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Mesenchymal stem cell-derived exosomes as drug delivery vehicles: an update

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Abstract

Exosomes are extracellular vesicles with a diameter of 40-100 nm, which can be produced by several cells. As natural nanoscale vesicles, exosomes have the characteristics of low toxicity, low immunogenicity, strong homing ability, as well as the ability to carry several molecules, which make them potential drug delivery vehicles. Mesenchymal stem cells (MSCs) are an ideal source of exosomes because they can secrete and produce a large number of these vesicles. MSC-derived exosomes (MSCs-Exo) have regeneration and tissue repair functions similar to those of MSCs and can prevent the risk of graft versus host disease and infection caused by MSC transplantation. Therefore, MSCs-Exo are expected to become an effective substitute for the biological functions of MSCs. In this review, combined with the progress of preclinical and clinical studies, the potential therapeutic applications of MSCs-Exo in cardiovascular diseases, neurological disorders and malignancies was evaluated and discussed.

Introduction

Mesenchymal stem cells (MSCs) are multipotent stem cells with the ability of self-renewal and multidirectional differentiation. These cells are one of the most widely used stem cells and play an important role in regenerative medicine. MSCs arise from a wide range of sources and can be produced by a variety of tissues, such as bone marrow, adipose tissue, muscle, placenta, umbilical cord, umbilical cord blood and dental pulp[1,2]. MSCs have a variety of biological functions, including tissue repair, immunosuppression and neuroprotection[3,4]. Accumulating evidence from preclinical and clinical studies indicated that the biological functions of MSCs are closely related to their paracrine actions, including their exosome-secreting ability[5,6].

Exosomes are extracellular vesicles secreted from cells under physiological and pathological conditions and can be used as an auxiliary tool for the diagnosis and treatment of several diseases[7-9]. Exosomes contain RNA molecules and proteins, which suggests that they can act as vehicles for bioactive compounds. Lai et al[10] first identified exosomes derived from MSCs (MSCs-Exo) while they were isolating MSC medium. This study further showed that purified MSCs-Ex can play a similar role as that of MSCs in reducing the infarct size in a mouse model of myocardial ischemia/reperfusion (MI/R) injury [10], thus providing a novel perspective for the study of mechanisms underlying the biological functions of MSCs. The secretion of MSC-Exo is similar to the secretion of exosomes derived from other sources. In particular, endosomes derive from plasma membrane invagination and then germinate inward to form nano-sized vesicles, resulting in multivesicular bodies that contain intraluminal vesicles. However, multivesicular bodies can have two different fates: i) one is to migrate towards the cell surface and fuse with the plasma membrane, releasing the exocrine body outside the cell by exocytosis; ii) the other is to fuse with lysosomes to degrade their content. Exo-

somes originate from the fusion between multivesicular bodies and the plasma membrane. In addition, MSCs-Exo have other characteristics in common with exosomes: they are composed of transmembrane proteins (CD9, CD63, CD81), integrin, major histocompatibility complex I and II molecules, heat shock proteins, polyvesicular synthesis related proteins, nucleic acids, cholesterol, glycerol phosphate and sphingomyelin[11,12]. However, MSCs-Exo express specific markers, such as CD29, CD90, CD73 and CD44[13,14]. Biological functions of MSCs-Exo are similar to those of MSCs. Moreover, MSCs-Exo reduce the risks associated with cell transplantation, are easily obtained, stored and used, have low immunogenicity and their production process is highly controllable[15]. These characteristics make MSCs-Exo potential natural drug delivery vehicles. Indeed, MSCs-Exo are being increasingly used in the treatment of cardiovascular diseases, neurological disorders and malignancies.

Extraction and identification of exosomes

At present, the most commonly used method for exosome extraction is ultracentrifugation, which represents the "gold standard" for this procedure. However, this method can lead to exosome aggregation or contamination by other particles and cell fragments[16]. In addition, exosomes can be extracted by gradient density centrifugation, ultrafiltration centrifugation, molecular exclusion chromatography, polymer precipitation, immunoassay (magnetic beads, enzyme linked immunosorbent assay, flow cytometry and microfluidic techniques) and commercial kits, but there is still no ideal separation method to ensure content, purity and biological activity of exosomes at the same time[17,18]. Since the extraction methods are based on the structure and size of exosomes and on the capture of some membrane proteins, it is difficult to distinguish exosomes from other vesicles and macromolecular protein complexes[19]. Therefore, exosome identification assay is necessary, including observation of exosome morphology under electron microscope, nano-tracking analysis of exosome size and quantity, and western blot analysis of exosome surface protein (CD9, CD63 and CD81) expression[20].

Drug loading methods and types of exosomes

Direct drug loading

The drug is directly loaded into the purified exosome by co-incubation with the exosome, electroporation and chemical transfection. Small lipophilic molecules can be passively loaded into the exosome lipid bilayer membrane by co-incubating them with the exosomes, although the drug loading during this procedure is limited[21]. Electroporation means that repairable pores are instantly produced on the lipid bilayer membrane of the exosomes by applying a certain voltage by the electric field, thus introducing the drug into the exosomes. The parameters of electroporation are controllable; therefore, this procedure has wide application prospects[9]. However, some studies indicated that this method can induce the aggregation of exosomes, although the use of optimized parameters and pulse medium can effectively reduce the occurrence of this technical issue[22]. Chemical transfection usually employs commercial transfection reagents to load drugs into exosomes[23], but this method cannot completely separate drug-loaded exosomes from transfection agents. Thus, the potential toxicity of residual transfection reagents limits the application of this method.

