

Multifunctional role of microRNAs in mesenchymal stem cell-derived exosomes in treatment of diseases

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Abstract

Mesenchymal stem cells can be replaced by exosomes for the treatment of inflammatory diseases, injury repair, degenerative diseases, and tumors. Exosomes are small vesicles rich in a variety of nucleic acids [including messenger RNA, Long non-coding RNA, microRNA (miRNA), and circular RNA], proteins, and lipids. Exosomes can be secreted by most cells in the human body and are known to play a key role in the communication of information and material transport between cells. Like exosomes, miRNAs were neglected before their role in various activities of organisms was discovered. Several studies have confirmed that miRNAs play a vital role within exosomes. This review focuses on the specific role of miRNAs in MSC-derived exosomes (MSC-exosomes) and the methods commonly used by researchers to study miRNAs in exosomes. Taken together, miRNAs from MSC-exosomes display immense potential and practical value, both in basic medicine and future clinical applications, in treating several diseases.

Key Words: MicroRNA; Mesenchymal stem cells; Exosomes; Modulation of mesenchymal stem cells; Inflammatory diseases; Injury repair

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Core Tip: Mesenchymal stem cell (MSC)-derived exosomes (MSC-exosomes) have obvious therapeutic effects on inflammation, organ damage, and tumors. Exosomes are

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membranes containing many substances, such as nucleic acids, proteins, and lipids. In many studies, microRNAs (miRNAs) have been found to be the core substance of therapeutic effect after exosomes are engulfed by cells. MiRNAs in exosomes secreted by different stem cells are diverse. In turn, different miRNAs target different genes to treat matched diseases. This point of view proves that miRNAs in MSC-exosomes have a broad research space.

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INTRODUCTION

Mesenchymal stem cells (MSCs) are adult stem cells that exist in a variety of tissues (such as bone marrow, cord blood and cord tissue, placental tissue, adipose tissue, and menstrual blood) and have the potential for multidirectional differentiation^[1-3]. MSCs have the potential to differentiate into multiple tissues and escape immunity, making it a good candidate for cell therapy^[4]. Although MSCs have been shown to be effective in treating many refractory diseases, the ethical and safety problems of stem cells, as well as the inevitable aspect of promoting tumor growth, still pose great threats to their development^[5,6].

Exosomes are small vesicles that carry a variety of substances and are important for information transmission and material communication between cells. Recent studies have shown that exosomes exert significant improvements in various diseases, such as tissue injury^[7,8], neurodegenerative diseases^[9,10], tissue fibrosis^[11-13], diabetes^[14,15], and even tumors^[16,17], suggesting that exosomes have great therapeutic potential. Researchers have found that MSCs do not function through cell transplantation and inflammatory response, but through the secretion of small extracellular vesicles, the exosomes^[6]. Subsequent research has further confirmed that diseases, which can be treated with MSCs, can also be treated with MSC-derived exosomes (MSC-exosomes), such as myocardial infarction^[18], liver fibrosis^[19], and tumors^[20]. Previous studies have demonstrated that MSC-exosomes exert similar effects on myocardial repair as do MSCs, and in some cases perform better than MSCs^[21].

Material transfer in stem cells mediated by exosomes has several advantages, including flexibility of use, easy preservation, stability of materials in vesicles, and substantial enrichment from culture medium. MSC-exosomes play a very important role in the treatment of diseases. There are many substances in exosomes, and exactly what substances are playing a key role is still being explored. In numerous studies, microRNA (miRNA) frequency is very high, suggesting that miRNAs in exosomes may play an important role in treatment. Therefore, this review will introduce MSC-exosomes, miRNAs, miRNA in exosomes, and how miRNA plays a crucial role in MSC-exosomes in specific diseases.

EXOSOMES

History of exosomes

Exosomes are membranous vesicles with a diameter of 30-150 nm, which are released extracellularly by the fusion of intracellular vesicles and cell membranes. Exosomes are specific extracellular vesicles, which include apoptotic bodies, micro-vesicles, and exosomes. The first exosome was discovered by Peter Wolf in 1967, who called it "platelet dust" at that time^[22]. In 1987, Johnstone named it "exosome", which originated from the endosome formed by the endocytosis process and was eventually released from the inside to the outside of the cell^[23]. Exosomes were initially thought of as a way for cells to excrete waste, and were ignored for about a decade. It was until 1996, when G. Raposo discovered that immune cells similar to B lymphocytes also secrete antigen-presenting exosomes, that people began to notice^[24]. In 2007, Valadi *et al*^[25] discovered

that cells can exchange genetic material with each other *via* RNA in exosomes. In 2010, exosomes secreted by MSCs were shown to be significant in the treatment of myocardial infarction, and since then, there has been increasing research on exosomes derived from MSCs^[7]. In 2013, it was found that miRNAs in exosomes in the plasma of tumor patients could be used as non-invasive biological markers of tumors, and the role of miRNAs in exosomes began to receive attention^[26]. Subsequently, miRNAs in astrocyte-derived exosomes were found to promote brain tumor metastasis by targeting the gene phosphatase and tensin homolog deleted on chromosome ten (*PTEN*)^[27]. Moreover, miRNAs in adipose-derived exosomes have also been shown to regulate gene expression in other tissues^[28]. These are important discoveries proving that cells can exchange information and substances through exosomes, laying a foundation for further studies on exosomes.

