Mesenchymal stem cell-derived exosomes therapy: research progress and mechanism of action

Sicheng Pan*

University of New Hampshire, New Hampshire, USA

*Corresponding author: sp1145@wildcats.unh.edu

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Abstract: Stem cell-derived exosomes are an important component of stem cell research and are getting more and more attention. Mesenchymal stem cell-derived exosomes are one of the main sources of stem cell-derived exosomes. However, there is still a long way to go before mesenchymal stem cell-derived exosomes therapy can be used clinically, and it needs a better understanding of the specific cell sources, mechanisms of disease treatment, target spot. It is essential to keep abreast of the latest developments in this rapidly evolving field and know which sources can be used and which ways can be treated which diseases. This article summarizes current and developing mesenchymal stem cell-derived exosomes therapies for treating diseases such as a tumor, neurodegenerative diseases, allergic diseases, wound healing, renal injury, and liver diseases; and provides some necessary guidance for future exosome applications.

1. Introduction

In 1967, extracellular vesicles (EVs) were first identified in plasma by Peter Wolf.[1] This finding allows further research on the function of EVs. During the years, scientists found that EVs play an important role in intercellular communication, which mediate multiple cellular processes, and can be used as the transfer carriers between cell membrane, cytoplasm, proteins, lipids, and RNA.[2] In EVs are a large family of membrane vesicles containing microvesicles, apoptotic blebs, and exosomes.[3]

These three types of EVs are distinguished based on size, exosomes are the smallest type of extracellular vesicle, in size. Compared with the other membrane vesicles, the exosomes specifically refer to the membrane vesicles with a size between 30 nm and 150 nm.[4] In addition, exosomes were first identified in rat reticulocytes in 1983.[5]

Some electron microscopy methods, such as scanning electron microscopy (SEM) and transmission electron microscopy (TEM), were used as standard tools for identifying exosomes (TEM). For example, exosomes would exhibit a cup-shaped morphology that is flattened spheres with 30~150 nm diameter if the exosomes are in the view of an electron microscope. Recently, cryo-electron microscope (cryo-EM) has emerged as a powerful alternative approach for assessing the morphology of EVs. Under cryo-EM, exosomes would show a round-shape, which keeps the membranes in a close to a natural state. The reason is that under the EM, exosomes would undergo extreme dehydration that would cause the collapse of the membranes. Nevertheless, exosomes would keep fully hydrated under the cryo-EM. [4]

Since exosomes were first found, many cell types have been proved to release EVs. Furthermore, exosomes have also been detected in multiple biological fluids in vivo, including plasma, nasal lavage fluid, bronchial lavage fluids, saliva, and breast milk. [6]

1.1. Composition of exosomes

Exosomes are thought to be the parental cell with a mini-version because the component of the exosomes, which specifically refers to the complex structures of specially classified three main components – proteins, lipids, and nucleic acids – and their respective contents. The amount of each component and the ratio between components highly rely on the types of exosomes and status of cell

source. Exosomes extracted from various cell sources and types contain approximately 4400 types of proteins, 194 types of lipids, 1639 types of mRNA, and 764 types of miRNA, according to identification test results. [7]

Exosomes have been found that have DNA and multiple types of RNAs, including miRNA, mRNA, and long non-protein-coding RNA, which is an important characteristic that is different from the other biological vesicles.[8] When separating exosomes, it is necessary to accurately quantify these nucleic acids because they may be served as biomarkers to reflect multiple diseases. [3] Exosomes have the ability to transfer mRNA to target cells and then translate it into proteins. Exosome miRNAs play an important role in tumorigenesis, angiogenesis, and exocytosis. Some good examples include miR-375, let-7, miR-151, miR-1, miR-15, miR-16.[8] Exosomes also contain miRNA related to tumor metastasis. For example, exosomes released by the breast cancer cell lines MCF-10A and MDA-MB-231 contain a large amount of miR-105, which can reduce the expression of the ZO-1 gene in endothelial cells resulting in inhibition of breast cancer metastasis to the lung and brain.[8, 9] In addition, miR-21 and miR-29a, which also belong to miRNA, are able to bind Toll-like receptors (TLR) and then activate immune cells[8, 10]