Indirect drug loading

The drug is co-incubated or chemically transferred into the exosome-secreting cells. As the mechanism of drug delivery sorting into an exocrine action is more complex, it is difficult to control this process. Therefore, the practicability of this drug loading method is not strong. In addition, a new type of protein carrier which loads proteins into exosomes through optically reversible protein-protein interactions has been recently reported[24]. This method allows to transfer most of the proteins into the cells, and also significantly improves the loading efficiency of exosomes.

Types of exosomes

Exosomes can carry bioactive molecules and chemical drugs, such as RNA (miRNA [25], LncRNA[26,27], siRNA[28]), proteins[29], signaling molecules[30], paclitaxel[31], curcumin[32] and doxorubicin[33]. MSCs-Exo not only act as drug delivery carriers, but also display a variety of biological functions similar to those of MSCs. Therefore, exosomes can also be used as "drugs"[34,35].

The advantages of exosomes as drug delivery vehicles

At present, liposome is a relatively mature drug vehicle, even though it has some limitations, such as the toxicity of synthetic liposome membrane and

low biocompatibility of targeted ligands[36]. In the context of drug delivery carriers, exosomes display different advantages compared to synthetic liposomes, namely: 1) exosomes are extracellular vesicles actively secreted by cells, which can be regarded as natural liposomes and can overcome the limitations of synthetic liposomes mentioned above; 2) exosomes arise from the organism itself and have low immunogenicity[36]; 3) exosomes can enter the blood circulation and the brain through the blood-brain barrier, and the intranasal administration allows the drug to quickly reach brain lesions, which opens up the possibility for non-invasive treatments of intracerebral diseases[38]; 4) the particle size distribution of exosomes is 40-100 nm, which results in high permeability and retention effect at the site of solid tumors[10]; 5) exosomes have inherent homing and migration abilities and can be artificially manipulated to express specific molecules or improve their targeting ability[39-41].

Clinical applications of MSCs-Exo as drug delivery vehicles

MSCs-Exo retain the physiological functions of MSCs. Therefore, MSCs-Exo can be used as "drugs". In addition, MSCs-Exo can play a role as drug delivery vehicles to maximize drug effects.

Cardiovascular diseases

During the past decades, researchers have investigated the effects of MSCs-Exo in cardiovascular diseases. Emerging evidence indicated that MSCs-Exo can reduce the damage caused by MI/R through a variety of signaling pathways, such as the activation of Wnt/β-catenin signaling and the induction of autophagy by AMPK/mTOR and Akt/mTOR pathways[34,42]. In addition, MSCs-Exo can increase the levels of ATP and NADH in MI/R-injured heart, reduce the degree of oxidative stress and significantly reduce local and systemic inflammatory responses [43]. In rat models of myocardial infarction, cardiac stem cells pre-treated with MSCs-Exo display higher survival rates and are able to promote the long-term recovery of cardiac function[44].

Neurological disorders

Under the upsurge in MSCs-Exo use for the treatment of cardiovascular diseases, researchers also investigated the therapeutic role of MSCs-Exo in neurological disorders. In rat stroke models, MSCs-Exo can improve functional recovery, enhance neurite remodeling, neurogenesis and angiogenesis[45]. In rat models of acute ischemic stroke, MSCs-Exo can reduce the area of cerebral infarction and improve neurological function [37]. Therefore, MSCs-Exo may represent a novel, promising strategy for the treatment of stroke. Some studies also showed that MSCs-Exo can down-regulate vascular endothelial growth factor-A (VEGF-A) to ameliorate blue light stimulation in retinal pigment epithelial cells and improve laser-induced retinal injury[46].

Malignancies

MSCs-Exo can also play an important therapeutic role in malignancies. At present, the main therapeutic approaches for treatment of solid tumors include surgical resection, chemotherapy, radiotherapy and hormone therapy. However, some of the abovementioned treatments have disadvantages, such as drug resistance and toxic effects on healthy tissues. Exosomes may overcome the shortcomings of the aforementioned approaches, displaying a high potential as targeted delivery carriers for solid tumors. Lee et al[47] demonstrated that MSCs-Exo can significantly down-regulate VEGF expression in breast cancer cells, inhibiting angiogenesis *in vitro* and *in vivo*. Lin et al[48] showed that MSCs-Exo can promote the migration of breast cancer cells through Wnt signal transduction pathway. Therefore, the exact mechanisms of action of MSCs-Exo in distinct tumor microenvironments need to be further investigated.

Other diseases

MSCs-Exo can repair osteochondral injury and promote a better recovery of steroid-induced early avascular necrosis of the femoral head by delivering mutant hypoxia inducible factor-1-alpha (HIF-1α)[49]. In a mouse model of acute liver failure induced by lipopolysaccharide/D-galactosamine, exosomes derived from human umbilical cord MSCs have been shown to repair the damaged liver tissue[50]. In a mouse model of acute liver injury induced by carbon tetrachloride, the antioxidant and hepatoprotective effects of MSCs-Exo were superior than those of bifendate[51]. In a mouse model of autoimmune hepatitis, compared with MSCs-Exo, MSC-Exo containing miR-223 have been shown to significantly reduce serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well the expression of pro-inflammatory cytokines at both protein and mRNA levels in hepatocytes[52].

Conclusions

Exosomes are natural nanovesicles, which have several advantages as drug delivery vehicles. The functions of tissue repair and regeneration exerted by MSCs have been widely used for clinical purposes. MSCs-Exo exhibit both the aforementioned properties, and their biological characteristics can be altered by artificially modifying or interfering with the culture environment, which indicates that MSCs-Exo have wide clinical application prospects as delivery vehicles in the future. Although exosomes have several advantages and tend to be used in clinical research, we still lack a comprehensive understanding of the whole process of exosome production, transport and target-tissue uptake, which are all critical aspects that still need to be addressed carefully and cautiously.

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