Biogenesis of exosomes

Exosomes are formed by the invagination of the cell membrane into the endosome, and then into multivesicle bodies (MVB), which are finally secreted to the extracellular fluid. Late endosomal membrane invagination leads to the formation of intraluminal vesicles (ILVs) in large MVBs^[29]. At present, among the biosynthesis mechanisms of exosomes, the endosomal sorting complex required for transport (ESCRT) pathway has received the most attention. It is a complex system composed of four proteins. They are ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III. The cooperation between these results in MVB synthesis. MVB then fuses with the cytoplasmic membrane, releasing ILVs outside the cell to form exosomes^[30]. Not only ESCRT proteins but also other proteins, including Flotillin, TSG101, CD6, and CD63, are involved in this process. In the mechanism of exosome formation, some researchers believe that RAL-1 is not only involved in the formation of MVBs, but also in the fusion of MVBs and cell membranes, which is of great significance for further study of exosomes^[31]. Although the endosomal dependent pathway is considered to be the main synthesis pathway of exosomes, some studies have shown that direct budding of the plasma membrane also plays an important role in exosome biogenesis^[32]. Moreover, the transmembrane protein syndecans 1 to 4 directly regulate ILVs during exosome formation by co-accumulation with syntenin and ALG-2 interacting protein X in exosomes^[33]. Additionally, neutral sphingomyelinase can also promote ILV formation by promoting the budding of MVBs^[34]. Due to the small diameter of exosomes and the complexity of the synthesis process, the synthesis process of exosomes is still being discussed further.

Isolation methods of exosomes

At present, ultracentrifugation is still the gold standard for exosome isolation^[35], as well as the most common method. However, the biggest challenge that ultracentrifugation faces is time consumption. If researchers want to conduct numerous experiments on exosomes, it is bound to take much time to extract. There are many ways to extract exosomes, and there will be more in future. These methods of isolating exosomes have their own advantages and disadvantages^[158-161] (Table 1). The biggest problem at present is that we cannot unite these advantages, that is, easy to obtain, high purity, and less exosome damage. Among the many methods, the most advanced is microfluidic technology, which is also one of the most studied and attention-grabbing at present. It includes immunoaffinity-based microfluidics^[36], size-based microfluidic technologies^[37], and contact-free microfluidics-versatile tools^[38]. Immunoaffinity-based microfluidics is one of the most widely used microfluidic technologies and has shown a commercialization trend. However, due to its high cost, difficulty in maintaining the integrity of exosome structure, and applicability only to specific subgroups, its development prospects are not promising^[38]. The first size-dependent microfluidic system is the Exosome Total Isolation Chip^[39]. The advantage of this method is that exosomes can be extracted with only a few samples, which is convenient for clinical detection. Besides, the process of this method is relatively simple. The brilliance of contact-free microfluidics-versatile tools lies in the fact that they do not require sophisticated instruments and external electric field forces, and can achieve exosome recovery up to 80% and purity up to 90% without contact^[38]. This device achieves size-dependent, continuous exosome separation by applying viscoelastic forces on exosomes through a sheath-like solution consisting of a low concentration (0.1%) of biocompatible polyoxyethylene.

Identification of exosomes

The most commonly used identification method for exosomes is electron microscopy, which display a saucer-like structure with a clear membrane^[40]. The electron

Table 1 Exosome isolation methods

Isolation method	Principle	Advantages	Limitations
Ultracentrifugation	Exosomes are purified by physical centrifugation according to their size and specific gravity	(1) The most common method; (2) Bulk extractability; and (3) Low cost	(1) The operation is complex and time-consuming; (2) Increased impurities; (3) Loss due to adsorption on the tube wall; and (4) Expensive equipment is needed ^[158]
Ultrafiltration	According to the size of exosomes, exosomes are separated by filter membrane	(1) Simple operation; (2) Rapid process; and (3) High yield	(1) Low-purity; and (2) Stress and shear forces can cause exosome damage
Size exclusion chromatography	The biofluid dissolves in the mobile phase and passes through the stationary phase, in which the various components of the mixture move at different speeds and are separated ^[159]	(1) High recovery rate; and (2) The structural integrity of exosomes is maintained	(1) Time-consuming; and (2) Low-purity
Precipitation ^[160,161]	By chemical extraction, the exosome liquid is combined with the liquid in the kit, and eventually the exosomes are deposited.	(1) Simple operation; (2) Rapid process; (3) No need for special equipment	Increased impurities
Immune affinity capture	Immune isolation is performed by magnetic bead-specific adsorption of exosome surface antigens	(1) Easy operation; (2) Rapid process; (3) High purity; and (4) High yield	(1) Does not apply to large-volume cell supernatant; and (2) High cost
Microfluidic technologies (ExoChip)	A microfluidic platform based on nano-acoustic filters, viscoelastic fluid separation, lateral displacement, and immune affinity separates exosomes from biological fluids	(1) Rapid separation; (2) High purity; and (3) Saving the sample	The research is not sufficient and is not widely used at present

microscope also includes transmission electron microscope^[41], scanning electron microscope^[42], cryo-electron microscope^[43], and atomic force microscope^[44], and the fine morphology of exosomes can be observed. Exosomes can also be identified by nanoparticle tracking analysis and dynamic light particles^[45]. This method can help determine the distribution range of particle size of the detected substance and further determine whether the substance is an exosome. In addition to particle size and morphology, surface biomarkers of exosomes also need to be detected. Western blot, flow spectrometry, mass spectrometry, and enzyme-linked immunosorbent assay are also the methods used. Exosome extraction methods are developing day by day, and new exosome identification methods are also emerging. In 2019, Jeppesen *et al*^[46] used RNA-seq techniques to analyze exosome components, and structural illumination microscope imaging techniques to observe exosome biomarkers, and defined the respective components of exosomes and non-vesicle compartments, providing a deeper insight into the heterogeneity of exosomes. In addition, the flow field-flow fractionation was also used to analyze different subpopulations of exosomes, and it was further found that proteins in exosomes were significantly correlated with enzyme metabolism and hypoxia, microtubules, and coagulation proteins, as well as specific pathways, such as glycolysis and mammalian target of rapamycin (mTOR) signaling^[47]. The rapid development of exosome identification methods has enabled us to deepen our understanding of the fine structure of exosomes and the mechanism of disease treatment, thus enabling us to apply exosomes to more diseases.

