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REVIEW

MSC-Derived Extracellular Vesicles: Roles and Molecular Mechanisms for Tissue Repair

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Abstract: Mesenchymal stem cells (MSCs) are pluripotent stem cells that have great potential in the field of regenerative medicine. Extracellular vesicles that derived from MSCs inherit the bioactive molecules, including lipids, proteins, nucleic acids, from the donate cells. With similar biological functions as MSCs, MSC-EVs show lower toxicity, better biocompatibility, stability, and less immune rejection. Therefore, MSC-EVs are emerging as a cell-free alternative therapy for MSC-based cell therapy. Here, we reviewed the characteristics of different subtype of MSC-EVs, the functional molecules in MSC-EVs for tissue repair, the potential applications of MSC-EVs for different tissue injuries in recent three years, and the clinical progress as well as the existing challenges in MSC-EV based therapy. This review would provide some insights for the future researches and clinical translation of MSC-EVs in regenerative medicine.

Keywords: mesenchymal stem cells, extracellular vesicles, cell-free therapy, tissue repair, regenerative medicine

Introduction

Tissue repair and regeneration remain as a great challenge in regenerative medicine. Tissue damages occur in cells, tissues, or organs due to various factors such as degenerative diseases, organ failure, or mechanical injury.[1] Degenerative diseases such as osteoarthritis and Alzheimer's disease (AD), are one of the major driving factors for tissue damage. As of 2020, over 500 million people are affected by osteoarthritis, accounting for approximately 7.6% of the global population.[2] In the entire AD continuum, the overall prevalence among people aged >50 is 22%. Especially in the elderly and advanced disease stages, the rate accounts for 54%. Furthermore, multiple organ dysfunction syndrome is often triggered by acute sepsis. Its main manifestations include high vascular permeability, release of inflammatory mediators, microcirculation disorders, and self-reactive endothelial damage. All of these would directly lead to organ damage.[3,4] In addition, there are also extensive traumatic injuries caused by fractures or complex surgeries. The incidence of related conditions such as infection, hematoma, and nerve damage reach 8.5%–20%.[5] Therefore, there is an urgent need for regenerative therapies in tissue damage.

Generally, the tissue repair processes undergo three stages: acute inflammatory phase, tissue repair phase, and remodeling phase.[6–8] After tissue damage, blood vessels rapidly dilate, the permeability of blood vessel walls increase, and plasma proteins and white blood cells rapidly infiltrate into the interstitium of injured tissue. Then various immune cells, such as macrophages, will be activated and migrate to damaged tissue, releasing signaling molecules to recruit more immune cells to participate in the inflammatory response.[9] Afterwards, the damaged tissue and immune cells release various inflammatory mediators, such as prostaglandins (PGE), interleukins (ILs), and tumor necrosis factor (TNF),[10] which can trigger inflammatory reactions such as local congestion and exudation. When the inflammation subsides, the damaged tissue enters the repair stage. In the early stage of repair, fibroblasts rapidly proliferate in the damaged area and synthesize collagen. At the same time, epithelial cells will migrate and proliferate to cover the wound

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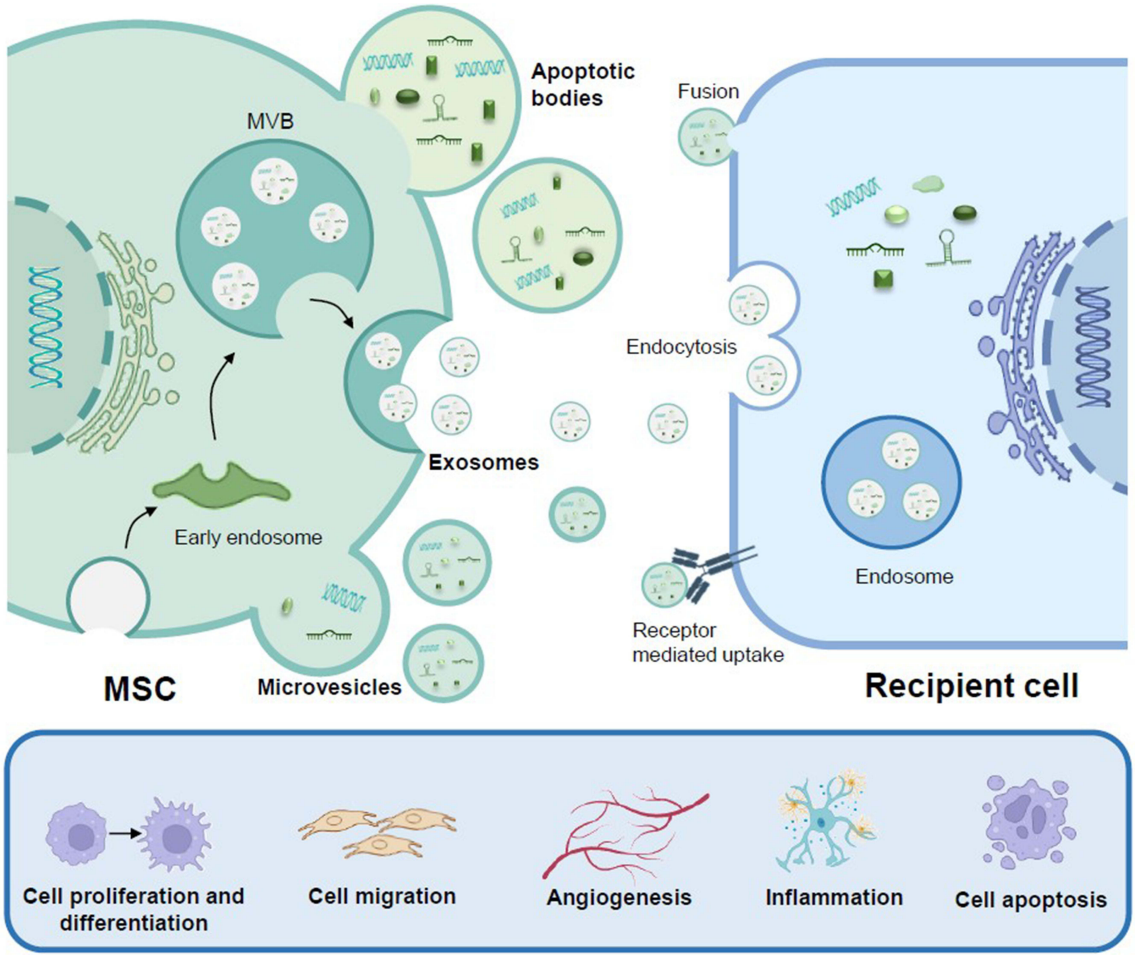
Graphical Abstract



surface, preventing infection and loss of moisture. Then endothelial cells in blood vessels form new blood vessels to restore blood supply to the damaged cells and provide oxygen, nutrients, and immune cells for wound healing.[11] In the middle stage of repair, fibroblasts continue to synthesize collagen, and the deposition and arrangement of these collagens support the repair area, providing a structural basis for subsequent repair and functional recovery, also preventing further damage. In the late stage of tissue repair, fibroblasts and myoblasts synthesize and deposit extracellular matrix (ECM) proteins to form scars.[12] Following by the repair phase, the tissue enters the remodeling phase.[13] During this period, the inflammatory response gradually weakens, the number of immune cells decreases, and stem cells differentiate into various cell types, promoting the restoration of tissue structure and function. Afterwards, the newly formed tissues gradually interact with the surrounding environment, and form a new physiological balance to maintain the stability and function of the body (Figure 1).

Mesenchymal stem cells (MSCs), also referred as mesenchymal stromal cells or drug signaling cells, are multipotent cells that originate from mesodermal tissues[14] and have the potential for multidirectional differentiation[15] immune regulation,[16] and paracrine secretion.[17] According to the statement from the International Society for Cell and Gene Therapy (ISCT)®,[18] MSCs can be characterized by the expression of surface antigens CD73, CD90 and CD105, the lack of expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR, as well as plastic adherence during in vitro growth. MSCs mainly exist in the bone marrow,[19] but they can also be isolated from peripheral tissues, including umbilical cord,[20] placenta,[21] adipose tissue[22,] amniotic fluid,[23] Wharton's jelly,[24] and skin,[25] etc. Furthermore, oral

