from HIF-1 α -overexpressing MSCs increased angiogenic activity, which promoted cardiac tissue repair in a mouse model^[100].

EVs can avoid immune responses, penetrate the blood-brain barrier, and avoid the degradation by RNase during migration^[101,102]. These characteristics make them an attractive and promising drug delivery tool^[103]. Chemicals, RNAs, and peptides can be delivered as therapeutic agents to patients. MSCs pretreated with paclitaxel showed strong antitumor activity by uptake and then releasing the drug^[104]. MiRNAs show therapeutic potential for many diseases by targeting transcriptional and posttranscriptional regulation. EVs prove to be an effective vehicle for miRNA delivery. MiR-93-5p-overexpressing MSC-sEVs showed a myocardial protective effect by inhibiting inflammatory response and autophagy^[105]. MiR-122 inhibits liver fibrosis by inhibiting the proliferation of hepatic cells. EVs from ADMSCs overexpressing miR-122 alleviate collagen deposition and enhance the therapeutic efficacy of ADMSCs for the treatment of liver fibrosis^[68]. EVs from miR-133b-overexpressing MSCs have increased neuroprotective and regenerative activity^[106].

CONCLUSION

As a cell-free therapy, EVs minimize safety concerns with the administration of live cells. MSC-derived sEVs have therapeutic potential in brain, heart, liver, lung, skin, and bone diseases. Next, guidelines and standards for purity and quality control of

isolated MSC-derived sEVs will be the main challenge in establishing platforms for clinical grade sEV production. Standardized and improved protocols for EV isolation and storage, as well as quantifiable, robust, and reproducible assays that predict the therapeutic capacity of MSC-sEVs, will promote the application of MSC-sEVs from the laboratory to the clinic.

REFERENCES

- 1 **Prockop DJ.** Marrow stromal cells as stem cells for nonhematopoietic tissues. *Science* 1997; **276**: 71-74 [PMID: [9082988](#) DOI: [10.1126/science.276.5309.71](#)]
- 2 **Rubio D,** Garcia S, De la Cueva T, Paz MF, Lloyd AC, Bernad A, Garcia-Castro J. Human mesenchymal stem cell transformation is associated with a mesenchymal-epithelial transition. *Exp Cell Res* 2008; **314**: 691-698 [PMID: [18201695](#) DOI: [10.1016/j.yexcr.2007.11.017](#)]
- 3 **Breitbart M,** Bostani T, Roell W, Xia Y, Dewald O, Nygren JM, Fries JW, Tiemann K, Bohlen H, Hescheler J, Welz A, Bloch W, Jacobsen SE, Fleischmann BK. Potential risks of bone marrow cell transplantation into infarcted hearts. *Blood* 2007; **110**: 1362-1369 [PMID: [17483296](#) DOI: [10.1182/blood-2006-12-063412](#)]
- 4 **Schrepfer S,** Deuse T, Reichenspurner H, Fischbein MP, Robbins RC, Pelletier MP. Stem cell transplantation: the lung barrier. *Transplant Proc* 2007; **39**: 573-576 [PMID: [17362785](#) DOI: [10.1016/j.transproceed.2006.12.019](#)]
- 5 **Harrell CR,** Jovicic N, Djonov V, Arsenijevic N, Volarevic V. Mesenchymal Stem Cell-Derived Exosomes and Other Extracellular Vesicles as New Remedies in the Therapy of Inflammatory Diseases. *Cells* 2019; **8**: 1605 [PMID: [31835680](#) DOI: [10.3390/cells8121605](#)]
- 6 **Mardpour S,** Hamidieh AA, Taleahmad S, Sharifzad F, Taghikhani A, Baharvand H. Interaction between mesenchymal stromal cell-derived extracellular vesicles and immune cells by distinct protein content. *J Cell Physiol* 2019; **234**: 8249-8258 [PMID: [30378105](#) DOI: [10.1002/jcp.27669](#)]
- 7 **Harrell CR,** Jankovic MG, Fellabaum C, Volarevic A, Djonov V, Arsenijevic A, Volarevic V. Molecular Mechanisms Responsible for Anti-inflammatory and Immunosuppressive Effects of Mesenchymal Stem Cell-Derived Factors. *Adv Exp Med Biol* 2019; **1084**: 187-206 [PMID: [31175638](#) DOI: [10.1007/5584_2018_306](#)]
- 8 **Théry C,** Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, Antoniou A, Arab T, Archer F, Atkin-Smith GK, Ayre DC, Bach JM, Bachurski D, Baharvand H, Balaj L, Baldacchino S, Bauer NN, Baxter AA, Bebawy M, Beckham C, Bedina Zavec A, Benmoussa A, Berardi AC, Bergese P, Bielska E, Blenkiron C, Bobis-Wozowicz S, Boilard E, Boireau W, Bongiovanni A, Borràs FE, Bosch S, Boulanger CM, Breakefield X, Breglio AM, Brennan MÁ, Brigstock DR, Brisson A, Broekman ML, Bromberg JF, Bryl-Górecka P, Buch S, Buck AH, Burger D, Busatto S, Buschmann D, Bussolati B, Buzás EL, Byrd JB, Camussi G, Carter DR, Caruso S, Chamley LW, Chang YT, Chen C, Chen S, Cheng L, Chin AR, Clayton A, Clerici SP, Cocks A, Cocucci E, Coffey RJ, Cordeiro-da-Silva A, Couch Y, Coumans FA, Coyle B, Crescitelli R, Criado MF, D'Souza-Schorey C, Das S, Datta Chaudhuri A, de Candia P, De Santana EF, De Wever O, Del Portillo HA, Demaret T, Deville S, Devitt A, Dhondt B, Di Vizio D, Dieterich LC, Dolo V, Dominguez Rubio AP, Dominici