Components of exosomes

Exosomes are known to be small extracellular vesicles containing proteins, nucleic acids (DNA, miRNA, lncRNA, mRNA, tRNA, and circRNA), and cholesterol. Exosomes have a diameter of about 30-150 nm, and the surface markers are mainly CD63, CD81, CD9, tumor susceptibility gene 101 protein (TSG101), heat shock 70 kDa protein (HSP70), and heat shock 90 kDa protein (HSP90) (Figure 1). Proteomic analysis of exosomes from different sources has been performed many times by researchers^[48-51]. About 1600 proteins were found in biofluid-derived exosomes, of which 300 were common in at least two groups, and only two were shared by more than four^[52]. After proteomics detection of MSC-exosomes and enrichment analysis of the pathways involved, it was found that proteins in exosomes were mostly related to heparin binding, phospholipid binding, integrin, immune response, and cell adhesion functions^[53]. In addition, deep sequencing of miRNAs was also performed to further understand the profiles and expression of miRNAs in human MSC-exosomes. The let-7 family of human embryonic-derived MSCs was found to be widespread, and is associated with the self-renewal characteristics of stem cells^[54]. New targets and approaches for the treatment of acute leukemia have also been explored by comparing miRNA differences in exosomes derived from bone marrow MSCs (BM-MSCs) in

Proteins: Heat shock proteins (HSP70, HSP90), MVB biogenesis proteins (ALIX, TSG101), Apoptosis ligand (FasL), Embrane transport proteins (TRAIL, flotillin), Tetraspannins (CD9, CD81, and CD63), Downstream pathway protein (Wnt), GAPDH, Annexins *ect.*

Nucleic acids: mRNA, miRNA, lncRNA, DNA, *ect.*

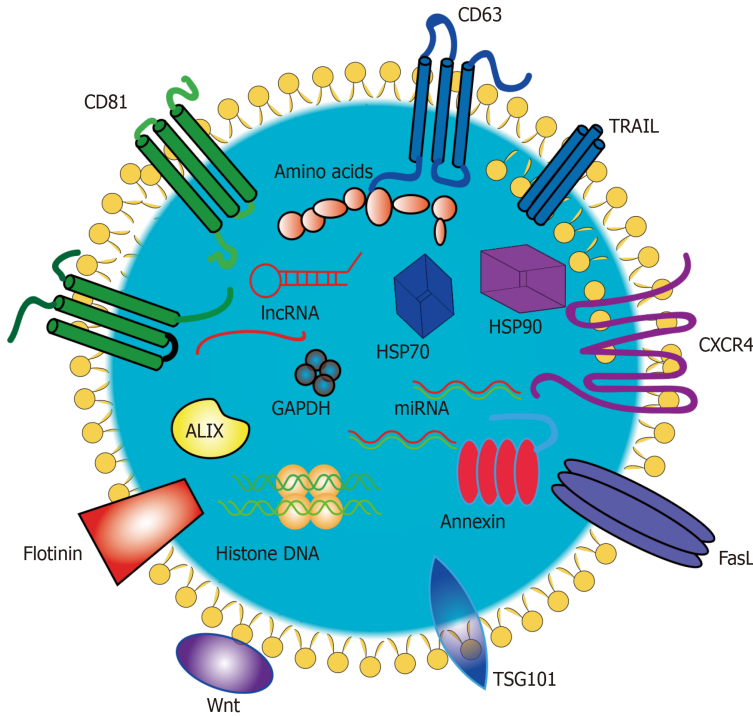


Figure 1 Exosomes are small vesicles that are secreted by cells and wrapped in membranes made up of lipid bilayer molecules. Exosomes contain proteins, nucleic acids, and other substances. Their proteins include heat shock proteins, MVB biogenesis proteins, cytoskeleton proteins, apoptosis, ligand, embrane transport proteins and so on. Their nucleic acids include mRNA, miRNA, lncRNA, DNA, and so on. ALIX: ALG-2 interacting protein X; CXCR4: CXC-chemokine receptor 4; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; HSP70: Heat shock 70 kDa protein; TSG101: Tumor susceptibility gene 101 protein.

patients with acute leukemia and exosomes derived from BM-MSCs in normal people. In addition to sequencing miRNAs, the researchers further understood the genes and pathways targeted by miRNAs through network analysis. It was found that genes targeted by miRNAs are mainly related to cardiac regeneration, repair, and angiogenesis, and the pathways involved mainly include Wnt signaling, pro-fibrotic signaling *via* transforming growth factor- β (TGF- β) stimulation, platelet derived growth factor (PDGF), proliferation, and apoptosis^[55].

The research on whether there are other substances in exosomes is still in progress. In the past, research was limited due to the very small size of exosomes, but this gradually improved as science and technology developed further. As mentioned above, Jeppesen *et al*^[46] re-evaluated exosomes by advanced methods and re-determined exosome composition. Exosomes were previously considered to be carriers of extracellular DNA secretion. Studies have shown that extracellular double-stranded DNA does not exist in exosomes and cannot be the target of liquid biopsies in cancer patients. In addition, Annexin A1 was identified as a marker protein for the formation of vesicles in the classic plasma membrane of exosomes^[56]. The discovery of new substances in exosomes may provide new ideas for using them as mediators for diagnosis and treatment.