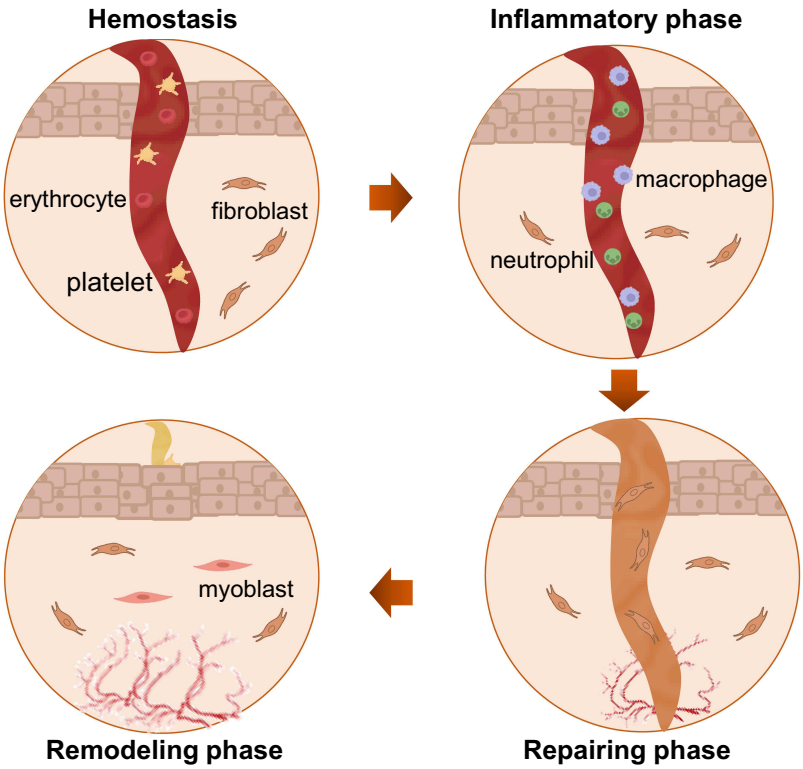


Figure 1 Schematic illustration of the process of tissue repair.

tissues are also a major source of MSCs.[26] The oral tissue-derived MSCs include dental pulp stem cells, stem cells from human exfoliated deciduous teeth, periodontal ligament stem cells, gingival mesenchymal stem cells, dental follicle stem cells, alveolar bone-derived MSCs, and stem cells from apical papilla.[27–30] MSCs derived from different tissues exhibit heterogeneous characteristics and regulate various biological functions, including multi-lineage differentiation, angiogenesis, and anti-inflammatory effects, etc. Moreover, MSCs lack the expression of MHC-II on their surface, making them less immunogenic and advantageous for allogeneic transplantation.[31]

Extracellular vesicles (EVs) are nano-sized membrane particles secreted by cells. Almost all type of cells can secrete membrane-bound vesicles. According to the size or origin, EVs can be roughly classified into microvesicles, exosomes, and apoptotic bodies.[32] Notably, they can mediate the intracellular communication and thereby play important roles in immune responses, anti-inflammatory processes, angiogenesis, and anti-tumor activities.[33] When compared with MSC, MSC derived-EVs (MSC-EVs) show better stability, biosafety and storability.[34] MSC-EVs are promising candidates in treating various diseases, such as autoimmune diseases and diabetes, etc.

This review summarized the various types of MSC-EVs and their bioactive molecules for tissue repair, as well as the application of MSC-EVs in various disease models in recent three years. This could provide a theoretical basis for clinical translation of MSC-EVs.

Characteristics of MSC-EVs

As a kind of multipotent cells, MSCs are derived from various tissue sources and possess the capacity for self-renewal and can differentiate into various types of cells, encompassing mesodermal lineages such as chondrocytes, osteocytes, adipocytes, myocytes, and fibroblasts; ectodermal lineages like neurons; and endodermal lineages including hepatocytes.[35] Derived from natural MSCs, MSC-EVs showed innate biomimetic-properties and high biocompatibility. They also inherited the various biomolecules from the donate MSCs, thereby possessing similar functions as the parental MSCs. They can transfer the bioactive substances, such as proteins, lipids, DNA, and microRNA (miRNA), to the recipient cells, which endow them with the capability to participate in intercellular signal transduction and regulate

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multiple functions (Figure 2). Notably, as a cell-free therapy, MSC-EVs have lower toxicity, better biocompatibility, stability, and a lower risk of immune rejection compared to cell-based therapies.[36,37] Moreover, as a kind of top-bottom approach, MSC-EVs can directly act as nanosized-drug carrier and utilize the self-carrying biomolecules as therapeutic agents while avoid complicated and costive drug loading or engineering processes. Therefore, MSC-EV could be a promising candidate in treating various diseases.

According to the size and origin, MSC-EVs can be broadly categorized into three subtypes: MSC-derived exosome (MSC-Exo), MSC-derived microvesicles (MSC-MVs), and MSC-derived apoptotic body.[38] MSC-Exo typically ranges in size from 30 to 100 nm and is released through fusion of endosomal multivesicular bodies (MVB) structures with the plasma membrane. In detail, early sorting endosomes (ESEs) are firstly formed through plasma membrane invagination. Then, late sorting endosomes are generated by material exchange following acidification and maturation of ESEs. Subsequently, MVBs form via double plasma membrane invagination, containing numerous intraluminal vesicles (ILVs). Ultimately, ILVs are released as exosomes.[39] MSC-MVs are generated by shedding from the plasma membrane and have a diameter ranging from 100 nm to 1000 nm. MSC-derived apoptotic bodies, which usually form through apoptotic blebs during cell death, are the largest in size, ranging from 500 nm to 2000 nm. For the isolation of different MSC-EVs, the commonly used methods include ultracentrifugation, ultrafiltration, size-exclusion chromatography, polymer precipitation, immunoaffinity capture, microfluidic technology, and commercial EV isolation kits.[40] According to the actual demand, a suitable separation method could be chosen for the isolation of MSC-EVs.

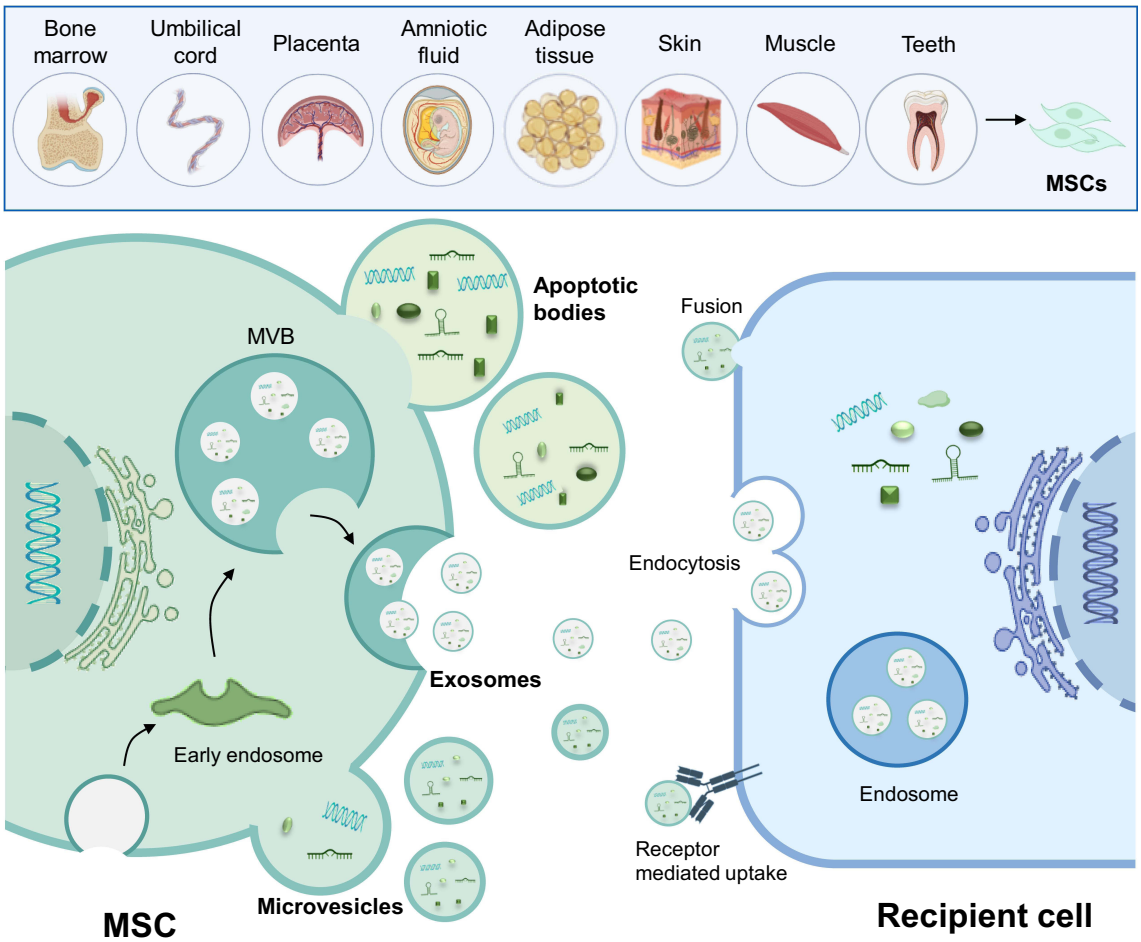

Figure 2 The biogenesis of MSC-EVs and their communicated roles between MSCs and recipient cells.
Abbreviations: MSC, Mesenchymal stem cell; MVB, Multivesicular Body.