M, Dourado MR, Driedonks TA, Duarte FV, Duncan HM, Eichenberger RM, Ekström K, El Andaloussi S, Elie-Caille C, Erdbrügger U, Falcón-Pérez JM, Fatima F, Fish JE, Flores-Bellver M, Förstner A, Frelet-Barrand A, Fricke F, Fuhrmann G, Gabrielsson S, Gámez-Valero A, Gardiner C, Gärtner K, Gaudin R, Gho YS, Giebel B, Gilbert C, Gimona M, Giusti I, Goberdhan DC, Görgens A, Gorski SM, Greening DW, Gross JC, Gualerzi A, Gupta GN, Gustafson D, Handberg A, Haraszti RA, Harrison P, Hegyesi H, Hendrix A, Hill AF, Hochberg FH, Hoffmann KF, Holder B, Holthofer H, Hosseinkhani B, Hu G, Huang Y, Huber V, Hunt S, Ibrahim AG, Ikezu T, Inal JM, Isin M, Ivanova A, Jackson HK, Jacobsen S, Jay SM, Jayachandran M, Jenster G, Jiang L, Johnson SM, Jones JC, Jong A, Jovanovic-Talman T, Jung S, Kalluri R, Kano SI, Kaur S, Kawamura Y, Keller ET, Khamari D, Khomyakova E, Khvorova A, Kierulf P, Kim KP, Kislinger T, Klingeborn M, Klinker DJ 2nd, Kornek M, Kosanović MM, Kovács ÁF, Krämer-Albers EM, Krasemann S, Krause M, Kurochkin IV, Kusuma GD, Kuypers S, Laitinen S, Langevin SM, Languino LR, Lannigan J, Lässer C, Laurent LC, Lavieu G, Lázaro-Ibáñez E, Le Lay S, Lee MS, Lee YXF, Lemos DS, Lenassi M, Leszczynska A, Li IT, Liao K, Libregts SF, Ligeti E, Lim R, Lim SK, Linē A, Linnemannstöns K, Llorente A, Lombard CA, Lorenowicz MJ, Lörincz ÁM, Lötvall J, Lovett J, Lowry MC, Loyer X, Lu Q, Lukomska B, Lunavat TR, Maas SL, Malhi H, Marcilla A, Mariani J, Mariscal J, Martens-Uzunova ES, Martin-Jaular L, Martinez MC, Martins VR, Mathieu M, Mathivanan S, Maugeri M, McGinnis LK, McVey MJ, Meckes DG Jr, Meehan KL, Mertens I, Minciacci VR, Möller A, Möller Jørgensen M, Morales-Kastresana A, Morhayim J, Mullier F, Muraca M, Musante L, Mussack V, Muth DC, Myburgh KH, Najrana T, Nawaz M, Nazarenko I, Nejsun P, Neri C, Neri T, Nieuwland R, Nimrichter L, Nolan JP, Nolte-t Hoen EN, Noren Hooten N, O'Driscoll L, O'Grady T, O'Loughlin A, Ochiya T, Olivier M, Ortiz A, Ortiz LA, Osteikoetxea X, Østergaard O, Ostrowski M, Park J, Pegtel DM, Peinado H, Perut F, Pfaffl MW, Phinney DG, Pieters BC, Pink RC, Pisetsky DS, Pogge von Strandmann E, Polakovicova I, Poon IK, Powell BH, Prada I, Pulliam L, Quesenberry P, Radeghieri A, Raffai RL, Raimondo S, Rak J, Ramirez MI, Raposo G, Rayyan MS, Regev-Rudzki N, Ricklefs FL, Robbins PD, Roberts DD,

- Rodrigues SC, Rohde E, Rome S, Rouschop KM, Rugghetti A, Russell AE, Saá P, Sahoo S, Salas-Huenaleo E, Sánchez C, Saugstad JA, Saul MJ, Schiffelers RM, Schneider R, Schøyen TH, Scott A, Shahaj E, Sharma S, Shatmyeva O, Shekari F, Shelke GV, Shetty AK, Shiba K, Siljander PR, Silva AM, Skowronek A, Snyder OL 2nd, Soares RP, Sódar BW, Soekmadji C, Sotillo J, Stahl PD, Stoorvogel W, Stott SL, Strasser EF, Swift S, Tahara H, Tewari M, Timms K, Tiwari S, Tixeira R, Tkach M, Toh WS, Tomasini R, Torrecilhas AC, Tosar JP, Toxavidis V, Urbanelli L, Vader P, van Balkom BW, van der Grein SG, Van Deun J, van Herwijnen MJ, Van Keuren-Jensen K, van Niel G, van Royen ME, van Wijnen AJ, Vasconcelos MH, Vechetti IJ Jr, Veit TD, Vella LJ, Velot É, Verweij FJ, Vestad B, Viñas JL, Visnovitz T, Vukman KV, Wahlgren J, Watson DC, Wauben MH, Weaver A, Webber JP, Weber V, Wehman AM, Weiss DJ, Welsh JA, Wendt S, Wheelock AM, Wiener Z, Witte L, Wolfram J, Xagorari A, Xander P, Xu J, Yan X, Yáñez-Mó M, Yin H, Yuana Y, Zappulli V, Zarubova J, Žekas V, Zhang JY, Zhao Z, Zheng L, Zheutlin AR, Zickler AM, Zimmermann P, Zivkovic AM, Zocco D, Zuba-Surma EK. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles* 2018; **7**: 1535750 [PMID: 30637094 DOI: 10.1080/20013078.2018.1535750]
- 9 **Arslan F**, Lai RC, Smeets MB, Akeroyd L, Choo A, Aguor EN, Timmers L, van Rijen HV, Doevendans PA, Pasterkamp G, Lim SK, de Kleijn DP. Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress and activate PI3K/Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/reperfusion injury. *Stem Cell Res* 2013; **10**: 301-312 [PMID: 23399448 DOI: 10.1016/j.scr.2013.01.002]
 - 10 **Lin KC**, Yip HK, Shao PL, Wu SC, Chen KH, Chen YT, Yang CC, Sun CK, Kao GS, Chen SY, Chai HT, Chang CL, Chen CH, Lee MS. Combination of adipose-derived mesenchymal stem cells (ADMSC) and ADMSC-derived exosomes for protecting kidney from acute ischemia-reperfusion injury. *Int J Cardiol* 2016; **216**: 173-185 [PMID: 27156061 DOI: 10.1016/j.ijcard.2016.04.061]
 - 11 **Kim DK**, Nishida H, An SY, Shetty AK, Bartosh TJ, Prockop DJ. Chromatographically isolated CD63+CD81+ extracellular vesicles from mesenchymal stromal cells rescue cognitive impairments after TBI. *Proc Natl Acad Sci USA* 2016; **113**: 170-175 [PMID: 26699510 DOI: 10.1073/pnas.1522297113]