Functions of MSC-exosomes

Exosomes can be secreted by almost any type of cell in the body, and the function of exosomes depends on the cell type from which they originate. For example, exosomes

derived from tumor cells can accelerate tumor progression and even influence the function of normal cells at the distal location, promoting the formation of a pre-metastasis microenvironment^[57]. Besides, exosomes released by neurons can repair damaged brain cells and play an important role in the development of neurons and neural circuits^[58]. The difference is that MSC-exosomes mainly play a therapeutic role, such as regulating immunity^[59-61] and promoting repair of tissue damage^[62-64], which is basically consistent with the effect of stem cells on human tissues. MSCs have previously been used as a treatment for severe infectious diseases, mainly to neutralize destructive inflammation and promote the repair of damaged organs^[65,66]. MSC-exosomes were not used to treat severe infectious diseases before 2020. Significantly, doctors treated severe coronavirus disease 2019 patients with exosomes derived from BM-MSCs during the outbreak. They observed an 83% survival rate, with three of the 24 patients remaining in critical condition and four experiencing non-treatment-related deaths^[67]. This indicates that MSC-exosomes also have a good effect on the severe multi-organ damage caused by infectious diseases, suggesting a new application of MSC-exosomes. The effect of MSC-exosomes on tumors has always been controversial, and most literature shows that MSC-exosomes have a tumor promoting effect, namely, promoting tumor angiogenesis, proliferation, and migration^[68,69]. In order for MSC-exosomes to inhibit and kill tumors, many scientists have modified exosomes in various ways, including loading overexpression of certain miRNAs^[70,71], carrying anti-cancer drugs or suicide genes^[72,73], engineering stem cells^[74,75], or in combination with other anti-cancer approaches^[76,77]. The extensive use of exosomes provides a promising avenue for disease treatment, especially the exosomes derived from MSCs, which are of high safety and can perform functions in place of stem cells. In general, the use of MSC-exosomes in cell-free therapy is helpful for the treatment of many diseases^[78]. It regulates inflammation in inflammatory diseases, promotes tissue repair in tissue damage diseases, and kills tumors as an adjuvant tumor therapy.

Thus far, the study of exosomes derived from stem cells has reached the clinical stage^[62] (Table 2). However, miRNAs have rarely been involved in these clinical trials, although many studies have been done on miRNAs in MSC-exosomes in animal models. The clinical application of miRNAs in the treatment of exosomes derived from stem cells is a very important research direction in the future. Therefore, in the table, we proposed a miRNA hypothesis that may be associated with MSC-exosome treatment of diseases combined with studies in animal experiments^[79-83]. Clinical trials of MSC-exosomes have focused on diseases, such as multi-organ failure, coronavirus pneumonia, and type 1 diabetes. Some clinical studies are not specific to specific diseases, but only to explore the safety of exosome aerosol administration through the airway, which will provide possibilities for diverse exosome administration methods. A clinical study was conducted at Cairo University in Egypt to explore the important role of miR-136, miR-494, and miR-495 in the diagnosis of eclampsia with exosomes derived from umbilical cord mesenchymal stem cells. This study demonstrated the clinically important role of miRNAs in MSC-exosomes, not just in mouse models^[84].

MICRORNAS

MicroRNA was discovered in 1993 by Victor Ambros and Gary Ruvkun. The first miRNA is lin-4^[85,86], which is known as small molecule timing RNA. Although these two articles were published in *Cell*, they were not taken seriously at that time. Further, miRNAs did not receive much attention over the next 20 years. The launch of the human genome project in 1990 was helpful in the discovery of miRNAs. Finally, in October 2001, Tuschli, Bartel, and Ambro published three papers in *Science* that named this RNA microRNA (miRNA)^[87-89]. MiRNAs are a class of non-coding RNAs with 20-22 base sequences, which can regulate gene expression through post-transcriptional regulation of target mRNA. The seed regions (nucleotide sites 2-8) of miRNA can bind to the mRNA, and then the miRNA can guide the RNA-induced silencing complex (RISC) to reach the binding site, prompting the mRNA to degrade or inhibiting its translation^[90]. MiRNAs have been identified by researchers to be involved in many important life processes, including cell proliferation, apoptosis^[91], cell death, fat metabolism^[92], and cell differentiation^[93,94].

Recent advances in miRNAs have greatly promoted both clinical diagnosis and basic research. Wang *et al* constructed an *in vivo* miRNA imaging system, consisting of cellular MnO₂ nanoscale sponges and autocatalytic DNA enzymes. Since some miRNAs are closely related to tumor formation *in vivo*, this method is convenient for the diagnosis of tumor etiology and is of great significance for the evaluation of tumor

Table 2 Representative clinical trials of mesenchymal stem cell-derived exosomes

Exosome origin	Diseases	Administration method	Status	miRNAs that may be associated with MSC therapy for this disease
Allogenic mesenchymal stromal cells	Cerebrovascular disorders	Intravenous injection	Completed	MiRNA-184, miRNA-210, miR-133b, miR-17-92 ^[81,82,162]
Allogenic adipose mesenchymal stem cells	COVID-19	Aerosol inhalation	Phase I	Has not been reported
Allogenic mesenchymal stromal cells	Multiple organ failure	Intravenous injection	Not yet Recruiting	Has not been reported
Human UC-MSCs	Macular holes	Intravitreal injection	Phase I	Has not been reported
Human UC-MSCs	Dry eyes	Eye drops	Phase II	Has not been reported
Adipose mesenchymal stem cell	Alzheimer's disease	Nasal drip	Phase II	MiR-146a-5p ^[79]
Human UC-MSCs	Diabetes mellitus type 1	Intravenous infusion	Phase III	MiR-1908, miR-203a ^[80]
MSCs	COVID-19	Inhalation	Phase II	Has not been reported
Human UC-MSCs	Chronic ulcer	Applying and closed by transparent dressing	Completed	Has not been reported