Functional Molecules in MSC-EVs for Tissue Repair

MSC-EVs have shown great potential in tissue repair. The bioactive molecules including miRNA, long non-coding RNA (lncRNA), circular RNA (circRNA), proteins and lipids inherited from the donor cells are highlighted for the pro-regenerative effects.

MiRNA in MSC-EVs for Tissue Repair

MiRNA is a class of endogenous non-coding RNA molecules with a length of about 19–25 nucleotides, which play an important role in the differentiation, proliferation and apoptosis of cells. Inherited from the donate MSCs, MSC-EVs contain abundant miRNAs, which play important roles in many aspects of tissue repair (Figure 3).

Typically, miRNA in MSC-EV can regulate cell proliferation and differentiation by regulating gene expression in target cells, thus accelerating the repair process of damaged tissues. It was reported that miR-21-5p and miR-125b-5p in human umbilical cord blood MSCs derived exosomes were correlated with the inhibition of transforming growth factor-β (TGF-β) signaling pathway for myofibroblast differentiation, thereby reducing scar formation while accelerating wound healing.[41] MiR-21-5p was also engineered to adipose stem-cell-derived exosomes (ADSC-Exo) to promote the proliferation and migration of keratinocytes via Wnt/β-catenin signaling, promoting diabetic wound healing.[42] MiR-93-3p in bone marrow MSC-Exo promoted the proliferation and migration while reduced the apoptosis of HaCaT cells (human keratinocytes) by suppressing apoptotic peptidase activating factor 1 (APAF1) for skin wound healing.[43] Similarly, miR-21 in ADSC-Exo could also promote the proliferation and migration of HaCaT cells, which was mediated by the enhanced expression of MMPs via PI3K/AKT signaling pathway.[44] MiR-29c and miR-129 in MSC-EVs were found to induce dedifferentiation of myofibroblasts and thereby exerted antifibrotic effect in pulmonary fibrosis.[45] MiR-145-5p was highly enriched in placental MSC-EVs, which promoted the proliferation, migration, and antiapoptotic abilities of high glucose-induced senescent fibroblasts by suppressing the expression of cyclin dependent kinase inhibitor 1A and activating ERK/AKT signaling pathway. As a result, miR-145-5p mimics could improve the delayed skin wound healing caused by these abnormal fibroblasts.[46] MiR-24 in human umbilical cord MSC-EVs was found with ability to shift macrophage polarization from M1 towards M2 type by targeting kelch like ECH associated protein 1 (KEAP1) and disrupting the downstream Nrf2/HO-1 signaling, providing protective effect on myocardial ischemia–reperfusion injury[47.] MiR-139-3p and miR-125a-5p in MSC-EVs showed similar effects on macrophage polarization. Mechanically, miR-139-3p realized this effect by suppressing signal transducer and activator of transcription 1 (STAT1)[48] while miR-125a-5p acted via inhibiting TNF receptor associated factor 6/Interferon regulatory factor 5 (TRAF6/IRF5) signaling pathway.[49]

Besides regulating cell proliferation and differentiation, miRNAs in MSC-EV can also regulate angiogenesis, thereby improving blood supply to damaged tissues and promoting tissue repair. For example, miR-125a-3p in ADSC derived exosome can be transferred to endothelial cells to promote the angiogenesis for wound healing by inhibiting phosphatase and tensin homolog (PTEN) and activating phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway.[50] MiR-221-3p was found to be upregulated in atorvastatin pretreated MSC-Exo. It can facilitate the diabetic wound regeneration by activating AKT/eNOS pathway to enhance angiogenesis.[51] MiR-186-5p from MSC-EVs can be transferred to damaged human cardiac microvascular endothelial cells to develop new blood vessels by down regulating PARP9 and STAT1/pSTAT1 signaling pathway.[52] Rather than directly promoting angiogenesis, MSC-EVS carried miRNA could also regulate the structure of vascular. For instance, miR-5119 was identified to be enriched in hypoxia stimulated MSC-EVs, which could improve the vascular remodeling via regulating calcium signaling pathway.[53] MiR-146a, which was highly expressed in MSC-EVs, could mitigate the senescence of endothelial cell to rescue angiogenesis as these senescent cells could disrupt the integrity of normal blood vessel endothelium. The mechanism indicated that miR-146a inhibited the phosphorylation of Src and downstream VE-cadherin and Caveolin-1 to realize the stimulatory effect on senescence.[54]

MiRNAs in MSC-EV also have anti-inflammatory effects, helping to create a microenvironment conducive to tissue repair. MiR-155 inhibition has been demonstrated with modulating inflammatory profile in diabetic wound healing.[55] On the basis of this role, miR-155 inhibitor was loaded in MSC-Exo, which showed potent anti-inflammatory effect by

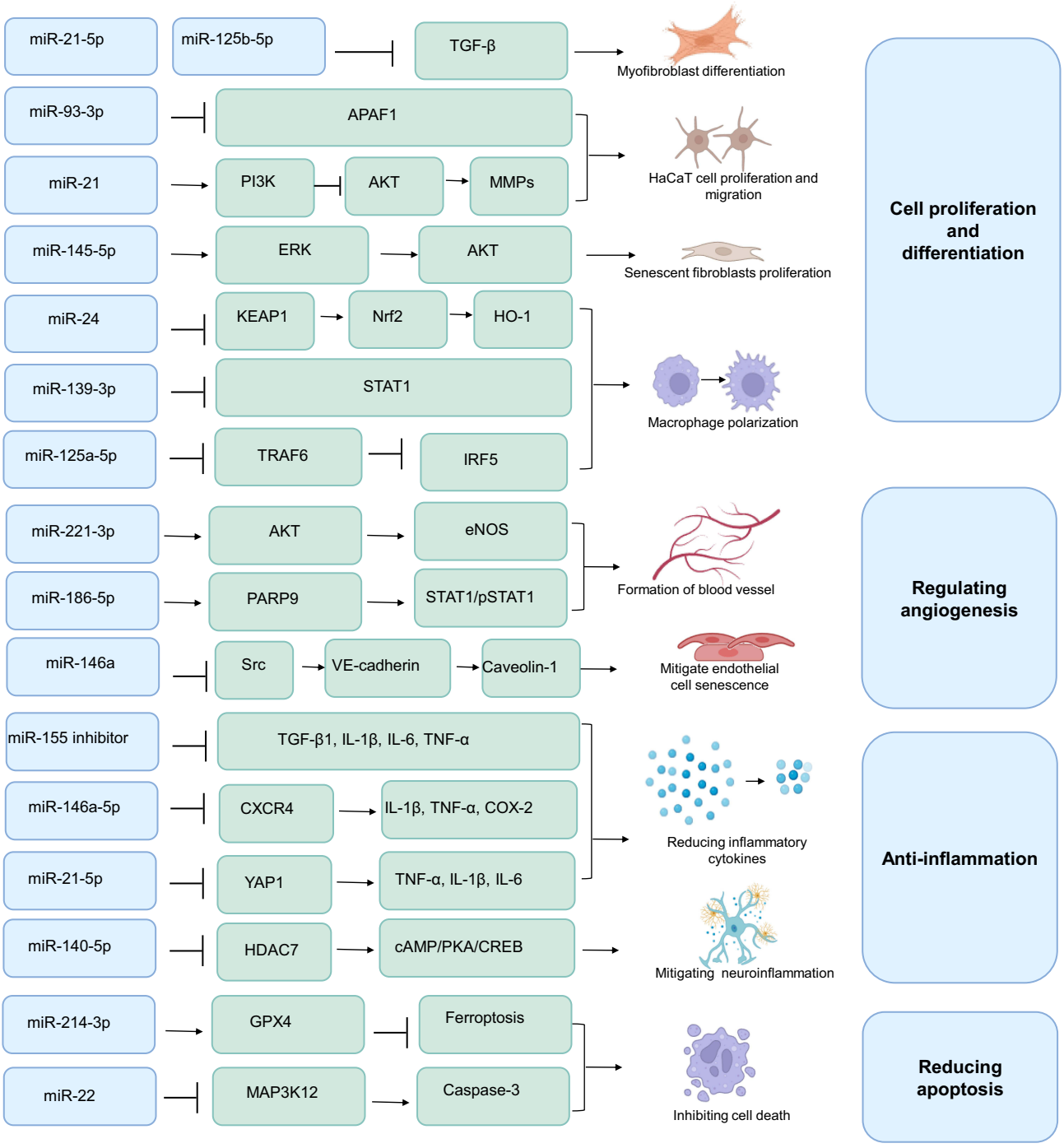

Figure 3 Roles and mechanisms of miRNAs in MSC-EVs to promote tissue repair.