Proteins in exosomes are very complex. An important component is the membrane protein. The membrane protein in the exosomes firstly contains a series of specific or selective proteins related to the plasma membrane, which includes ligands and receptors. These ligands and receptors can also advance their interactions with target cells, potentially providing cellular specificity. [11] Several tetra-transmembrane proteins (such as CD81, CD82, CD37, and CD63) are among these proteins, as are a few proteins involved in cell adhesion and signaling, cytoskeletal structure, lipid rafts, and membrane transport. [12] The second type of membrane protein in exosomes is proteins related to intercellular communication. This type of protein is primarily used to mediate the fusion of exosomes and plasma membranes, which is a process that regulates the behavior of its target cells by delivering its cargo directly or indirectly to these receptor cells. The third type of membrane proteins in exosomes is lineage-specific and disease-specific exosome membrane proteins. Lineage-specific exosome membrane proteins are related with their parental cell, and vary according to the cell type and physiological state of their parent. Disease-specific membrane proteins in exosomes are potential biomarkers of status; exosomes exhibit altered components when produced by cells subjected to pathological conditions or other stresses.[11]

Exosomes have a typical lipid bilayer with a thickness of about 5 nm on average. The lipid bilayer contains several components, including cholesterol, phosphoglycerides with long and saturated fatty-acyl chains, sphingolipids, and ceramide, which can be used to distinguish exosomes from lysosomes.[3] Compared with the cell membrane of its source cells, the contents of phosphatidylcholine and diacylglycerol on the surface of exosomes were decreased. However, the substance of phosphatidylserine on the surface of the exosomes expanded, which is advantageous to the receptor cells internalize that assume a significant part in the biological function of the exosomes. [8, 13]

1.2. Separation methods

Currently, exosome separation techniques include ultracentrifugation-based isolation techniques, size-based isolation techniques, immunoaffinity capture-based techniques, exosome precipitation, and microfluidics-based isolation techniques.[8] Ultracentrifugation-based isolation techniques is the most common method used in the separation. Its mechanism is based on the theory that particle composition in the suspension would be sedimented depending on the various density, size, and shape when suspension liquid is subjected to centrifugal force-centrifugation.

1.3. Mesenchymal Stem Cells (MSCs)

Stem cells have the ability to self-renew and differentiate in multiple directions. Mesenchymal stem cells is one of the most common types of stem cells which has been proved by Friedenstein in the second half of the 1970s.[14] MSCs were described as a group of adherent fibroblast-like cells capable of differentiating into bone, which were called osteogenic progenitor cells by Friedenstein.

[15] While bone marrow (BM) stromal cells were first identified, MSCs can exist in multiple tissues, which include umbilical cord, bone marrow, fat tissue, and amniotic fluid. Furthermore, MSCs have the ability to differentiate into a variety of cell types within the human body, including bone cells and cartilage.[16] MSCs have powerful immunomodulatory properties which exist in various animal species. Although the mechanisms are variable and only partially elucidated, MSCs have been considered as a potential clinical approach for regulating the immune response in vivo. These immune response modulators play a specific role in maintaining peripheral tolerance, transplant tolerance, autoimmunity, tumor evasion, as well as fetal-maternal tolerance. [15]

2. MSCs derived exosomes

MSCs are a suitable cell type for the production of exosomes because of their scalable capacity. Compared with MSCs, there is growing evidence that MSC-derived exosomes may represent a viable alternative to cell therapy with compelling advantages. For example, MSC-derived exosomes have no risk of tumor formation than the parental MSCs.[16] In MSC-derived exosomes, more than 150 types of miRNAs and more than 850 types of proteins have been identified.[17] These miRNAs have been linked to physiological and pathological processes including biological development, epigenetic regulation, immune regulation (miR-155 and miR-146), tumorigenesis, and tumor progression (miR-23b, miR-451, miR-223, miR-24, miR-125b, miR-31, miR-214, and miR-122)[18]. Moreover, cytokines and growth factors in MSC-derived exosomes can contribute to immunoregulation. In MSC-derived exosomes, VEGF, extracellular matrix metalloproteinase inducer (EMMPRIN), and MMP-9 have been shown to play a significant role in stimulating angiogenesis, which may be necessary for tissue repair. [19].