 - 12 **Zhang B**, Shi Y, Gong A, Pan Z, Shi H, Yang H, Fu H, Yan Y, Zhang X, Wang M, Zhu W, Qian H, Xu W. HucMSC Exosome-Delivered 14-3-3ζ Orchestrates Self-Control of the Wnt Response via Modulation of YAP During Cutaneous Regeneration. *Stem Cells* 2016; **34**: 2485-2500 [PMID: 27334574 DOI: 10.1002/stem.2432]
 - 13 **Suzuki E**, Fujita D, Takahashi M, Oba S, Nishimatsu H. Therapeutic Effects of Mesenchymal Stem Cell-Derived Exosomes in Cardiovascular Disease. *Adv Exp Med Biol* 2017; **998**: 179-185 [PMID: 28936740 DOI: 10.1007/978-981-10-4397-0_12]
 - 14 **Lu Z**, Chen Y, Dunstan C, Roohani-Esfahani S, Zreiqat H. Priming Adipose Stem Cells with Tumor Necrosis Factor-Alpha Preconditioning Potentiates Their Exosome Efficacy for Bone Regeneration. *Tissue Eng Part A* 2017; **23**: 1212-1220 [PMID: 28346798 DOI: 10.1089/ten.tea.2016.0548]
 - 15 **Shabbir A**, Cox A, Rodriguez-Menocal L, Salgado M, Van Badiavas E. Mesenchymal Stem Cell Exosomes Induce Proliferation and Migration of Normal and Chronic Wound Fibroblasts, and Enhance Angiogenesis In Vitro. *Stem Cells Dev* 2015; **24**: 1635-1647 [PMID: 25867197 DOI: 10.1089/scd.2014.0316]
 - 16 **Liu J**, Chen T, Lei P, Tang X, Huang P. Exosomes Released by Bone Marrow Mesenchymal Stem Cells Attenuate Lung Injury Induced by Intestinal Ischemia Reperfusion via the TLR4/NF-κB Pathway. *Int J Med Sci* 2019; **16**: 1238-1244 [PMID: 31588189 DOI: 10.7150/ijms.35369]
 - 17 **Ricklin D**, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. *Nat Immunol* 2010; **11**: 785-797 [PMID: 20720586 DOI: 10.1038/ni.1923]
 - 18 **Roos A**, Xu W, Castellano G, Nauta AJ, Garred P, Daha MR, van Kooten C. Mini-review: A pivotal role for innate immunity in the clearance of apoptotic cells. *Eur J Immunol* 2004; **34**: 921-929 [PMID: 15048702 DOI: 10.1002/eji.200424904]
 - 19 **Kemper C**, Atkinson JP, Hourcade DE. Properdin: emerging roles of a pattern-recognition molecule. *Annu Rev Immunol* 2010; **28**: 131-155 [PMID: 19947883 DOI: 10.1146/annurev-immunol-030409-101250]
 - 20 **Barile L**, Lionetti V, Cervio E, Matteucci M, Gherghiceanu M, Popescu LM, Torre T, Siclari F, Moccetti T, Vassalli G. Extracellular vesicles from human cardiac progenitor cells inhibit cardiomyocyte apoptosis and improve cardiac function after myocardial infarction. *Cardiovasc Res* 2014; **103**: 530-541 [PMID: 25016614 DOI: 10.1093/cvr/cvu167]
 - 21 **Garikipati VNS**, Shoja-Taheri F, Davis ME, Kishore R. Extracellular Vesicles and the Application of System Biology and Computational Modeling in Cardiac Repair. *Circ Res* 2018; **123**: 188-204 [PMID: 29976687 DOI: 10.1161/CIRCRESAHA.117.311215]
 - 22 **Zhu LP**, Tian T, Wang JY, He JN, Chen T, Pan M, Xu L, Zhang HX, Qiu XT, Li CC, Wang KK, Shen H, Zhang GG, Bai YP. Hypoxia-elicited mesenchymal stem cell-derived exosomes facilitates cardiac repair through miR-125b-mediated prevention of cell death in myocardial infarction. *Theranostics* 2018; **8**: 6163-6177 [PMID: 30613290 DOI: 10.7150/thno.28021]
 - 23 **Zhao J**, Li X, Hu J, Chen F, Qiao S, Sun X, Gao L, Xie J, Xu B. Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization. *Cardiovasc Res* 2019; **115**: 1205-1216 [PMID: 30753344 DOI: 10.1093/cvr/cvz016]

- 10.1093/cvr/cvz040]
- 24 **Wang K**, Jiang Z, Webster KA, Chen J, Hu H, Zhou Y, Zhao J, Wang L, Wang Y, Zhong Z, Ni C, Li Q, Xiang C, Zhang L, Wu R, Zhu W, Yu H, Hu X, Wang J. Enhanced Cardioprotection by Human Endometrium Mesenchymal Stem Cells Driven by Exosomal MicroRNA-21. *Stem Cells Transl Med* 2017; **6**: 209-222 [PMID: [28170197](#) DOI: [10.5966/sctm.2015-0386](#)]
 - 25 **Luo L**, Tang J, Nishi K, Yan C, Dinh PU, Cores J, Kudo T, Zhang J, Li TS, Cheng K. Fabrication of Synthetic Mesenchymal Stem Cells for the Treatment of Acute Myocardial Infarction in Mice. *Circ Res* 2017; **120**: 1768-1775 [PMID: [28298296](#) DOI: [10.1161/CIRCRESAHA.116.310374](#)]
 - 26 **Kishore R**, Khan M. More Than Tiny Sacks: Stem Cell Exosomes as Cell-Free Modality for Cardiac Repair. *Circ Res* 2016; **118**: 330-343 [PMID: [26838317](#) DOI: [10.1161/CIRCRESAHA.115.307654](#)]
 - 27 **Wei Y**, Wu Y, Zhao R, Zhang K, Midgley AC, Kong D, Li Z, Zhao Q. MSC-derived sEVs enhance patency and inhibit calcification of synthetic vascular grafts by immunomodulation in a rat model of hyperlipidemia. *Biomaterials* 2019; **204**: 13-24 [PMID: [30875515](#) DOI: [10.1016/j.biomaterials.2019.01.049](#)]
 - 28 **Du W**, Zhang K, Zhang S, Wang R, Nie Y, Tao H, Han Z, Liang L, Wang D, Liu J, Liu N, Han Z, Kong D, Zhao Q, Li Z. Enhanced proangiogenic potential of mesenchymal stem cell-derived exosomes stimulated by a nitric oxide releasing polymer. *Biomaterials* 2017; **133**: 70-81 [PMID: [28433939](#) DOI: [10.1016/j.biomaterials.2017.04.030](#)]