Abbreviations: TGF-β, Transforming Growth Factor-β; APAF1, Apoptotic Protease Activating Factor 1; PI3K, Phosphoinositide 3-Kinase; AKT, Rac-alpha Serine/Threonine-Protein Kinase; MMP, Matrix Metalloproteinase; ERK, Extracellular Signal-Related Kinase; KEAP1, Kelch-like ECH-associated Protein 1; Nrf2, Nuclear Factor Erythroid-Related Factor 2; HO-1, Heme Oxygenase-1; STAT1, Signal Transducer and Activator of Transcription 1; TRAF6, TNF Receptor-Associated Factor 6; IRF5, Interferon Regulatory Factor 5; eNOS, Endothelial Nitric Oxide Synthase; PARP9, Poly [ADP -ribose] polymerase 9; pSTAT1, Phosphorylated Signal Transducer and Activator of Transcription 1; Src, Rous Sarcoma Virus Oncogene Homolog; VE-cadherin, Vascular Endothelial Cadherin; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; CXCR4, C-X-C Chemokine Receptor Type 4; COX-2, Cyclooxygenase-2; YAP1, Yes-associated Protein 1; HDAC7, Histone Deacetylase 7; cAMP, Cyclic Adenosine Monophosphate; PKA, Protein Kinase A; CREB, cAMP-response Element-Binding Protein; GPX4, Glutathione Peroxidase 4; MAP3K12, Mitogen-Activated Protein Kinase 12; Caspase-3, Cysteine-aspartic Acid Protease 3.

decreasing the level of pro-inflammatory factors (TGF-β1, IL-1β, IL-6, and TNF-α) in diabetic wounds.[56] MiRNA-146a-5p in amniotic fluid derived MSC-Exo could also reduce the secretion of pro-inflammatory cytokines including IL-1β, TNF-α, and COX-2 by downregulating the expression of C-X-C chemokine receptor type 4 (CXCR4)[57]. Moreover, miR-146a-5p could inhibit inflammation response in a different way by ameliorating NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)-inflammasome.[58,59] MiR-125a-3p in MSC-Exo was reported to improve the inflammatory environment caused by neutrophils in spinal cord injury by diminishing the formation of neutrophil extracellular traps (NETs)[60]. In another study, miR-199a in MSC-Exo showed similar effects on NETs formation, thereby alleviating the inflammation after myocardial ischemia/reperfusion injury.[61] Another miRNA, miR-21-5p in MSC-Exo, could modulate multiple signaling molecules to inhibit inflammatory responses. On one hand, it can inhibit yes-associated protein 1 (YAP1) to attenuate the inflammation after myocardial infarction.[62] On the other hand, its upregulation resulted in the downregulation of programmed cell death 4 (PDCD4) to decrease the secretion of inflammatory cytokines after retinal ischemia-reperfusion injury.[63] In addition to the miRNAs mentioned above, miR-140-5p in MSC-EVs was reported to mitigate subarachnoid hemorrhage triggered neuroinflammation and brain injury through the inhibition of histone deacetylases 7 (HDAC7) for activating cAMP/PKA/CREB axis.[64]

Studies have shown that MSC-EV can protect damaged tissues by inhibiting cell apoptosis through the miRNA it carries. MiR-214-3p in human umbilical cord MSC-EVs was identified to increase the expression of glutathione peroxidase 4 (GPX4, an enzyme protecting against ferroptosis marker), attenuating the ferroptosis of HT22 neuronal cell and improving neuronal injury.[65] MiR22 in MSC-EVs could target mitogen-activated protein kinase kinase kinase 12 (MAP3K12) to decrease caspase-3 expression, inhibiting apoptosis of retinal ganglion cells after damage.[66] Collectively, as the most well-characterized contents in MSC-EVs, miRNAs play pivotal roles in the communication between MSCs and recipient cells for tissue repair.

lncRNA in MSC-EVs for Tissue Repair

LncRNA is a class of non-coding RNA with a length >200 nt, which can interact with transcription factors and RNA-binding proteins and regulate the expression of target genes in transcriptional regulation, post-transcriptional regulation and post-translational modification.[67] MSC-EVs entrap a variety of lncRNAs to regulate the tissue repair through various ways (Figure 4). The most typical acting way for lncRNA is to bind with miRNA as a competitive endogenous RNA to inhibit the function of miRNA through molecular sponging effect, then regulating the miRNA-related signaling pathways. For example, lncRNA fetal-lethal non-coding developmental regulatory RNA (FENDRR) released from MSC-Exo

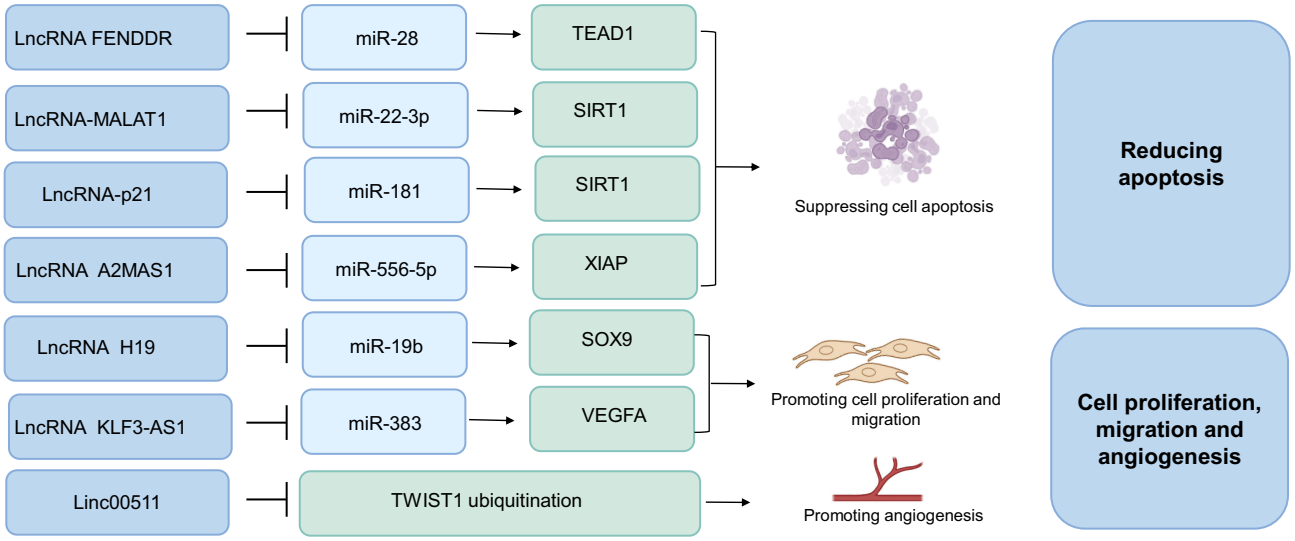

Figure 4 Roles and mechanisms of lncRNAs in MSC-EVs to promote tissue repair.
Abbreviations: TEAD1, TEA Domain Transcription Factor 1; SIRT1, Sirtuin 1; XIAP, X-linked Inhibitor of Apoptosis Protein; SOX9, SRY-box Transcription Factor 9; VEGFA, Vascular Endothelial Growth Factor A; TWIST1, Twist Family BHLH Transcription Factor 1.

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bound to miR-28, which inhibited miR-28 to bind with TEA domain transcription factor 1 (TEAD1). As a result, the expression of TEAD1 was increased after MSC-Exo treatment, reducing the injury to human vascular endothelial cells reflecting on the decreased cell apoptosis in atherosclerosis.[68] Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (lncRNA-MALAT1) acted as a functional molecule in human umbilical cord MSC-Exo to suppress the apoptosis of epithelial cells and improve spinal cord injury. Mechanically, lncRNA-MALAT1 reduced the inhibitory effect of miR-22-3p on its targeted sirtuin 1 (SIRT1) via miRNA sponging. The downstream signaling of SIRT1 was then activated shown as the enhanced phosphorylation of AMP-activated protein kinase (AMPK) and increased level of antiapoptotic Bcl-2.[69] LncRNA-p21 in MSC-Exo shared similar target as lncRNA-MALAT1, which bound to miR-181 to suppress its negative effect on SIRT1. Therefore, lncRNA-p21 expressed MSC-Exo protected epithelial cells against apoptosis and alleviated acute lung injury.[70] Another lncRNA, long non-coding RNA alpha-2-macroglobulin antisense RNA 1 (Lnc RNA A2MAS1) in MSC-Exo also acted as a sponge with miRNA to reduce cell apoptosis for the protective effect against myocardial ischemia-reperfusion injury. In detail, exosomal lnc A2M-AS1 bound to miR-556-5p, impairing the inhibition of miR-556-5p to its target, X-linked inhibitor of apoptosis protein (XIAP).[71] Besides inhibiting apoptosis, lncRNAs also regulate other roles via miRNA sponging. MSC derived exosomal lncRNA H19 was demonstrated to bind with miR-152-3p to abolish the suppression of miR-152-3p on PTEN. The increased PTEN expression then inhibited PI3K/AKT signaling pathway to promote the proliferation and migration of fibroblasts, accelerating the wound healing of diabetic foot ulcers.[72] LncRNA H19 in ADSC-Exo could bind to another miRNA, miR-19b, via molecular sponge. Therefore, it upregulated the target of miR-19 (SRY-related high-mobility-group box 9, SOX9) to activate Wnt/β-catenin signaling pathway, accelerating the proliferation and migration of HSF cells in skin wound[73.] LncRNA krüppel-like factor 3 antisense RNA 1 (KLF3-AS1) in MSC-Exo promoted diabetic cutaneous wound healing by stimulating angiogenesis, which was mediated by interaction between lncRNA KLF3-AS1 with miR-383 to boost vascular endothelial growth factor A (VEGFA).[74]