2.1. Tumor

MSC-derived exosomes can act as mediators in tumor niches and play an assortment of jobs in tumorigenesis, angiogenesis, and metastasis. Several studies have been conducted to support the functions of MSC-derived exosomes, which can act as tumor growth inhibitors. However, the specific relationship between MSC-derived exosomes and tumor cells remains controversial. MSC-derived exosomes are a two-edged sword in terms of tumor growth because they affect tumor development in both a supportive and inhibiting manner. The extensive study for the miRNA content of exosomes revealed that MSC-derived EVs can be rich in a variety of tumor-promoting miRNAs, such as miR-21 and miR-34a. Although some MSC-derived exosomes have such tumor-promoting ability, not all of them would promote tumor growth. Exosomes produced from human umbilical cord Wharton's jelly MSCs were found to inhibit bladder tumor cell proliferation in vitro and in vivo, according to Wu et al. [20] And there are many other examples showed that some exosomes can stop and even reverse tumor growth. Angiogenesis, in addition to tumor growth, is a crucial physiological multistep process involved in carcinogenesis. Some exosomes contain a variety of angiogenic factors that can stimulate angiogenesis, while some others contain factors that can block angiogenesis. For instance, paracrine substances released by placental mesenchymal stem cells (pMSC) are known to induce angiogenesis and cell migration, and some of these factors are found in exosomes. [21] Furthermore, exosomes derived from menstrual stem cells, a type of MSC, can inhibit prostate tumor-induced angiogenesis by inhibiting reactive oxygen species. [22] In addition, the features of MSC-derived exosomes that promote tumor or antitumor function may vary depending on the cell culture method and tumor model used, as both the host tumor microenvironment and the systemic environment are linked to tumor suppression or promotion.[23].

2.2. Cardiovascular Diseases

The greatest cause of death in the world's population is cardiovascular disease (CVD). MSCs can secrete exosomes rich in microRNA (miRNA), which act on the heart and blood vessels, causing anti-apoptosis, cardiac regeneration, anti-cardiac remodeling, anti-inflammatory, neovascularization, and anti-vascular remodeling effects, according to new research. Therefore, MSC-derived exosomes

treatment is considered as a new approach for the therapeutic potential of MSCs. [24] MSC-derived exosomes have demonstrated promising effects in a variety of cardiovascular illnesses, according to recent findings. In myocardial infarction (MI), MSC-derived exosomes can prevent apoptosis under ischemic conditions by increasing the amount of miR-22. Moreover, MSC-derived exosomes also antagonize the cardiac fibrosis. [25, 26] MSC-derived exosomes have been shown to reduce oxidative stress, increase ATP and NADH, limit inflammatory activities, and activate the PI3K/Akt pathway in reperfusion injury. These have protective effects on CMC survival and left ventricular function maintenance following ischemia-reperfusion damage. [27] In preclinical models of pulmonary hypertension, MSC-derived exosomes may efficiently modulate macrophage activity to promote anti-inflammatory and proregression phenotypes, which are linked to both histological and functional advantages (PH).[28].

2.3. Neurodegenerative Diseases

The central nervous system's intricacy, as well as the multifaceted nature of CNS disorders, have long been regarded as the most difficult obstacles to diagnosing and treating these conditions. [29] Intercellular communication mediated by EVs may be an effective therapeutic strategy for a variety of CNS diseases. The characteristics of exosomes allow them to transmit biological information to various cells in the body to regulate their physiological functions. As a result, MSC-derived exosomes have the potential to be a useful and promising tool for neuronal regeneration in neurodegenerative disorders. [30, 31]Exosomes generated from MSCs have been studied in a range of neurodegenerative disease models, including Alzheimer's disease (AD), multiple sclerosis (MS), stroke, neuroinflammation, traumatic brain injury (TBI), spinal cord injury (SCI), and recurrent epilepsy (SE). [32].

The efficacy of MSC-derived exosomes can be explained in two ways. One is the ability to remove or repress harmful processes, implying that MSC-derived exosomes can halt disease progression and perhaps prevent disease conditions from worsening. MSC-derived exosomes can reduce amyloid beta (Aβ) aggregates in AD, reduce demyelination in MS, and inhibit apoptosis which can be observed in stroke, TBI, and SCI. Moreover, immunoregulation, which includes blocking the release of pro-inflammatory cytokines and activating anti-inflammatory factors, can be seen in all neurodegenerative disorders. There are four regenerative pathways associated with MSC-derived exosomes, one of which is the encouragement of regeneration. Neuroprotection, neurogenesis, neuromodulation, and angiogenesis are the four types of neurogenesis.[32] Aside from these four main mechanisms, MSC-derived exosomes can also prevent damage by reducing oxidative stress and restoring the blood-brain barrier's integrity.