 - 29 **Yuan X**, Wu Q, Wang P, Jing Y, Yao H, Tang Y, Li Z, Zhang H, Xiu R. Exosomes Derived From Pericytes Improve Microcirculation and Protect Blood-Spinal Cord Barrier After Spinal Cord Injury in Mice. *Front Neurosci* 2019; **13**: 319 [PMID: [31040762](#) DOI: [10.3389/fnins.2019.00319](#)]
 - 30 **Xiong Y**, Mahmood A, Chopp M. Emerging potential of exosomes for treatment of traumatic brain injury. *Neural Regen Res* 2017; **12**: 19-22 [PMID: [28250732](#) DOI: [10.4103/1673-5374.198966](#)]
 - 31 **Riazifar M**, Mohammadi MR, Pone EJ, Yeri A, Lässer C, Segaliny AI, McIntyre LL, Shelke GV, Hutchins E, Hamamoto A, Calle EN, Crescitelli R, Liao W, Pham V, Yin Y, Jayaraman J, Lakey JRT, Walsh CM, Van Keuren-Jensen K, Lotvall J, Zhao W. Stem Cell-Derived Exosomes as Nanotherapeutics for Autoimmune and Neurodegenerative Disorders. *ACS Nano* 2019; **13**: 6670-6688 [PMID: [31117376](#) DOI: [10.1021/acsnano.9b01004](#)]
 - 32 **Zhou X**, Chu X, Yuan H, Qiu J, Zhao C, Xin D, Li T, Ma W, Wang H, Wang Z, Wang D. Mesenchymal stem cell derived EVs mediate neuroprotection after spinal cord injury in rats via the microRNA-21-5p/FasL gene axis. *Biomed Pharmacother* 2019; **115**: 108818 [PMID: [31102912](#) DOI: [10.1016/j.biopha.2019.108818](#)]
 - 33 **Ophelders DR**, Wolfs TG, Jellema RK, Zwanenburg A, Andriessen P, Delhaas T, Ludwig AK, Radtke S, Peters V, Janssen L, Giebel B, Kramer BW. Mesenchymal Stromal Cell-Derived Extracellular Vesicles Protect the Fetal Brain After Hypoxia-Ischemia. *Stem Cells Transl Med* 2016; **5**: 754-763 [PMID: [27160705](#) DOI: [10.5966/sctm.2015-0197](#)]
 - 34 **Gorabi AM**, Kiaie N, Barreto GE, Read MI, Tafti HA, Sahebkar A. The Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes in Treatment of Neurodegenerative Diseases. *Mol Neurobiol* 2019; **56**: 8157-8167 [PMID: [31197655](#) DOI: [10.1007/s12035-019-01663-0](#)]
 - 35 **Lee M**, Ban JJ, Yang S, Im W, Kim M. The exosome of adipose-derived stem cells reduces β -amyloid pathology and apoptosis of neuronal cells derived from the transgenic mouse model of Alzheimer's disease. *Brain Res* 2018; **1691**: 87-93 [PMID: [29625119](#) DOI: [10.1016/j.brainres.2018.03.034](#)]
 - 36 **Ding M**, Shen Y, Wang P, Xie Z, Xu S, Zhu Z, Wang Y, Lyu Y, Wang D, Xu L, Bi J, Yang H. Exosomes Isolated From Human Umbilical Cord Mesenchymal Stem Cells Alleviate Neuroinflammation and Reduce Amyloid-Beta Deposition by Modulating Microglial Activation in Alzheimer's Disease. *Neurochem Res* 2018; **43**: 2165-2177 [PMID: [30259257](#) DOI: [10.1007/s11064-018-2641-5](#)]
 - 37 **Katsuda T**, Oki K, Ochiya T. Potential application of extracellular vesicles of human adipose tissue-derived mesenchymal stem cells in Alzheimer's disease therapeutics. *Methods Mol Biol* 2015; **1212**: 171-181 [PMID: [25085563](#) DOI: [10.1007/7651_2014_98](#)]
 - 38 **Mendes-Pinheiro B**, Anjo SI, Manadas B, Da Silva JD, Marote A, Behie LA, Teixeira FG, Salgado AJ. Bone Marrow Mesenchymal Stem Cells' Secretome Exerts Neuroprotective Effects in a Parkinson's Disease Rat Model. *Front Bioeng Biotechnol* 2019; **7**: 294 [PMID: [31737616](#) DOI: [10.3389/fbioe.2019.00294](#)]
 - 39 **Ghahari L**, Safari M, Rahimi Jaber K, Jafari B, Safari K, Madadian M. Mesenchymal Stem Cells with Granulocyte Colony-Stimulating Factor Reduce Stress Oxidative Factors in Parkinson's Disease Iran Biomed J 2020; **24**: 89-98 [PMID: [31677610](#) DOI: [10.29252/ibj.24.2.89](#)]
 - 40 **Sadan O**, Bahat-Stromza M, Barhum Y, Levy YS, Pisman Y, Peretz H, Ilan AB, Bulvik S, Shemesh N, Krepel D, Cohen Y, Melamed E, Offen D. Protective effects of neurotrophic factor-secreting cells in a 6-OHDA rat model of Parkinson disease. *Stem Cells Dev* 2009; **18**: 1179-1190 [PMID: [19243240](#) DOI: [10.1089/scd.2008.0411](#)]
 - 41 **Storti G**, Sciolli MG, Kim BS, Orlandi A, Cervelli V. Adipose-Derived Stem Cells in Bone Tissue Engineering: Useful Tools with New Applications. *Stem Cells Int* 2019; **2019**: 3673857 [PMID: [31781238](#) DOI: [10.1155/2019/3673857](#)]
 - 42 **Liu W**, Li L, Rong Y, Qian D, Chen J, Zhou Z, Luo Y, Jiang D, Cheng L, Zhao S, Kong F, Wang J, Zhou Z, Xu T, Gong F, Huang Y, Gu C, Zhao X, Bai J, Wang F, Zhao W, Zhang L, Li X, Yin G, Fan J, Cai W. Hypoxic mesenchymal stem cell-derived exosomes promote bone fracture healing by the transfer of miR-126. *Acta Biomater* 2020; **103**: 196-212 [PMID: [31857259](#) DOI: [10.1016/j.actbio.2020.01.011](#)]

- 10.1016/j.actbio.2019.12.020]
- 43 **Liang B**, Liang JM, Ding JN, Xu J, Xu JG, Chai YM. Dimethylxaloylglycine-stimulated human bone marrow mesenchymal stem cell-derived exosomes enhance bone regeneration through angiogenesis by targeting the AKT/mTOR pathway. *Stem Cell Res Ther* 2019; **10**: 335 [PMID: 31747933 DOI: 10.1186/s13287-019-1410-y]