Instead of miRNA binding, lncRNA can directly bind with functional molecules for tissue repair. Linc00511 in ADSC-Exo was demonstrated to inhibit the ubiquitination of Twist homolog 1 (TWIST1), promoting angiogenesis for diabetic foot ulcers healing.[75] LncRNA KLF3-AS1 was found to directly bind with musashi-1 (MSI1) to attenuate the inflammatory response after cerebral ischemia reperfusion injury via sphingosine kinase 1 (Sphk1)/NF-κB signaling pathway.[76]

CircRNA in MSC-EVs for Tissue Repair

CircRNA is a recently discovered form of non-coding RNA. The 5′ and 3′ ends of circRNA are connected to form a stable integrated circular structure, which makes circRNA more resistant to being degraded by RNA exonucleases.[77]

CircRNA executes its function in tissue repair via multiple modalities (Figure 5). The principal action mode of circRNA is to serve as molecular sponge, sequestering miRNAs and thus functioning as competitive endogenous RNAs (ceRNAs) to modulate the expression of relevant genes. For example, in the context of treating wounds in diabetic mice, numerous circRNAs have demonstrated promising therapeutic implications. The circ-Erbb2ip originating from ADSC-Exo promoted angiogenesis by triggering the miR-670-5p/Nrf1 axis, thus expediting wound healing in diabetic mice.[78] Meanwhile, circ-Astn1 in ADSC-Exos instigated wound healing in diabetic mice via the miR-138-5p/SIRT1/FOXO1 axis.[79] Moreover, circ-Snhg11 in BMSC-Exo suppressed the expression of miR-144-5p, in turn upregulating the expression of SLC7A11/GPX4 to mediate the anti-ferroptosis signaling pathway for angiogenesis.[80] In addition, circARHGAP12 can directly interact with miR-301b-3p, regulating the expression of ATG16L1 and ULK2, enhancing autophagy in MSCs, and therefore inhibiting MSC apoptosis. These effects thereby promoted blood vessel reconstruction and epithelialization of MSCs in diabetic wounds.[81]

CircRNA is also capable of repairing other tissue damages such as spinal cord injury and myocardial damage. Studies have shown that hypoxic pre-conditioning of ADSC-Exo (H-ADSC-Exo), which delivered circ-Wdfy3, downregulated the expression of miR-423-3p. Concomitantly, it upregulated the expression of GPX4, decreased the levels of reactive oxygen species (ROS) and inflammatory factors following spinal cord injury, suppressed ferroptosis, and ultimately facilitated spinal cord repair.[82] Likewise, H-ADSC-Exo can also reduce ferroptosis through the circ-stt3b/miR-15a-5p/GPX4 signaling pathway to alleviate cardiac damage after myocardial infarction.[83]

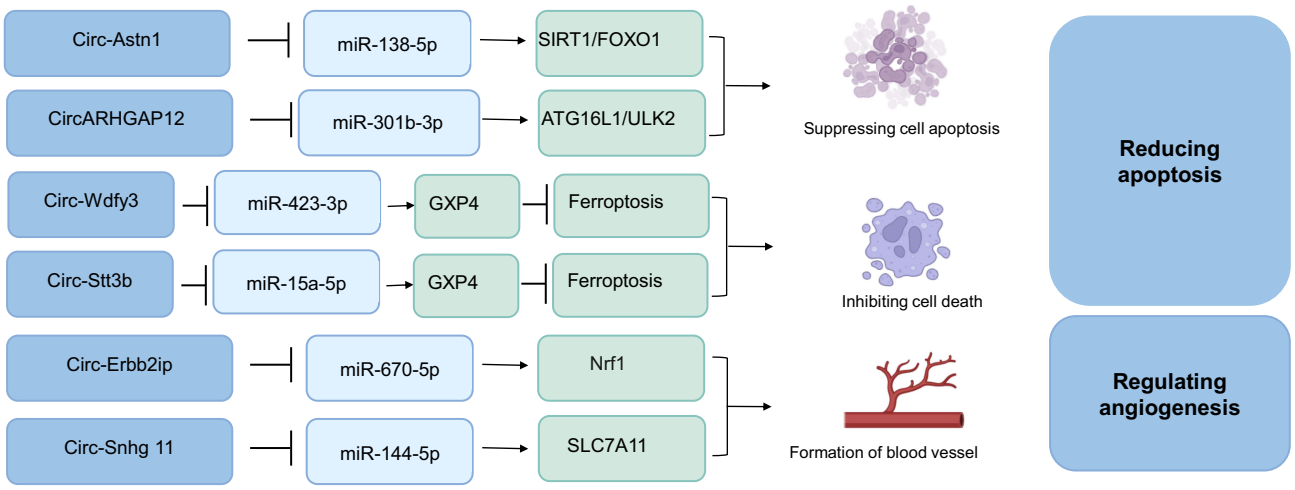

Figure 5 Roles and mechanisms of circRNAs in MSC-EVs to promote tissue repair.
Abbreviations: SIRT1, Sirtuin 1; XIAP, X-linked Inhibitor of Apoptosis Protein; FOXO1, Forkhead Box O1; ATG16L1, Autophagy-related Protein 16-like 1; ULK2, Unc-51-like Autophagy-activating Kinase 2; GPX4, Glutathione Peroxidase 4; SLC7A11, Solute Carrier Family 7 Member 11.

Proteins in MSC-EVs for Tissue Repair

MSC-EVs contain a great amount of protein cargoes. The clinical samples of MSC-EVs were harvested for proteomic analysis from healthy donors. Detected by mass spectrometry, more than 3000 proteins were identified in MSC-EVs while around 600 proteins were shared among different donors. Regarding to wound healing, MSC-EVs contained important proteins, such as programmed cell death protein 10, disabled homolog 2-interacting protein, neuropilin-1, tumor necrosis factor alpha-induced protein 2, Sushi repeat-containing protein and fibronectin 1 to regulate cell proliferation and angiogenesis.[84]

Besides these proteins, there are several other functional proteins in MSC-EVs participating in wound healing. CD73, a kind of ectoenzyme on the surface of MSCs, can convert adenosine monophosphate into adenosine to mitigate inflammatory response. CD73-overexprsssing MSC-EVs showed significant anti-inflammatory effect against autoimmune uveitis, thereby reducing tissue damages. Mechanically, the treatment of EVs inhibited the proliferation of T cells and the differentiation of Th1 cells while increased the proportion of regulatory T cells through enhancing adenosine levels.[84] TGF-β has been reported to mediated partial of anti-inflammation of MSCs. It was found that TGF-β was necessary in MSC-EVs to normalize the inflammatory factors for neuroprotection in hyperammonemic rats.[85] Steroid receptor coactivator-3 (SRC-3) expressed MSC-Exo was also involved in neurological actions. It protected against neuronal damage through inhibiting ferroptosis of neurons in cerebral ischemia injury.[86]

Moreover, proteins in MSC-EVs possess pro-angiogenic potential for tissue repair. Hypoxia-inducible factor 2-alpha (HIF2α) overexpressing MSC-EVs remarkably stimulated the tube formation ability of human umbilical vein endothelial cells (HUVECs) via upregulating the expression of miR-146a to activate AKT/ERK signaling pathway.[87] Integrin α5 (Itgα5) and neuropilin-1 in MSV-C-EVs were found to regulate angiogenesis as well as lymphangiogenesis through the VEGF-C–Itgα5 and VEGF-C-neuropilin-1 axes in ischemic tissues.[88] Another integrin, integrin beta-1 (ITGB1) in MSC-EVs improved the proliferation and differentiation of MSCs by activating the TGF-β/Smad2/3 axis, thereby promoting cartilage regeneration[89] (Figure 6).

Other Molecules in MSC-EVs for Tissue Repair

In addition to acting as transporter for nucleic acids and proteins, MSC-EVs also act as transporters for other molecules. MSC-EVs have been reported to be a kind of lipid mediators, which would transmit the oxylipins in MSCs to cardiomyoblasts to improve the inflammation in cardiac microenvironment.[90] The surface glycans in MSC-EVs could be a critical factor in EV-based cell communication. The roles of N-glycosylation in Wharton's Jelly MSC-EVs were explored. The results showed that N-glycans in MSC-EVs are essential for their interaction with HUVECs, as well as the induction of cell migration and angiogenesis.[91] MSC-EVs carry a lot of bioactive molecules, and in addition to these known molecules that have been studied, more molecular recognition patterns still need to be explored.