2.4. Allergic Diseases and Wound Healing

MSC-derived exosomes are effective for allergic disease and wound healing. In terms of allergic disease, Cho and colleagues discovered in 2018 that exosomes derived from human adipose tissue-derived MSCs (ASC-exosomes) can alleviate atopic dermatitis in a mouse model, demonstrating that ASC-exosomes reduced the levels of lgE, eosinophil, infiltrating mast cells, and CD86+ and CD206+ cells in mice with atopic dermatitis. [33] A study on excessive scar formation in wound healing discovered that miRNAs (miR-21, -23a, -125b, and 145) in MSC-derived exosomes play a key role in inhibiting myofibroblast formation by inhibiting transforming growth. The therapeutic application of MSC-derived exosomes may offer a unique technique to minimize scar formation during wound healing, because excessive scar formation produced by myofibroblast aggregation has considerable clinical importance in the process of cutaneous wound healing. [34] In addition, MSC-derived exosomes can accelerate skeletal muscle regeneration and angiogenesis in vitro and in vivo, which is mediated at least in part by miRNAs like miR-494.[35].

2.5. Renal Injury

Some studies currently consider MSC-derived exosomes as a promising new therapy for chronic kidney injury. Ebrahim and colleagues evaluated the potential of MSC-derived exosomes in boosting

autophagy activity and the effect on diabetic nephropathy using five groups of rats (DN). The results showed notable improvement of renal function and the histological restoration of renal tissues after MSC-derived exosomes therapy. LC3 and Beclin-1 were significantly increased, and the expression of mTOR and fibrosis markers in renal tissue was significantly decreased, which means that MSC-derived exosomes act as a new therapy method to treat diabetic nephropathy by autophagy induction through the mTOR signaling pathway.[36] MSC-derived exosomes are also a promising tool for the healing of acute kidney injury induced by cisplatin and ischemia/reperfusion, in addition to treating chronic kidney injury. The benefits of human umbilical cord MSC-derived exosomes (HucMSC-Ex) were investigated in a sepsis model using cecal ligation and puncture (CLP) to assess survival rate, serum renal indicators, morphological alterations, and apoptosis. The findings revealed that hucMSC-Ex can dramatically lower serum creatinine (Cr) and blood urea nitrogen (BUN) levels, as well as block renal tubular cell death. The survival percentage of the hucMSC-Ex group was significantly higher than the survival rate of the CLP control group (28 percent) (45 percent). [37] Another study showed that a combination of adipose MSCs and ANMSC-derived exosomes can protect kidneys from acute ischemia-reperfusion injury.[38].

2.6. Liver Diseases

Exosomes generated from MSCs have been shown to be useful in a variety of animal models of liver illnesses, including hepatocellular carcinoma (HCC), hepatic fibrosis, and drug-induced acute liver injury (DIALI).[39] Tan et al. used the classic carbon tetrachloride (CCl4)-induced liver injury mouse paradigm to study the role of MSC-derived exosomes in acute liver injury. The findings revealed that, when compared to the control group, MSC-derived exosomes could reduce the injury, which was characterized by increased hepatocyte proliferation, implying that MSC-derived exosomes could induce hepatoprotective effects against toxic-induced injury by activating proliferation and regeneration responses.[40] Jiang et al., on the other hand, discovered that hucMSC-Ex can aid in liver healing. They found that hucMSC-Ex could prevent CCl4-induced liver damage and tumor growth in mice. They also compared hucMSC-Ex to Bifendate, a synthetic intermediate of schisandrin C that protects rats from drug-induced liver impairment. The results revealed that hucMSC-Ex had a stronger hepatoprotective impact than DDB.[41].

3. Conclusion and Perspective

MSC-derived exosomes take advantage of their innate ability to transport genetic material, protect it from extracellular degradation, and deliver it to recipient cells in a highly selective manner, allowing them to fully exploit the superiority of some diseases, such as tumors, cardiovascular diseases, neurodegenerative diseases, allergic diseases, and wound healing.[42] Advances in the rapid development of exosomes research make it be expected to be an alternative therapeutic approach. And recent research has shown good therapeutic effects in many animals' disease models.

Recently, according to www.clinicaltrials.gov, 112 clinical trials involved exosomes are listed. Based on the good results of preclinical data, the number of global clinical trials targeting exosomes therapy is increasing year by year. However, the global clinical trials about MSC-derived exosomes therapy still stay in the primary stage. That is because there are serval problems that need to be considered and solved although MSC-derived exosomes have great prospects and great research value. For example, because of the lack of established cell culture and the optimal protocols for production, the output of MSC-derived exosomes often confines clinical research. The lack of optimal protocols for isolation also causes an embarrassing condition that cannot ensure the uniformity of MSC-derived exosomes. Moreover, the storage of exosomes can be a constraint. And there is still no reliable potency measurement for assessing the efficacy of MSC-derived exosomes therapy, which needs researchers to improve.[43].

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