UC-MSCs: Umbilical cord mesenchymal stem cells; MSCs: Mesenchymal stem cells; COVID-19: Corona virus disease 2019.

treatment^[95,96]. Iwasaki *et al*^[97] found that urine contained miR-6807-5p and miR-6856-5p, which could be used to detect gastric cancer. In addition to the detection of *Helicobacter pylori*, this method is the second one that can realize the early and non-invasive detection of gastric cancer, which means that this method can be mutually verified with the detection of *Helicobacter pylori* and improve the accuracy of non-invasive detection. At present, the most common function of miRNAs is to target and negatively regulate mRNA levels of genes and mediate their degradation. However, in 2018, Mihnea Paul Dragomir *et al*^[98] published a snapshot in *Cell*, which introduced seven other non-classical molecular mechanisms of miRNAs and summarized new ideas for miRNA research for researchers, including: (1) The precursor of miRNA, pri-miRNA, can be translated into peptides; (2) miRNA can bind to other functional proteins and change their functions; (3) miRNA can activate Toll-like receptors; (4) miRNA can upregulate protein expression; (5) miRNA can target and regulate mitochondrial related mRNA to change mitochondrial function; (6) miRNA can activate the gene transcription process; and (7) miRNA can negatively regulate other non-coding RNAs. These can broaden the thinking for researchers studying miRNAs and no longer restrict miRNAs to only regulating 3'-untranslated region (UTR) fragments of target genes.

MiRNAs differ in MSC-exosomes from different sources. Through sequencing, it was found that the miRNAs mainly contained in adipose-derived MSC-exosomes are miR-486-5p, miR-10a-5p, miR-10b-5p, miR-191-5p, and miR-222-3p, while the miRNAs mainly contained in bone marrow-derived MSC-exosomes are miR-143-3p, miR-10b-5p, miR-486-5p, miR-22-3p, and miR-21-5p^[99]. MiR-21, miR-23a, miR-125b, and miR-145 are the main miRNAs contained in MSC-exosomes from the umbilical cord^[100]. This means that MSC-exosomes may affect different target genes due to different sources when acting through miRNAs, thus treating different diseases.

MSC-EXOSOMES INFLUENCE DISEASES THROUGH MIRNAS

Exosomes secreted by stem cells to the outside of the cell are absorbed together with substances inside the vesicle, including nucleic acids and proteins, and finally play a role in other cells. MiRNA is currently the most studied RNA in exosomes^[101]. As for the effect of miRNA on genes, there are usually two aspects: One is that miRNA directly acts on the 3'-UTR of target mRNA to degrade it; the other is that miRNA acts on the translation process of mRNA to repress its translation. Several studies have found that miRNAs can enter the nucleus and act on gene enhancers to activate genes and promote their expression^[102,103]. This suggests that we may discover a new

mechanism of action for miRNAs in MSC-exosomes to treat diseases in the future. Different types of miRNA target different genes and can affect multiple diseases. Previous studies have found that although both MSCs and extracellular vesicles contain miRNAs, the miRNAs contained by both are not completely equivalent, and only 44 miRNAs are co-expressed. Gene ontology analysis of miRNAs that were highly expressed in MSC-exosomes showed that these miRNAs were mainly related to the growth and development of multiple organs, cell survival, and immune regulation^[104]. However, studies regarding the functional aspects of MSC-exosomes are not limited to this, but also include injury repair, treatment of degenerative diseases, and tumor intervention. In the following sections, the role of miRNAs in MSC-exosomes in these types of diseases and the genes or pathways they target will be introduced (Figure 2).

Inflammatory regulation

MSC-exosomes can regulate inflammation through miRNAs and reduce inflammation and anti-fibrosis^[164-165] (Table 3). Stem cells come from different sources and have different miRNAs that play a regulatory role in different diseases. It has been found that stem cell-derived exosomes can use miRNAs to correct immune disorders in organ tissues, such as allergic airway, Duchenne muscular dystrophy, and myocardial ischemia-reperfusion injury^[105-107]. That article shows that allergic airway miR-146a-5p downregulates the expression of interleukin-9 (IL-9) and interleukin-13 (IL-13) in Group 2 innate lymphoid cells, subsequently regulating allergic diseases^[105]. This suggests that miR-146a-5p in MSC-exosomes is associated with allergic diseases, and the role of this miRNA has also been reported in previous studies^[108]. In myocardial ischemia-reperfusion injury, the process of ischemia-reperfusion causes a cascade of heart inflammation. Here, the researchers showed that miRNAs in exosomes can influence macrophage transformation from M1 to M2 anti-inflammatory phenotype, thereby regulating immunity. Dil fluorescence staining showed that exosomes could be endoscopically absorbed into the cytoplasm of macrophages, thereby transforming pro-inflammatory M1 into anti-inflammatory M2, accompanied by the reduction of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α)^[107]. In addition, miR-233 in MSC-exosomes protects the heart from inflammatory cytokines and reduces stimulation and damage to the heart during sepsis^[109].