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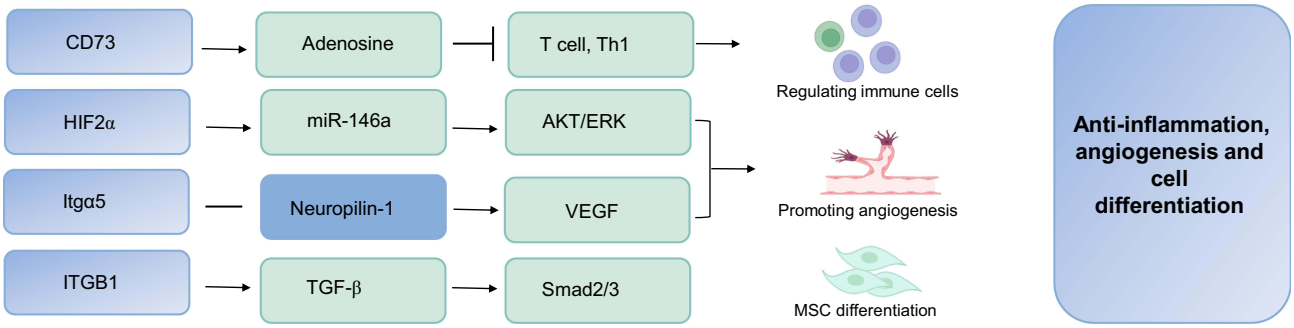

Figure 6 Roles and mechanisms of proteins in MSC-EVs to promote tissue repair.
Abbreviations: CD73, Cluster of Differentiation 73; T cell, T lymphocyte; Th1, T helper cell 1; HIF2α, Hypoxia-Inducible Factor 2α; AKT, Rac-alpha Serine/Threonine-Protein Kinase; ERK, Extracellular Signal-Related Kinase; Itgα5, Integrin alpha 5; VEGF, Vascular Endothelial Growth Factor; TGF-β, Transforming Growth Factor-β; Smad2/3, Sm mothers against decapentaplegic homolog 2/3.

Application of MSC-EVs for Tissue Repair

MSC-EVs have been widely applied for different tissue repairs, which were briefly summarized in Table 1.

MSC-Exo for Tissue Repair

Exosomes, derived from multivesicular endosomes, are extracellular vesicles with a cup-shaped morphology and a diameter ranging from 30 to 100 nm. Their predominant surface markers include CD81, CD9, CD63, and heat shock protein 70 (HSP70).[104] As an intracellular mediators, they play a crucial role in bio-communication among cells.[39,105]

Table 1 The Application of MSC-EVs in Diseases

Type of MSC-EVs	Source of MSC	Disease	Mechanism of Action	Year	Reference
DPSC-Exo	Dental pulp mesenchymal stem cells	Subarachnoid hemorrhage	Inhibiting microglial pyroptosis by delivering miR-197-3p to suppress FOXO3 expression	2024	[92]
F-MSC-Exo	Bone marrow mesenchymal stem cells	Osteoarthritis	Targeting TRAF6 by enriching miR-146b-5p and inhibits the PI3K/AKT/mTOR pathway	2023	[93]
HF-MSC-Exo	Hair follicle mesenchymal stem cells	Ulcerative colitis	Inhibiting the PI3K/AKT/mTOR signaling pathway	2024	[94]
Sep@Exo	N/A	The regeneration of bone defects in diabetic patients	Providing SHP2 to recipient cells, activating mitophagy, and eliminating mtROS	2024	[95]
3D-hUMSC-Exos	Human umbilical mesenchymal stem cells	Vitiligo	Targeting Sirt1 and Bak1.	2024	[96]
BMSC-Exo	Human bone marrow mesenchymal stem cells	Corneal stroma scarring and thinning and partial limbal stem cell deficiency	Expressing miR-150-5p targeting PDCD4 gene	2025	[97]
BMSC-Exo	Hypoxia-Preconditioned Bone marrow mesenchymal stem cells	Intervertebral disc degeneration	Inducing mitophagy through the BNIP3-ANAX2 axis	2024	[98]

(*Continued*)

Table 1 (Continued).

Type of MSC-EVs	Source of MSC	Disease	Mechanism of Action	Year	Reference
MSC-MV	The Chengdu Stem Cell Biobank	Rheumatoid arthritis	Down-regulating the expression of IL-1β, TNFα, MMP-13, and ADAMTS-5 in cartilage	2024	[99]
hUMSC-MV	Human umbilical cord mesenchymal stem cells	Renal ischemia-reperfusion injury	Targeting and negatively regulating PDCD4 in HK-2 cells.	2020	[100]
BMSC-MV	Bone marrow mesenchymal stem cells	Alzheimer's disease	Downregulating the levels of TNF-α, and p-AKT and increasing the expression of SHIP-1.	2021	[101]
hUMSC-AB	Human umbilical cord-derived mesenchymal stem cells	Intrauterine adhesions	Reducing fibrosis and promoting endometrial regeneration.	2021	[102]
BMSC-AB	Bone marrow mesenchymal stem cells	Myocardial infarction	Activating lysosomal function and promote the expression of TFEB	2020	[103]

Abbreviations: DPSC-Exo, Dental pulp mesenchymal stem cells derived exosome; F-MSC-Exo, Exosomes derived from fucoidan-directed induction mesenchymal stem cells; HF-MSC-Exo, Hair follicle mesenchymal stem cells derived exosome; Sep@Exo, The engineered exosome carrying Sephin1 (Sep); 3D-hUMSC-Exos, Human umbilical mesenchymal stem cells derived exosomes in 3D; BMSC-Exo, Bone marrow mesenchymal stem cells derived exosomes; MSC-MV, Mesenchymal stem cells derived microvesicles; hUMSC-MV, Human umbilical cord mesenchymal stem cells derived microvesicles; BMSC-MV, Bone marrow mesenchymal stem cells derived microvesicles; hUMSC-AB, Human umbilical cord mesenchymal stem cells derived apoptotic body; BMSC-AB, Bone marrow mesenchymal stem cells derived apoptotic body. FOXO3, Forkhead box O3; TRAF6, TNF receptor associated factor 6; the PI3K/AKT/mTOR pathway, The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) signaling pathway; SHP2, SH2 domain-containing protein-tyrosine phosphatase-2; PDCD4, Programmed Cell Death 4; BNIP3, BCL2 Interacting Protein 3; ANAX2, Annexin A2/ANXA2 Protein; IL-1β, Interleukin-1β; TNFα, Tumour necrosis factor-alpha; MMP-13, matrix metallopeptidase 13 gene; ADAMTS-5, recombinant a disintegrin and metalloproteinase with thrombospondin 5.

Owing to the remarkable immune regulatory properties, antioxidative stress capabilities, and anti-apoptotic effects, MSC-Exo has been effectively employed in the treatment of tissue injuries and wound healing. As the most well-studied internal factors, miRNA in MSC-Exo has been extensively explored for tissue repair. miRNA-224-3p in BMSC-Exo regulated angiogenesis, and knockdown of miRNA-224-3p expression enhanced angiogenesis and prevented the progression of traumatic osteonecrosis of the femoral head.[106] Another study has shown that miR-197-3p in dental pulp MSC-Exo inhibited FOXO3 expression and reduced NLRP3 inflammasome activation to alleviate brain edema and neuroinflammation after subarachnoid hemorrhage and inhibited microglial pyroptosis.[92] Furthermore, placental MSC-Exo was enriched in miR-125b-5p, miR-30c-5p, and miR-23a-3p, which targeted the expression of the 3′-untranslated region of Smad2 and Smad3, thereby down-regulating the TGF-β/Smad signaling pathway and reversing uterine fibrosis. It eventually repaired the damaged endometrium.[107]

Moreover, some external factors facilitated MSC-Exo to play a better role in tissue repair and regeneration. It has been reported that exosomes derived from fucoidan pretreated MSCs increased the level of miR-146b-5p. This kind of MSC-Exo effectively inhibited TRAF6 activation, thereby suppressing inflammatory responses and preventing extracellular matrix degradation. At the same time, they promoted chondrocyte autophagy and provided protection for osteoarthritic chondrocytes.[93] BMSC-Exo-loaded cell-derived extracellular matrix (ECM) mimics enhanced TGF-β1-mediated activation of the Nrf2 signaling pathway and simultaneously disrupted NET, which effectively alleviated cartilage degradation in osteoarthritis.[108] Nerve growth factor (NGF)-stimulated MSC-Exo transferred multi-component miRNAs and activated MAPK and PI3K-AKT signaling pathways, resulting in the formation of massive nerve and vascular structures and significant innervation of bone regeneration.[109]