 - 44 **Wei H**, Chen J, Wang S, Fu F, Zhu X, Wu C, Liu Z, Zhong G, Lin J. A Nanodrug Consisting Of Doxorubicin And Exosome Derived From Mesenchymal Stem Cells For Osteosarcoma Treatment In Vitro. *Int J Nanomedicine* 2019; **14**: 8603-8610 [PMID: 31802872 DOI: 10.2147/IJN.S218988]
 - 45 **Cosenza S**, Ruiz M, Toupet K, Jorgensen C, Noël D. Mesenchymal stem cells derived exosomes and microparticles protect cartilage and bone from degradation in osteoarthritis. *Sci Rep* 2017; **7**: 16214 [PMID: 29176667 DOI: 10.1038/s41598-017-15376-8]
 - 46 **Liu X**, Yang Y, Li Y, Niu X, Zhao B, Wang Y, Bao C, Xie Z, Lin Q, Zhu L. Integration of stem cell-derived exosomes with in situ hydrogel glue as a promising tissue patch for articular cartilage regeneration. *Nanoscale* 2017; **9**: 4430-4438 [PMID: 28300264 DOI: 10.1039/c7nr00352h]
 - 47 **Toh WS**, Lai RC, Hui JHP, Lim SK. MSC exosome as a cell-free MSC therapy for cartilage regeneration: Implications for osteoarthritis treatment. *Semin Cell Dev Biol* 2017; **67**: 56-64 [PMID: 27871993 DOI: 10.1016/j.semcdb.2016.11.008]
 - 48 **Wang Y**, Yu D, Liu Z, Zhou F, Dai J, Wu B, Zhou J, Heng BC, Zou XH, Ouyang H, Liu H. Exosomes from embryonic mesenchymal stem cells alleviate osteoarthritis through balancing synthesis and degradation of cartilage extracellular matrix. *Stem Cell Res Ther* 2017; **8**: 189 [PMID: 28807034 DOI: 10.1186/s13287-017-0632-0]
 - 49 **Pourakbari R**, Khodadadi M, Aghebati-Maleki A, Aghebati-Maleki L, Yousefi M. The potential of exosomes in the therapy of the cartilage and bone complications; emphasis on osteoarthritis. *Life Sci* 2019; **236**: 116861 [PMID: 31513815 DOI: 10.1016/j.lfs.2019.116861]
 - 50 **Nanchal RS**, Truitt JD. Recent advances in understanding and treating acute respiratory distress syndrome. *F1000Res* 2018; **7**: F1000 Faculty Rev-1322 [PMID: 30210781 DOI: 10.12688/f1000research.15493.1]
 - 51 **Antebi B**, Mohammadipoor A, Batchinsky AI, Cancio LC. The promise of mesenchymal stem cell therapy for acute respiratory distress syndrome. *J Trauma Acute Care Surg* 2018; **84**: 183-191 [PMID: 29019797 DOI: 10.1097/TA.0000000000001713]
 - 52 **Liu A**, Zhang X, He H, Zhou L, Naito Y, Sugita S, Lee JW. Therapeutic potential of mesenchymal stem/stromal cell-derived secretome and vesicles for lung injury and disease. *Expert Opin Biol Ther* 2020; **20**: 125-140 [PMID: 31701782 DOI: 10.1080/14712598.2020.1689954]
 - 53 **Zhu YG**, Feng XM, Abbott J, Fang XH, Hao Q, Monsel A, Qu JM, Matthay MA, Lee JW. Human mesenchymal stem cell microvesicles for treatment of Escherichia coli endotoxin-induced acute lung injury in mice. *Stem Cells* 2014; **32**: 116-125 [PMID: 23939814 DOI: 10.1002/stem.1504]
 - 54 **Khatiri M**, Richardson LA, Meulia T. Mesenchymal stem cell-derived extracellular vesicles attenuate influenza virus-induced acute lung injury in a pig model. *Stem Cell Res Ther* 2018; **9**: 17 [PMID: 29378639 DOI: 10.1186/s13287-018-0774-8]
 - 55 **Stone ML**, Zhao Y, Robert Smith J, Weiss ML, Kron IL, Laubach VE, Sharma AK. Mesenchymal stromal cell-derived extracellular vesicles attenuate lung ischemia-reperfusion injury and enhance preconditioning of donor lungs after circulatory death. *Respir Res* 2017; **18**: 212 [PMID: 29268735 DOI: 10.1186/s12931-017-0704-9]
 - 56 **Mansouri N**, Willis GR, Fernandez-Gonzalez A, Reis M, Nassiri S, Mitsialis SA, Kourembanas S. Mesenchymal stromal cell exosomes prevent and revert experimental pulmonary fibrosis through modulation of monocyte phenotypes. *JCI Insight* 2019; **4**: e128060 [PMID: 31581150 DOI: 10.1172/jci.insight.128060]
 - 57 **Shentu TP**, Huang TS, Cernele-Kohan M, Chan J, Wong SS, Espinoza CR, Tan C, Gramaglia I, van der Heyde H, Chien S, Hagood JS. Thy-1 dependent uptake of mesenchymal stem cell-derived extracellular vesicles blocks myofibroblastic differentiation. *Sci Rep* 2017; **7**: 18052 [PMID: 29273797 DOI: 10.1038/s41598-017-18288-9]
 - 58 **Barberà JA**, Román A, Gómez-Sánchez MÁ, Blanco I, Otero R, López-Reyes R, Otero I, Pérez-Peñate G, Sala E, Escribano P. Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Summary of Recommendations. *Arch Bronconeumol* 2018; **54**: 205-215 [PMID: 29472044 DOI: 10.1016/j.arbres.2017.11.014]
 - 59 **Hogan SE**, Rodriguez Salazar MP, Cheadle J, Glenn R, Medrano C, Petersen TH, Ilagan RM. Mesenchymal stromal cell-derived exosomes improve mitochondrial health in pulmonary arterial hypertension. *Am J Physiol Lung Cell Mol Physiol* 2019; **316**: L723-L737 [PMID: 30652491 DOI: 10.1152/ajplung.00058.2018]
 - 60 **Willis GR**, Fernandez-Gonzalez A, Reis M, Mitsialis SA, Kourembanas S. Macrophage Immunomodulation: The Gatekeeper for Mesenchymal Stem Cell Derived-Exosomes in Pulmonary Arterial Hypertension? *Int J Mol Sci* 2018; **19**: 2534 [PMID: 30150544 DOI: 10.3390/ijms19092534]