Through a review and comparison of these articles regarding miRNAs in MSC-exosomes, we found that miRNAs in exosomes regulate inflammation mainly by regulating macrophages and T cells^[107,110,111]. MiRNAs derived from MSC can reduce Toll-like receptor 4 on the surface of macrophages, promote the transformation from M1 to M2, and then secrete various anti-inflammatory factors. In the study of myocardial ischemia-reperfusion injury, miRNA-181a acts on the target gene *c-fos*, downregulates its expression, and promotes the polarization of Treg cells (regulatory T cells) for immune regulation^[110]. Some studies have shown that miRNAs from MSC-exosomes act on diseased tissues to downregulate pro-fibrotic factors (TGF- β) and pro-inflammatory factors (TNF- α , IL-6, and IL-8). However, the exact regulatory mechanisms and target genes have not been fully elucidated, and thus deserve further research.

Injury repair

MiRNAs in MSC-exosomes also play an important role in injury repair (such as heart injury, spinal cord injury, and liver injury)^[112-115]. In these diseases, miRNAs achieve injury repair by promoting cell proliferation and differentiation, and reducing necrosis and apoptosis. MiRNAs in exosomes (such as miR-144, miR-21-5p, and miR-19a) play a role in preventing apoptosis after reaching the damaged tissues. The commonly described pathway indicates that miRNA downregulates *PTEN*, which activates the Akt signaling pathway, then decreases the expression of apoptotic proteins (caspase 3, caspase 8, caspase 9, *etc.*) and the number of apoptotic cells^[113,116,117]. Similarly, studies involving vaginal epithelial cells (VK2) have found that miRNAs in MSC-exosomes can promote VK2 cell proliferation and inhibit apoptosis by promoting cell cycle progression. Interestingly, some researchers have also found that miR-100-5p in MSC-exosomes can enhance autophagy in osteoarthritis by inhibiting the target gene *mTOR*, thus promoting bone growth and bone reconstruction. Collectively, these studies suggest that miRNAs in exosomes may exert a protective effect on cells in vital organs, such as the brain, heart, and lungs, after severe stress in the human body.

Recent studies on miRNAs in MSC-exosomes have found that an miRNA called miR-200a-3p can protect mitochondria through the KEAP1-Nrf2 signaling pathway in renal ischemia-reperfusion injury to promote the recovery of renal function^[118]. The

Table 3 Representative articles on inflammatory regulation

Exosome origin	Diseases	MicroRNA	Downstream molecular/pathways	MicroRNA methodology
Placenta-derived mesenchymal stromal cells	Duchenne muscular dystrophy	MiR-29c	TGF- β	Reporter gene assays ^[106]
Induced pluripotent stem cells	Group 2 innate lymphoid cell-dominant allergic airway	MiR-146a-5p	T helper 2 (Th2) cytokines	Anion-exchange chromatography; RNA sequencing ^[103]
Mouse BM-MSCs	Peripheral neuropathy in diabetes	MiR-17, miR-23a, and miR-125b	TLR4/NF- κ B signaling pathway.	MiRNA array; ultracentrifugation ^[164]
MSCs	Myocardial ischemia-reperfusion injury	MiR-182	TLR4 pathway	Differential centrifugation; miRNA sequencing ^[107]
Human UC-MSCs	Burn-induced excessive inflammation	MiR-181c	TLR4 pathway	PureExo Column; miRNA array analysis ^[164]
LPS-preconditioned MSCs	Wound healing	Let-7b	TLR4 pathway	Gradient centrifugation; miRNA microarray ^[111]
Human UC-MSCs	Hyperglycemia-induced retinal inflammation	MiR-126	HMGB1 signaling pathway	Ultracentrifugation ^[165]

BM-MSCs: Bone marrow MSCs; UC-MSCs: Umbilical cord mesenchymal stem cells; MSCs: Mesenchymal stem cells; TGF- β : Transforming growth factor- β ; TLR4: Toll-like receptor 4; HMGB1: High-mobility group box-1.

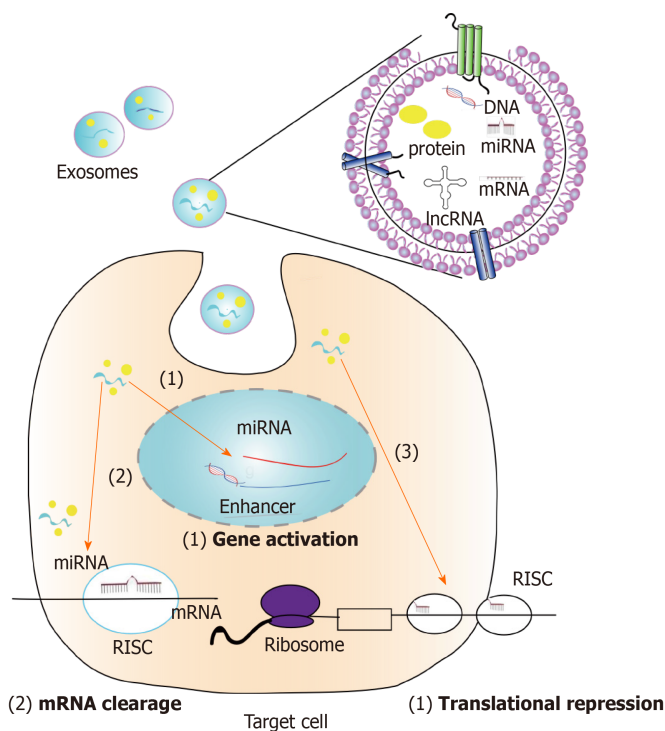


Figure 2 Exosomes were first isolated from the cultured supernatant of stem cells and injected intravenously into the model. The exosomes then reach the damaged site, are absorbed by the cells, and enter the cell: (1) Exosome-derived microRNA binds to enhancers in the nucleus to promote gene expression; (2) miRNA in exosomes bind to the 3'-UTR of the mRNA for mRNA degradation; and (3) exosomes inhibit mRNA translation. The second and third ways have been studied, and the first way is based on the assumption of existing studies. RISC: RNA-induced silencing complex.