Owing to the destruction of blood supply and the generation of anoxic environment, the damaged tissues often produce a large amount of ROS, which would lead to oxidative stress and the destruction of mitochondrial homeostasis. MSC-Exo can restore and maintain mitochondrial homeostasis by promoting mitochondrial biogenesis, enhancing mitochondrial function, regulating mitophagy, and reducing mitochondrial damage. For instance, hypoxia-

preconditioned hair follicle mesenchymal stem cells-derived exosomes can reduce inflammatory injury in ulcerative colitis by inhibiting the PI3K/AKT/mTOR signaling pathway, maintaining mitochondrial dynamic stability, reducing mitochondrial dysfunction, as well as enhancing mitophagy.[94] Liu et al developed a bioenergetic exosome (Suc-Exo). The ATP content of Suc-Exo was 5.42-fold higher than that of ordinary exosomes, which could regulate cellular energy metabolism by providing fuel for the TCA cycle. Under continuous energy supply, Suc-Exo promoted chondrogenic differentiation of BMSC and improved chondrocyte anabolism and mitochondrial homeostasis.[110] In another study, a kind of engineered exosome loaded with Sephin1 was constructed to activate mitophagy and eliminate mtROS to maintain ER homeostasis, promoting bone tissue repair, and shortening bone healing time in diabetic bone defects.[95]

In addition, MSC-Exo from different sources could exert various functions. Three-dimensional (3D) cell culture conditions of mesenchymal stem cell could potentiate the immune homeostasis and tissue regeneration ability of secreted exosomes. Wang et al found that 3D-cultured hUMSC-Exo enhanced Treg-mediated immunosuppression in vitiligo lesions and deliver miR-132-3p and miR-125b-5p to inhibit oxidative stress-induced melanoma cell damage.[96] Xu et al reported that 3D cultured MSC-Exo promoted the proliferation of corneal-derived cells and reduced the release of inflammatory factors by targeting the PDCD4 gene through miR-150-5p. It restored corneal morphology and function, reduced inflammation, promoted corneal epithelium and limbus repair, and reduced scar formation in the stroma.[97] The preconditioning of MSC under hypoxic environments has gained increasing attention for the potential to promote the secretion and functionality of exosome. For example, hypoxia-induced ADSC-Exo mediated miR-21-5p targeting sprouly1 in HUVEC to promote the activation of the PI3K/AKT signaling pathway, thereby enhancing HUVEC proliferation, migration, and angiogenesis and concomitant bone regeneration.[111] And hypoxia-induced BMSC-Exo delivered Bcl-2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3)-rich vesicles to alleviate intervertebral disc degeneration by activating the mitochondrial BNIP3/ANXA2/TFEB axis, which may provide a new target for the treatment of intervertebral disc lesion.[98]

The effects of MSC-Exo administration alone are limited, but the therapeutic effects can be enhanced by engineering or drug combinations. For example, the modification of upper central nervous system-specific rabies virus glycoprotein peptide on MSC-Exo can rescue the memory defects of AD mice.[112] MSC-Exo modified with lncRNA MIR155HG attenuated intimal hyperplasia of vein grafts following coronary artery bypass grafting.[113] When combining MSC-Exo with metformin, MSC-Exo can act as an anti-inflammatory agent without altering the dosage of metformin, thereby reducing the production of pro-inflammatory cytokines (including IL-1, IL-6, and TNF-α) and enhancing the effectiveness of metformin.[114] Lu et al developed a smart bilayer hydrogel loaded with diclofenac sodium (an anti-inflammatory drug) and BMSC-Exo, which reduced endogenous ROS production, promoted M2-type polarization of macrophages, regulated the inflammatory micro-environment, and promoted the recruitment and chondrogenic differentiation of late stem cell.[115] Human endometrial MSC-Exo was incorporated into polypyrrole chitosan to obtain an injectable hydrogel. The hydrogel reduced H_2O_2-induced apoptosis and promoted renal tubule formation, improving cardiac function after myocardial infarction (MI).[116]

Besides, MSC-Exo can also inhibit the apoptosis of renal tubular epithelial cells to effectively treat acute kidney injury,[117] repair diabetic lower limb ischemic injury,[118] improve the liver fibrosis environment,[119] reduce pulmonary vascular remodeling, successfully reverse pulmonary arterial hypertension,[120] and prevent experimental autoimmune disease progression in uveoretinitis[121] and repair damaged myocardium.[122] In summary, MSC-Exo, as a small-molecule non-cellular therapeutic strategy, can be widely used in various diseases to promote tissue damage and wound repair due to its biological characteristics.

MSC Derived Microvesicles for Tissue Repair

The origin of MVs can be traced back to the cell membrane, with the diameter ranging from 100 nm to 1000 nm. These vesicles are fragments derived from cells that remain attached to both the nuclear and plasma membranes. Following shedding from the cell membrane, MVs exhibit targeting specificity and selectively interact with specific ligands to exert their effects.[123] The MVs also serve as carriers of proteins, nucleic acids, lipids, and other bioactive substances.[124] It has been demonstrated that MVs show anti-apoptosis, anti-inflammation, and angiogenesis effects for tissue repair and wound healing.[125] The clinical application of MSC-MVs emerged relatively later compared to MSC-Exo. It was

developed in the past decade and witnessed rapid advancements and extensive utilization in various medical fields, including orthopedics, hepatology, pulmonology, nephrology, neurology, and other disciplines.

MSC-MV exhibits the capability of promoting bone repair and protecting cartilage tissue. Liang et al utilized the carrier function of MSC-MVs to construct a gene-activated scaffold through layer-by-layer assembly, which significantly facilitated angiogenesis for bone repair.[126] In collagen-induced arthritis mice, intravenous injection of MSC-MVs downregulated the expression of immune cell inflammatory factors (IL-1β, TNFα), MMP-13, and ADAMTS-5 in cartilage while maintained the stability of type I and II collagen, significantly reducing early cartilage destruction.[99] It has been shown that electrostatic field enhanced the release of mitochondria containing-MSC-MV, which played a key role in delaying cell aging and mitochondrial dysfunction, providing a new possibility for the treatment of intervertebral disc degeneration.[127]

The application of MSC-MV has been demonstrated in the repair of kidney injury. A study on kidney injury revealed that human umbilical cord MSC-MVs effectively delivered miR-21 to target PDCD4 in the renal tubular epithelium, inhibiting cell apoptosis and improving renal ischemia-reperfusion injury.[100] The administration of Wharton's jelly MSC-MVs effectively induced M2 macrophage polarization to mitigate renal fibrosis.[128]

MSC-MVs can also be used for neurological injury. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induces neurotoxicity resembling Parkinson's disease in mice. MSC-MV exhibited the potential to modulate the gut-microbiota-brain axis for ameliorating this neurotoxicity in both the brain and colon. In another study, MSC-MV can effectively down-regulate TNF-α and p-AKT levels to improving the neuroinflammatory symptoms in Alzheimer's disease. Moreover, it also reduced the apoptosis and improved the hippocampal and cortical histopathological alterations.[101]

MSC-Derived Apoptotic Bodies for Tissue Repair

The apoptotic bodies are large extracellular vesicles, ranging in diameter from 500 to 2000 nm, that are generated during the process of cell apoptosis. Apoptotic MSCs dismantle organelles and other materials into fragments, which are then encapsulated within distinct membrane-bound vesicles. These apoptotic bodies also encompass a diverse array of cellular components, including proteins, lipids, DNA, mRNA, and miRNAs.[129] They can act as an intercellular communication mediator, being involved in the regulation of immune response, cell proliferation, compensatory tissue regeneration, and other physiological processes.[130] Compared to exosomes and microvesicles, the therapeutic application of apoptotic bodies is relatively limited, leaving ample room for exploration.

MSC-derived apoptotic bodies have the potential to enhance wound healing through inducing macrophage polarization towards the M2 phenotype, suppress proinflammatory cytokine expression, and facilitate skin wound healing.[131] In another study, a kind of hyaluronic acid hydrogel loaded with MSC-derived apoptotic bodies was developed. The gel-system induced macrophage polarization towards the M2 phenotype and significantly suppressed the expression of proinflammatory cytokines, including IL-1β, TNFα, IL-6, and IFN-γ, facilitating endometrial regeneration.[102]

The application of MSC-derived apoptotic bodies in periodontitis treatment is also feasible. They enhanced the expression of dendritic cell-specific transmembrane protein on osteoclast membranes and facilitated the phagocytosis of apoptotic bodies by osteoclasts. Moreover, they effectively mitigated periodontitis-induced alveolar bone loss through miR-223-3p transferring to osteoclasts.[132]

In addition, apoptotic bodies released from transplanted MSCs could be engulfed by endothelial cells (ECs). The phagocytic apoptotic bodies stimulated the expression of transcription factor EB, which in turn enhanced the expression of autophagy-related genes in ECs and facilitated cardiac function recovery following myocardial infarction.[103] A recent study showed that hsa-miR-4485-3p in MSC apoptotic bodies inhibited osteogenesis by down-regulating the AKT pathway, and apoptotic bodies customized by knocking down hsa-miR-4485-3p exhibited potent osteogenic induction.[133] Apoptotic bodies have the potential for more comprehensive applications, and further researches and developments are needed to explore more application of apoptotic bodies generated by mesenchymal stem cells.