 - 61 **Braun RK**, Chetty C, Balasubramaniam V, Centanni R, Haraldsdottir K, Hematti P, Eldridge MW. Intraperitoneal injection of MSC-derived exosomes prevent experimental bronchopulmonary dysplasia. *Biochem Biophys Res Commun* 2018; **503**: 2653-2658 [PMID: 30093115 DOI: 10.1016/j.bbrc.2018.08.019]
 - 62 **Chaubey S**, Thueson S, Ponnalagu D, Alam MA, Gheorghe CP, Aghai Z, Singh H, Bhandari V. Early gestational mesenchymal stem cell secretome attenuates experimental bronchopulmonary

- dysplasia in part via exosome-associated factor TSG-6. *Stem Cell Res Ther* 2018; **9**: 173 [PMID: 29941022 DOI: 10.1186/s13287-018-0903-4]
- 63 **Willis GR**, Fernandez-Gonzalez A, Anastas J, Vitali SH, Liu X, Ericsson M, Kwong A, Mitsialis SA, Kourembanas S. Mesenchymal Stromal Cell Exosomes Ameliorate Experimental Bronchopulmonary Dysplasia and Restore Lung Function through Macrophage Immunomodulation. *Am J Respir Crit Care Med* 2018; **197**: 104-116 [PMID: 28853608 DOI: 10.1164/rccm.201705-0925OC]
 - 64 **Lou G**, Chen Z, Zheng M, Liu Y. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. *Exp Mol Med* 2017; **49**: e346 [PMID: 28620221 DOI: 10.1038/emmm.2017.63]
 - 65 **Tan CY**, Lai RC, Wong W, Dan YY, Lim SK, Ho HK. Mesenchymal stem cell-derived exosomes promote hepatic regeneration in drug-induced liver injury models. *Stem Cell Res Ther* 2014; **5**: 76 [PMID: 24915963 DOI: 10.1186/s13287-014-0465-5]
 - 66 **Yan Y**, Jiang W, Tan Y, Zou S, Zhang H, Mao F, Gong A, Qian H, Xu W. hucMSC Exosome-Derived GPX1 Is Required for the Recovery of Hepatic Oxidant Injury. *Mol Ther* 2017; **25**: 465-479 [PMID: 28089078 DOI: 10.1016/j.ymthe.2016.11.019]
 - 67 **Li T**, Yan Y, Wang B, Qian H, Zhang X, Shen L, Wang M, Zhou Y, Zhu W, Li W, Xu W. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. *Stem Cells Dev* 2013; **22**: 845-854 [PMID: 23002959 DOI: 10.1089/scd.2012.0395]
 - 68 **Lou G**, Yang Y, Liu F, Ye B, Chen Z, Zheng M, Liu Y. MiR-122 modification enhances the therapeutic efficacy of adipose tissue-derived mesenchymal stem cells against liver fibrosis. *J Cell Mol Med* 2017; **21**: 2963-2973 [PMID: 28544786 DOI: 10.1111/jcmm.13208]
 - 69 **Rani S**, Ritter T. The Exosome - A Naturally Secreted Nanoparticle and its Application to Wound Healing. *Adv Mater* 2016; **28**: 5542-5552 [PMID: 26678528 DOI: 10.1002/adma.201504009]
 - 70 **Lee DE**, Ayoub N, Agrawal DK. Mesenchymal stem cells and cutaneous wound healing: novel methods to increase cell delivery and therapeutic efficacy. *Stem Cell Res Ther* 2016; **7**: 37 [PMID: 26960535 DOI: 10.1186/s13287-016-0303-6]
 - 71 **Martin P**. Wound healing--aiming for perfect skin regeneration. *Science* 1997; **276**: 75-81 [PMID: 9082989 DOI: 10.1126/science.276.5309.75]
 - 72 **Lo Sicco C**, Reverberi D, Balbi C, Ulivi V, Principi E, Pascucci L, Becherini P, Bosco MC, Varesio L, Franzin C, Pozzobon M, Cancedda R, Tasso R. Mesenchymal Stem Cell-Derived Extracellular Vesicles as Mediators of Anti-Inflammatory Effects: Endorsement of Macrophage Polarization. *Stem Cells Transl Med* 2017; **6**: 1018-1028 [PMID: 28186708 DOI: 10.1002/sctm.16-0363]
 - 73 **Fang S**, Xu C, Zhang Y, Xue C, Yang C, Bi H, Qian X, Wu M, Ji K, Zhao Y, Wang Y, Liu H, Xing X. Umbilical Cord-Derived Mesenchymal Stem Cell-Derived Exosomal MicroRNAs Suppress Myofibroblast Differentiation by Inhibiting the Transforming Growth Factor- β /SMAD2 Pathway During Wound Healing. *Stem Cells Transl Med* 2016; **5**: 1425-1439 [PMID: 27388239 DOI: 10.5966/sctm.2015-0367]
 - 74 **Hoang DH**, Nguyen TD, Nguyen HP, Nguyen XH, Do PTX, Dang VD, Dam PTM, Bui HTH, Trinh MQ, Vu DM, Hoang NTM, Thanh LN, Than UTT. Differential Wound Healing Capacity of Mesenchymal Stem Cell-Derived Exosomes Originated From Bone Marrow, Adipose Tissue and Umbilical Cord Under Serum- and Xeno-Free Condition. *Front Mol Biosci* 2020; **7**: 119 [PMID: 32671095 DOI: 10.3389/fmolb.2020.00119]
 - 75 **Liang X**, Zhang L, Wang S, Han Q, Zhao RC. Exosomes secreted by mesenchymal stem cells promote endothelial cell angiogenesis by transferring miR-125a. *J Cell Sci* 2016; **129**: 2182-2189 [PMID: 27252357 DOI: 10.1242/jcs.170373]
 - 76 **Han Y**, Ren J, Bai Y, Pei X, Han Y. Exosomes from hypoxia-treated human adipose-derived mesenchymal stem cells enhance angiogenesis through VEGF/VEGF-R. *Int J Biochem Cell Biol* 2019; **109**: 59-68 [PMID: 30710751 DOI: 10.1016/j.biocel.2019.01.017]
 - 77 **Hu L**, Wang J, Zhou X, Xiong Z, Zhao J, Yu R, Huang F, Zhang H, Chen L. Exosomes derived from human adipose mesenchymal stem cells accelerates cutaneous wound healing via optimizing the characteristics of fibroblasts. *Sci Rep* 2016; **6**: 32993 [PMID: 27615560 DOI: 10.1038/srep32993]