localization of miRNAs in MSC-exosomes in intracellular specific organelles will promote the understanding of the role of miRNAs and accelerate the practical promotion of the application of stem cell-derived exosomes. Currently known miRNAs function in the cytoplasm, mitochondria, and nucleus, and whether miRNAs in MSC-exosomes play a role in other organelles deserves further exploration.

Tumor progression

Tumor treatment with MSC-exosomes is controversial, with some studies reporting

that MSC-exosomes can promote tumor development, while others believe that they can inhibit tumors^[166] (Table 4). A study regarding osteosarcoma indicated that miR-208a in MSC-exosomes promoted tumor progression by downregulating programmed cell death 4 (*PDCD4*) and activating the ERK1/2 pathway^[119]. In addition, miR-142-3p and miR-146a from MSC-exosomes have been proved to promote tumor growth through various pathways^[120,121]. In the osteosarcoma study, it is worth noting that MSCs are derived from bone marrow, and the role of stem cells in tumor promotion may be due to similar origins. Similarly, BM-MSCs can also promote the progression of multiple myeloma through miR-146a, further confirming this hypothesis^[121]. In these tumor-promoting processes, these miRNAs without exception promote the proliferation, migration, and invasion of tumors, but in other studies of MSC-exosomes, it also promotes angiogenesis. However, the role of miRNAs in promoting angiogenesis in tumors has not been well verified^[122].

Currently, miRNAs in MSC-exosomes have been mainly studied for tumor inhibition in tumor studies. In MSC-exosomes, an miRNA called miR-146a is a widely published tumor suppressor, which plays a significant role in tumor inhibition in multiple myeloma^[123-127]. MiR-23b in MSC-exosomes can inhibit tumor proliferation, maintain a dormant tumor state, improve life quality, and prolong the life of patients^[128]. In a study of hepatocellular carcinoma, MSC-exosomes did not directly contain anti-tumor miRNAs, but transfected miR-122, which can enhance drug sensitivity, into stem cells through plasmids, and secreted into tumor cells through exosomes to enhance the sensitivity of anti-tumor drug sorafenib^[129]. In addition to improving chemical sensitivity, studies have shown that miR-34c in MSC can improve tumor sensitivity to radiotherapy^[77]. This suggests that MSC-exosomes can be combined with other therapies, such as chemotherapy drugs and radiotherapy, when treating tumors. Since stem-cell derived exosomes have been reported to promote tumors, it should be safer to overexpress certain known anticancer miRNAs with stem cells or to secrete anticancer drugs with exosomes. Previous studies, for example, have shown that paclitaxel is added to MSCs, then the cells target tumor tissue and release paclitaxel^[130].

Other diseases

MSC-exosomes have been shown to play the same role as MSCs in many diseases. This indicates that the diseases that can be treated with MSCs can be further studied with exosomes from their sources, because exosomes themselves have advantages that stem cells do not, such as easy storage and higher safety. In some studies, researchers have found that Alzheimer's disease can be improved through stem cell therapy, and miR-146a has been proved to play an important role in this. It is also worth further exploring whether exosomes from this stem cell source contain this miRNA and whether exosomes can replace stem cells to affect brain degenerative diseases^[131]. One of the first diseases treated with stem cells is graft-versus-host disease (GVHD)^[132]. In recent years, studies have found that GVHD can be improved with the extracellular vesicles derived from BM-MSCs through miRNAs, which is related to the preservation of naive T cells^[133]. Exosomes are the most famous subgroup of extracellular vesicles. Extracellular vesicles display functions of exosomes, which have been studied further due to their extensive functions^[134]. In addition to degenerative diseases, MSCs reportedly play an important role in organ fibrosis, including liver fibrosis^[135], pulmonary fibrosis, and myocardial fibrosis. MSCs are involved in fibrosis, and can reverse fibrosis and restore the original functions of damaged organs and tissues^[136-138]. Regarding MSC-exosomes, which play a role in disease, the miRNAs that they contain function in a therapeutic capacity in various diseases. More critically, MSC-exosome transplantation into the body and prolonging the efficacy of this treatment require further research, as well as investigating specificity with regard to disease sites.

METHODS TO STUDY ASSOCIATION BETWEEN EXOSOMES AND MIRNAS

When exploring the distribution and function of miRNAs in exosomes, different researchers often choose different research methods according to their own conditions. The following will introduce the common methods used to study specific miRNAs in exosomes, so that researchers could choose the best methods for future work. Methods to study the association between exosomes and miRNAs mainly include small RNA sequence, RNA microarray, nanostring miRNA assay, and database bioinformatics analysis to find appropriate miRNAs in exosomes. The first and most common method

Table 4 Representative studies in which MSC-derived exosomes affect tumors through miRNAs