Clinical Progress in MSC-Derived Extracellular Vesicles for Tissue Regeneration

At present, extensive studies on MSC-EVs have focused on the basic biological functions and mechanisms of extracellular vesicles. The efficacy of MSC-EVs in various diseases is still restricted in the cellular and animal levels, and only a few MSC-EVs have entered the early clinical research stage. In a Phase I clinical trial, clinical-grade nebulized allogenic adipose mesenchymal stromal cell-derived extracellular vesicles were used to verify their safety in 24 healthy volunteers. The results showed that aerosolized inhalation of MSC-EVs was safe without serious side effects.[134] In another single-arm, open-label, phase I clinical trial, nine patients with complete subacute spinal cord injury received intrathecal human umbilical cord MSCs-Exos and were followed up for 12 months. During this period, no early or late adverse events attributed by the study intervention were observed. At the same time, the patients also had significant improvements in ASIA pinprick ($P = 0.039$) and light touch score ($P = 0.038$), SCIM III total score ($P = 0.027$), and NBD score ($P = 0.042$) at 12 months after the injection.[135] In a Phase I clinical trial for the treatment of psoriasis, MSC-Exo ointment was applied topically to the forearm of 10 healthy subjects for 24 days. There were no drug-related adverse events during the study period, and the subjects showed no adverse reactions such as dryness, pruritus, exudation/crusting, redness, scratching, skin thickening, insomnia, or swelling in the application area.[136] Additionally, a human adipose tissue stem cell-derived exosome-containing solution was enrolled in a Phase II clinical trial. Twenty-eight individuals participated in this study and were followed up for 12 weeks. At the last follow-up, the global aesthetic improvement scale score of the exosome-treated side was significantly higher than that of the control group ($p = 0.005$). The clinical improvement of skin wrinkles, elasticity, hydration, and pigmentation on the exosome-treated side was greater than that in the control group. No serious adverse events were observed.[137]

In 2019, the outbreak and rapid development of COVID-19 posed a significant threat to human life safety. The researches on MSC-EVs for the treatment of COVID-19 developed rapidly, and some studies have entered the Phase II clinical trial cycle. Human placental MSC-EVs were administered to two groups of patients with COVID-associated acute respiratory distress syndrome, noted as the control group and the intervention group. Compared with the control group (13/24 [54.16%]), MSC-EVs significantly reduced the mortality in the intervention group (4/21 [19.04%]) ($p = 0.015$). The mean time to death was 11.10 days in the control group compared with that of 28.06 days in the intervention group ($p < 0.001$).[138] Bone marrow MSC-EVs were also investigated for the treatment of COVID-19 respiratory failure in a prospective phase II, multicenter, double-anonymous, randomized, placebo-controlled administration trial. The post hoc subgroup analyses showed lower 60-day mortality with MSC-EVs than that with placebo (relative risk, 0.385; 95% CI, 0.159–0.931; $P = 0340$; $n = 50$).[139] Further, a phase IIa, single-arm, open-label, interventional trial (MEXCOVID trial) examined the safety and efficacy of aerosolized human adipose - derived MSC-derived exosomes (haMSC-Exos) in COVID-19 patients. Subsequently, the 5-day trial demonstrated that the COVID-19 patients had good tolerance, and all patients exhibited varying degrees of improvement in their lung lesions.[140]

As a cell-free therapy, MSC-EVs have shown the potential to treat various diseases. Although the clinical progress of MSC-EVs is still in the early stage (Table 2), a growing number of preliminary researches have laid a solid foundation for their subsequent development and will make continuous breakthroughs to bring insights for tissue repair.

Perspective and Conclusion

MSC-EVs are nanoscale particles paracrine from MSCs. They contain many bioactive molecules, including miRNA, lncRNA, proteins, and lipids that came from donor cells. These biologically active molecules have great potential to promote tissue repair. In recent years, MSC-EVs have become the focus of research in the field of cell-free therapy and regenerative medicine due to their participation in intercellular communication, anti-inflammation, immune regulation, angiogenesis, and other functions. A small number of MSC-EVs have been put into clinical trials. MSC-EVs are expected to become a new cell-free therapy for various diseases.

Despite MSC-EVs having shown promising results in laboratory studies, there are still many challenges in how to translate them into clinical applications. Firstly, the standardization and scale-up production of MSCs still present formidable challenges. The manufacturing process for MSC- EVs entails intricate bioprocessing steps encompassing

Table 2 The Summary of Clinical Study About MSC-EVs for Tissue Repair

Clinical Trial ID	Study Title	Phase	Number of Patients	Disease	Study Type	Source of MSC	Clinical Efficiency
NCT04313647[134]	Preclinical efficacy and clinical safety of clinical-grade nebulized allogenic adipose mesenchymal stromal cells-derived extracellular vesicles	I	24	Severe pneumonia caused by P. aeruginosa in mice	Single-arm clinical trial	Human adipose	Nebulized MSC-EVs were safe in healthy volunteers without serious side effects
IRCT20200502047277N1[135]	Safety and potential effects of intrathecal injection of allogeneic human umbilical cord mesenchymal stem cell-derived exosomes in complete subacute spinal cord injury: a first-in-human, single-arm, open-label, phase I clinical trial	I	9	Spinal cord injury	Single-arm, open-label, phase I clinical trial	Human umbilical cord	Intrathecal injection of allogeneic MSC-exosomes in patients with subacute SCI was safe
CTA2200019[136]	A phase 1, open-label study to determine safety and tolerability of the topical application of mesenchymal stem/stromal cell (MSC) exosome ointment to treat psoriasis in healthy volunteers	I	10	Psoriasis	Phase I, single center, open-label study	N/A	The topical application of the MSC exosome ointment (PTD 2021P) was well-tolerated by human subjects
2022R1A2C2091741[137]	Efficacy of combined treatment with human adipose tissue stem cell-derived exosome-containing solution and microneedling for facial skin aging: A 12-week prospective, randomized, split-face study	II	28	Facial skin aging	12-week prospective, randomized, split-face comparative study	Human adipose	The overall Aesthetic Improvement Scale score on the EV-treated side was significantly higher than that in control group, and the clinical improvement of skin wrinkles, elasticity, hydration, and pigmentation on the EV-treated side was greater than that in control group.
IRCT20130812014333N164[138]	Human placental mesenchymal stromal cell-derived small extracellular vesicles as a treatment for severe COVID-19: A double-blind randomized controlled clinical trial	II	43	COVID-19	Double-blind, randomized, controlled clinical trial	Human placental	Compared to the controls, treatment with MSC-EVs can significantly decrease the mortality rate

(*Continued*)

Table 2 (Continued).

Clinical Trial ID	Study Title	Phase	Number of Patients	Disease	Study Type	Source of MSC	Clinical Efficiency
NCT04493242[139]	Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicle Infusion for the Treatment of Respiratory Failure from COVID-19: A Randomized Placebo Controlled Dosing Clinical Trial	II	102	COVID-19	Multicenter, double-blind, randomized, placebo-controlled dosing trial	Bone	60-day mortality was decreased in EV-treated group compared to Placebo
NCT04276987[140]	Nebulized exosomes derived from allogenic adipose tissue mesenchymal stromal cells in patients with severe COVID-19: a pilot study	II a	7	COVID-19	Ingle-arm, open-labelled, interventional trial	Human adipose	All COVID-19 patients tolerated the MSC-Exo nebulization well, and there were different degrees of resolution of pulmonary lesions after aerosol inhalation of MSC-Exo.

Abbreviations: MSC-EVs, Mesenchymal stem cells derived extracellular vesicles; SCI, Spinal Cord Injury; COVID-19, Coronavirus disease, the disease caused by the SARS-CoV-2 coronavirus; MSC-Exo, Mesenchymal stem cells derived exosome.

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cell isolation, cultivation, collection, and purification. Secondly, it is difficult to control the quality of the final product of MSC-EVs. Both MSCs and EVs are biological products, and every step in their production process may affect the quality and effectiveness of the final product. Additionally, the clinical application of MSCs and EVs necessitates rigorous validation through comprehensive clinical trials to ensure their safety and efficacy. Therefore, continuous enhancement of the production and quality control processes for MSC-EVs will remain imperative in the future.

In conclusion, this review summarized the characteristics of three type of MSC-EVs including MSC-Exo, MSC-MV and MSC-derived apoptotic bodies. We detailly discussed the bioactive molecules involving miRNAs, lncRNAs, circRNAs and proteins in MSC-EVs for tissue repair. These functional molecules could regulate the cell proliferation, differentiation and apoptosis, angiogenesis as well as inflammatory response during the tissue repair process. We briefly described the application of different types of MSC-EVs in the treatment of various tissue injuries. We also reviewed the clinical progress and remained challenges of MSC-EVs for tissue repair. In the future, efforts should be focused on how to achieve the clinical translation and ensure safety and efficacy of MSC-EVs, with the ultimate goal of benefiting mankind.

Data Sharing Statement

Data sharing not applicable – no new data generated.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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