 - 78 **Zhang J**, Guan J, Niu X, Hu G, Guo S, Li Q, Xie Z, Zhang C, Wang Y. Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis. *J Transl Med* 2015; **13**: 49 [PMID: 25638205 DOI: 10.1186/s12967-015-0417-0]
 - 79 **Lener T**, Gimona M, Aigner L, Börger V, Buzas E, Camussi G, Chaput N, Chatterjee D, Court FA, Del Portillo HA, O'Driscoll L, Fais S, Falcon-Perez JM, Felderhoff-Mueser U, Fraile L, Gho YS, Görgens A, Gupta RC, Hendrix A, Hermann DM, Hill AF, Hochberg F, Horn PA, de Kleijn D, Kordelas L, Kramer BW, Krämer-Albers EM, Laner-Plamberger S, Laitinen S, Leonardi T, Lorenowicz MJ, Lim SK, Lötvald J, Maguire CA, Marcilla A, Nazarenko I, Ochiya T, Patel T, Pedersen S, Pocsfalvi G, Pluchino S, Quesenberry P, Reischl IG, Rivera FJ, Sanzenbacher R, Schallmoser K, Slaper-Cortenbach I, Strunk D, Tonn T, Vader P, van Balkom BW, Wauben M, Andaloussi SE, Théry C, Rohde E, Giebel B. Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper. *J Extracell Vesicles* 2015; **4**: 30087 [PMID: 26725829 DOI: 10.3402/jev.v4.30087]
 - 80 **Gardiner C**, Di Vizio D, Sahoo S, Théry C, Witwer KW, Wauben M, Hill AF. Techniques used for the isolation and characterization of extracellular vesicles: results of a worldwide survey. *J Extracell*

- Vesicles* 2016; **5**: 32945 [PMID: 27802845 DOI: 10.3402/jev.v5.32945]
- 81 **Dai S**, Wei D, Wu Z, Zhou X, Wei X, Huang H, Li G. Phase I clinical trial of autologous ascites-derived exosomes combined with GM-CSF for colorectal cancer. *Mol Ther* 2008; **16**: 782-790 [PMID: 18362931 DOI: 10.1038/mt.2008.1]
 - 82 **Morse MA**, Garst J, Osada T, Khan S, Hobeika A, Clay TM, Valente N, Shreeniwas R, Sutton MA, Delcayre A, Hsu DH, Le Pecq JB, Lysterly HK. A phase I study of dexosome immunotherapy in patients with advanced non-small cell lung cancer. *J Transl Med* 2005; **3**: 9 [PMID: 15723705 DOI: 10.1186/1479-5876-3-9]
 - 83 **Escudier B**, Dorval T, Chaput N, André F, Caby MP, Novault S, Flament C, Leboulleire C, Borg C, Amigorena S, Boccaccio C, Bonnerot C, Dhellin O, Movassagh M, Piperno S, Robert C, Serra V, Valente N, Le Pecq JB, Spatz A, Lantz O, Tursz T, Angevin E, Zitvogel L. Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: results of the first phase I clinical trial. *J Transl Med* 2005; **3**: 10 [PMID: 15740633 DOI: 10.1186/1479-5876-3-10]
 - 84 **Witwer KW**, Van Balkom BWM, Bruno S, Choo A, Dominici M, Gimona M, Hill AF, De Kleijn D, Koh M, Lai RC, Mitsialis SA, Ortiz LA, Rohde E, Asada T, Toh WS, Weiss DJ, Zheng L, Giebel B, Lim SK. Defining mesenchymal stromal cell (MSC)-derived small extracellular vesicles for therapeutic applications. *J Extracell Vesicles* 2019; **8**: 1609206 [PMID: 31069028 DOI: 10.1080/20013078.2019.1609206]
 - 85 **Ludwig AK**, De Miroschedji K, Doeppner TR, Börger V, Ruesing J, Rebmann V, Durst S, Jansen S, Bremer M, Behrmann E, Singer BB, Jastrow H, Kuhlmann JD, El Magraoui F, Meyer HE, Hermann DM, Opalka B, Raunser S, Epple M, Horn PA, Giebel B. Precipitation with polyethylene glycol followed by washing and pelleting by ultracentrifugation enriches extracellular vesicles from tissue culture supernatants in small and large scales. *J Extracell Vesicles* 2018; **7**: 1528109 [PMID: 30357008 DOI: 10.1080/20013078.2018.1528109]
 - 86 **Kordelas L**, Rebmann V, Ludwig AK, Radtke S, Ruesing J, Doeppner TR, Epple M, Horn PA, Beelen DW, Giebel B. MSC-derived exosomes: a novel tool to treat therapy-refractory graft-versus-host disease. *Leukemia* 2014; **28**: 970-973 [PMID: 24445866 DOI: 10.1038/leu.2014.41]
 - 87 **Busatto S**, Vilanilam G, Ticer T, Lin WL, Dickson DW, Shapiro S, Bergese P, Wolfram J. Tangential Flow Filtration for Highly Efficient Concentration of Extracellular Vesicles from Large Volumes of Fluid. *Cells* 2018; **7**: 273 [PMID: 30558352 DOI: 10.3390/cells7120273]
 - 88 **van Balkom BWM**, Gremmels H, Giebel B, Lim SK. Proteomic Signature of Mesenchymal Stromal Cell-Derived Small Extracellular Vesicles. *Proteomics* 2019; **19**: e1800163 [PMID: 30467989 DOI: 10.1002/pmic.201800163]
 - 89 **Noronha NC**, Mizukami A, Calíari-Oliveira C, Cominal JG, Rocha JLM, Covas DT, Swiech K, Malmegrim KCR. Priming approaches to improve the efficacy of mesenchymal stromal cell-based therapies. *Stem Cell Res Ther* 2019; **10**: 131 [PMID: 31046833 DOI: 10.1186/s13287-019-1224-y]
 - 90 **Katsuda T**, Kosaka N, Takeshita F, Ochiya T. The therapeutic potential of mesenchymal stem cell-derived extracellular vesicles. *Proteomics* 2013; **13**: 1637-1653 [PMID: 23335344 DOI: 10.1002/pmic.201200373]
 - 91 **Phan J**, Kumar P, Hao D, Gao K, Farmer D, Wang A. Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy. *J Extracell Vesicles* 2018; **7**: 1522236 [PMID: 30275938 DOI: 10.1080/20013078.2018.1522236]