Exosome origin	Disease	MiRNA	Downstream molecular/pathway(s)	Outcome
BM-MSCs	Osteosarcoma	MiR-208a	Downregulation of PDCD4 and activation of the ERK1/2 pathway	Promoting tumor progression ^[119]
BM-MSCs	Multiple myeloma	MiR-146a	The Notch pathway	Promoting tumor progression ^[121]
BM-MSCs	Colon cancer	MiR-142-3p	Downregulation of Numb	Promoting tumor progression
BM-MSCs	Breast cancer	MiR-23b	Decreased MARCKS expression	Inhibiting tumor progression ^[128]
MiR-122-transfected AMSCs	HCC	MiR-122	without research	Inhibiting tumor progression ^[129]
BM-MSCs	Prostate cancer	MiR-143	TFF3	Inhibiting tumor progression ^[70]
MSCs	Breast cancer	MiR-100	VEGF	Inhibiting tumor progression ^[166]

BM-MSCs: Bone marrow-derived mesenchymal stem cells; AMSCs: Adipose-derived mesenchymal stem cells; MSCs: Mesenchymal stem cells; HCC: Hepatocellular carcinoma; TFF3: Trefoil factor 3; VEGF: Vascular endothelial growth factor.

is high-throughput sequencing, or next generation sequencing. The process of small RNA sequencing is to extract exosomes from the cell supernatant or the plasma and then isolate miRNAs for next generation sequencing. Thereafter, target genes and related functions of miRNAs can be determined by combining with bioinformatics analysis. Perhaps a new and undiscovered miRNA can even be obtained for further functional analysis^[54,55,99,139]. Microarray is also a good high-throughput method to understand the miRNAs contained within exosomes^[133,140,141]. The disadvantage of microarray is that the sequence must be known, and probes are primarily designed for miRNA transcripts, hybridizing the probes with reverse-transcribed cDNA. After obtaining data using these two methods, qPCR, Northern blot, and miRNA-FISH techniques must be used for verification. Moreover, the nanostring miRNA assay could be used to analyze the content and species of miRNAs in exosomes, with accurate experimental results, but it is not widely used and the study cost is high^[142-144]. In addition, some researchers studied MSC-exosome biology not through high-throughput detection, but through databases, including miRBase (<http://www.mirbase.org/>), TargetScan (http://www.targetscan.org/vert_71/), and MiRDB (<http://www.mirdb.org/miRDB/policy.html>), to find a suitable miRNA, then apply qPCR, Western blot, or luciferase reporter gene assays for validations. These methods combined with KEGG analysis or GO analysis can also reveal the downstream pathway corresponding to miRNAs, which can further expand the research.

CONCLUSION AND PROSPECTION

The discovery that MSC-exosomes can perform a similar function to that of stem cells has led to a growing interest in the use of cell-free therapies for stem cells^[78,145]. Exosomes are less tumorigenic and immunogenic than stem cells, because they are very small and do not self-replicate. Exosomes have the unique advantages of being safer, more direct, and more effective than stem cells. This means that exosomes have a wide range of applications and can be mass-produced into drugs with excellent therapeutic effects for many diseases^[146]. As more and more studies have been conducted on MSC-exosomes, it has been found that in many cases, miRNAs play a crucial role in the therapeutic effect of MSC-exosomes on diseases. MiRNAs in MSC-exosomes have been reported to have significant effects on inflammatory diseases, trauma, degenerative diseases, and tumors. However, the miRNAs and their downstream pathway/target genes differ amongst different diseases. Some researchers sequenced miRNAs in MSC-exosomes, performed network analysis, and found that these were associated with Wnt signaling, TGF-β and PDGF stimulation, proliferation, and apoptosis, and function to oppose fibrosis and apoptosis, while promoting regeneration^[55]. This also provides scope and ideas for subsequent research

into miRNAs in MSC-exosomes. It is well known that MSC-exosomes can treat diseases, but if we want to further understand the mechanism behind disease treatment, we also need to know which components in exosomes play a crucial role. Therefore, researchers highlight specific miRNAs in their studies that regulate inflammation, promote repair, and target tumors^[47]. Of course, once we understand which miRNA is at work, researchers can overexpress specific miRNA in cell culture and exosome collection to achieve targeted therapy of refractory diseases.

The use of MSC and MSC-exosomes for tumor treatment has always been controversial. Due to the strong proliferation and regeneration capacity of stem cells and the presence of tumor stem cells, it has always been a controversial topic whether stem cells can promote tumors or not. However, loading anticancer drugs or suicide genes from exosomes or overexpression of anticancer miRNAs is a safer approach^[72]. The combination of MSC-exosomes with other anticancer methods presents great potential for cancer treatment^[48].

Currently, the common source of exosomes is BM-MSCs, but BM-MSCs faces problems of invasive injury to volunteers (patients) and rapid aging after *in vitro* amplification, making itself an imperfect source for mass production of exosomes^[105]. Although MSC-exosomes from the umbilical cord are abundant and have proven therapeutic effects on multiple liver fibrosis, brain injury and other diseases, they are difficult to obtain due to low availability of sources^[19,149]. In contrast, human menstrual blood-derived stem cells have the advantages of easy access, strong proliferation capacity, and no ethical controversy, and can be used as a good source of exosomes^[150-154].

In the future, the research trend of miRNAs lies in competing endogenous RNAs^[49], which are a new regulation model of gene expression. Currently, it is known that miRNAs can cause gene silencing by binding mRNA, while ceRNAs (lncRNAs and circRNAs) can regulate gene expression through competitive binding of miRNAs, thereby affecting cell function^[155-157]. Not only miRNAs, but lncRNAs and circRNAs are found in MSC-exosomes. If the relationship among miRNAs, mRNAs, lncRNAs, and circRNAs in exosomes derived from MSCs can be explored, the mechanism of MSC-exosomes in the treatment of diseases will be more thoroughly explored and exosomes can be rapidly applied to the human body.

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