 - 92 **Zhang Y**, Chopp M, Zhang ZG, Katakowski M, Xin H, Qu C, Ali M, Mahmood A, Xiong Y. Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury. *Neurochem Int* 2017; **111**: 69-81 [PMID: 27539657 DOI: 10.1016/j.neuint.2016.08.003]
 - 93 **Almeria C**, Weiss R, Roy M, Tripisciano C, Kasper C, Weber V, Egger D. Hypoxia Conditioned Mesenchymal Stem Cell-Derived Extracellular Vesicles Induce Increased Vascular Tube Formation *in vitro*. *Front Bioeng Biotechnol* 2019; **7**: 292 [PMID: 31709251 DOI: 10.3389/fbioe.2019.00292]
 - 94 **Domenis R**, Cifù A, Quaglia S, Pistis C, Moretti M, Vicario A, Parodi PC, Fabris M, Niazi KR, Soon-Shiong P, Curcio F. Pro inflammatory stimuli enhance the immunosuppressive functions of adipose mesenchymal stem cells-derived exosomes. *Sci Rep* 2018; **8**: 13325 [PMID: 30190615 DOI: 10.1038/s41598-018-31707-9]
 - 95 **Harting MT**, Srivastava AK, Zhaorigetu S, Bair H, Prabhakara KS, Toledano Furman NE, Vykoukal JV, Ruppert KA, Cox CS Jr, Olson SD. Inflammation-Stimulated Mesenchymal Stromal Cell-Derived Extracellular Vesicles Attenuate Inflammation. *Stem Cells* 2018; **36**: 79-90 [PMID: 29076623 DOI: 10.1002/stem.2730]
 - 96 **Lopatina T**, Bruno S, Tetta C, Kalinina N, Porta M, Camussi G. Platelet-derived growth factor regulates the secretion of extracellular vesicles by adipose mesenchymal stem cells and enhances their angiogenic potential. *Cell Commun Signal* 2014; **12**: 26 [PMID: 24725987 DOI: 10.1186/1478-811X-12-26]
 - 97 **Chen TS**, Arslan F, Yin Y, Tan SS, Lai RC, Choo AB, Padmanabhan J, Lee CN, de Kleijn DP, Lim SK. Enabling a robust scalable manufacturing process for therapeutic exosomes through oncogenic immortalization of human ESC-derived MSCs. *J Transl Med* 2011; **9**: 47 [PMID: 21513579 DOI: 10.1186/1479-5876-9-47]
 - 98 **He JG**, Li HR, Han JX, Li BB, Yan D, Li HY, Wang P, Luo Y. GATA-4-expressing mouse bone marrow mesenchymal stem cells improve cardiac function after myocardial infarction *via* secreted exosomes. *Sci Rep* 2018; **8**: 9047 [PMID: 29899566 DOI: 10.1038/s41598-018-27435-9]

- 99 **Kang K**, Ma R, Cai W, Huang W, Paul C, Liang J, Wang Y, Zhao T, Kim HW, Xu M, Millard RW, Wen Z, Wang Y. Exosomes Secreted from CXCR4 Overexpressing Mesenchymal Stem Cells Promote Cardioprotection via Akt Signaling Pathway following Myocardial Infarction. *Stem Cells Int* 2015; **2015**: 659890 [PMID: 26074976 DOI: 10.1155/2015/659890]
- 100 **Gonzalez-King H**, García NA, Ontoria-Oviedo I, Ciria M, Montero JA, Sepúlveda P. Hypoxia Inducible Factor-1 α Potentiates Jagged 1-Mediated Angiogenesis by Mesenchymal Stem Cell-Derived Exosomes. *Stem Cells* 2017; **35**: 1747-1759 [PMID: 28376567 DOI: 10.1002/stem.2618]
- 101 **Chen CC**, Liu L, Ma F, Wong CW, Guo XE, Chacko JV, Farhoodi HP, Zhang SX, Zimak J, Ségaliny A, Riazifar M, Pham V, Digman MA, Pone EJ, Zhao W. Elucidation of Exosome Migration across the Blood-Brain Barrier Model In Vitro. *Cell Mol Bioeng* 2016; **9**: 509-529 [PMID: 28392840 DOI: 10.1007/s12195-016-0458-3]
- 102 **Joo HS**, Suh JH, Lee HJ, Bang ES, Lee JM. Current Knowledge and Future Perspectives on Mesenchymal Stem Cell-Derived Exosomes as a New Therapeutic Agent. *Int J Mol Sci* 2020; **21**: 727 [PMID: 31979113 DOI: 10.3390/ijms21030727]
- 103 **Stremersch S**, De Smedt SC, Raemdonck K. Therapeutic and diagnostic applications of extracellular vesicles. *J Control Release* 2016; **244**: 167-183 [PMID: 27491882 DOI: 10.1016/j.jconrel.2016.07.054]
- 104 **Pascucci L**, Coccè V, Bonomi A, Ami D, Ceccarelli P, Ciusani E, Viganò L, Locatelli A, Sisto F, Doglia SM, Parati E, Bernardo ME, Muraca M, Alessandri G, Bondiolotti G, Pessina A. Paclitaxel is incorporated by mesenchymal stromal cells and released in exosomes that inhibit in vitro tumor growth: a new approach for drug delivery. *J Control Release* 2014; **192**: 262-270 [PMID: 25084218 DOI: 10.1016/j.jconrel.2014.07.042]
- 105 **Liu J**, Jiang M, Deng S, Lu J, Huang H, Zhang Y, Gong P, Shen X, Ruan H, Jin M, Wang H. miR-93-5p-Containing Exosomes Treatment Attenuates Acute Myocardial Infarction-Induced Myocardial Damage. *Mol Ther Nucleic Acids* 2018; **11**: 103-115 [PMID: 29858047 DOI: 10.1016/j.omtn.2018.01.010]
- 106 **Xin H**, Wang F, Li Y, Lu QE, Cheung WL, Zhang Y, Zhang ZG, Chopp M. Secondary Release of Exosomes From Astrocytes Contributes to the Increase in Neural Plasticity and Improvement of Functional Recovery After Stroke in Rats Treated With Exosomes Harvested From MicroRNA 133b-Overexpressing Multipotent Mesenchymal Stromal Cells. *Cell Transplant* 2017; **26**: 243-257 [PMID: 27677799 DOI: 10.3727/096368916X693031]



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