REVIEW

Research progress of stem cell-derived exosomes in injury repair

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ABSTRACT

After organ and tissue injury, the proliferation and differentiation of stem cells themselves play only a small role in the repair of injury, and their repair role is mainly played through the paracrine function of stem cells. Exosomes are nano-scale vesicles that are secreted into the extracellular space in an exocytic manner, and its own function will be regulated after the target cells absorb the exosomes. Stem cell-derived exosomes communicate between cells by transmitting proteins, lipids and micro-RNAs (miRNAs). The targeting and biological properties of stem cell-derived exosomes are determined by the level of miRNAs that they carry. After the exosomes reach the target cells and undergo fusion, the gene expression of the target cells is changed by degradation and expression. In addition, the RNA and protein of stem cell-derived exosomes can also limit the development of injury through cell homing. This article will review the mechanism of stem cell-derived exosomes in wound healing, joint injury, fracture healing and cardiac injury.

Key Words: Stem cells, Wound healing, Exosomes, microRNA, Injury repair

1. INTRODUCTION

Exosomes are nanoscale vesicles of about 30-150 nm in size that are actively or passively released into the extracellular space in the form of exocytosis after their generation.[1,2] It is composed of a lipid bilayer membrane structure and can be released by different types of cells such as fibroblasts, tumor cells, and lymphocytes, which are released with the circulation of body fluids to distant targets and absorbed by recipient cells to regulate their physiological functions.[3] In recent years, more and more research results have demonstrated that, only a small part of stem cells play a role in tissue repair through stem cell differentiation and proliferation, and the paracrine action is its main mode of action.[4–6] This article will review the role and the mechanism of stem cell-derived exosomes in wound healing, joint injury, fracture healing and cardiac injury.

2. ROLE AND MECHANISM OF STEM CELL-DERIVED EXOSOMES IN WOUND HEALING

In the field of injury repair, stem cells play a great role, and paracrine or autocrine is the main mode of cytokine production by stem cells. These cytokines can affect the proliferation and migration of repair cells.[7,8] Rodriguez et al.[9] showed that the healing rate of the experimental group was significantly increased in comparison with the control group when adipose-derived stem cells were used to treat the full-thickness skin defect, and the study results provided a new horizon for stem cells to repair the skin defect wound. Some

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studies have demonstrated that adipose-derived stem cells can promote the migration and proliferation of fibroblasts, and the paracrine is the main mode of action;[10] in addition, studies have shown that stem cell-derived exosomes have similar functions to their derived blasts in the repair of damaged blood vessels and wounds;[11] Quesemberry et al.[12] also indicated that stem cell-derived exosomes play a huge part as the main biological mechanism of stem cells.

After skin and soft tissue injury caused by trauma, burn, etc., the damaged wound may be delayed healing or form hypertrophic scar, which will have a certain impact on the quality of patients' life. Fang et al.[13] showed that the scar tissues of mice with skin defects repaired by stem cell-derived exosomes from umbilical cord stem cells were significantly alleviated after the wound healing. Through high-throughput RNA sequencing and functional analysis of exosome microRNAs (miRNAs), it was found that the exosomes were rich in miR-23a, miR-145, miR-21 and miR-125b. The above miRNAs could inhibit the signaling pathways of the transforming growth factor β2/Smad protein 2 and reduce the formation of α-smooth muscle actin. The mechanism is to inhibit the generation of excessive myofibroblasts through reducing myofibroblast transdifferentiation, playing a role in reducing the probability of cicatrization. The experimental results of Kang et al.[14] showed that hypoxia-inducible factor 1 was targeted and regulated by llliR-3l content during the process of angiogenesis in wound tissue, and miR-31 of the exosomes from adipose-derived stem cells could significantly promote the formation of blood vessels around the damaged wound. In addition, Hu et al.[15] reported that adipose-derived stem cell exosomes can optimize the function of fibroblasts and shorten the wound healing time; stem cell-derived exosomes can also shorten the wound healing time by up-regulating the expression of N-cadherin and cyclin-1.

3. Role and mechanism of stem cell-derived exosomes in joint injury

In the microenvironment of joint cavity after injury, stem cell-derived exosomes can be compensatorily secreted to inhibit the production of inflammatory factors, thereby delaying the inflammatory progress and protecting the damaged joint. Toh et al.[16] showed that the transport of a variety of proteins or RNAs carried by exosomes was closely associated with the pathological process of osteoarthritis; Nakamura et al.[17] demonstrated that the cartilage development was closely associated with the changes in miR-140 content, and in osteoarthritis, the expression of miR-140 was significantly decreased, and the Dnpep gene regulated by miR-140 showed a high expression. Li et al.[18] experimentally demonstrated that stem cell-derived exosomes can reduce the expression of inflammatory factors and treat osteoarthritis by regulating the content of miR-146a/b. In addition, it has been found that miR-22 from stem cell-derived exosomes also plays a role in the development of tissue hypertrophy and osteoarthritis;[19] miR-98, miR-9 and miR-146 can regulate the expression of tumor necrosis factor-α, and then regulate the progress of osteoarthritis. The above miRNAs involved in the regulation can not only reduce the inflammatory response of the joint, but also repair the damaged cartilage.

Stem cell-derived exosomes communicate between cells mainly by transmitting mRNAs, miRNAs, proteins and lipids, which in turn alter the biological properties of target cells.[20] The contents of various miRNAs in the homologous exosomes are not identical, so their targeting and biological properties are different as well. The differences in miRNA content are closely related to various life processes such as cell apoptosis, migration and proliferation; in osteoarthritis, the silencing of miRNA-34a can significantly reduce the number of apoptotic chondrocytes.[21] Zhang et al.[22] showed that anti-CD3 activated T cells could take up exosomes in the blood from the patients with rheumatoid arthritis, from which the exosomes, in conjunction with the normal exosomes, inhibited cell apoptosis by activating nuclear factor κB and serine/threonine kinase signaling pathway through signal transmission. The study on the mechanism of action of stem cell-derived exosomes in arthritis plays an important role in the treatment of arthritis.

4. Role and mechanism of stem cell-derived exosomes in fracture healing

The results from Hao et al.[23] demonstrated that stem cell-derived exosomes promote the neoangiogenesis in the site of injury by carrying selective bioactive substances, while contributing to the differentiation of pleuripotent stem cells into osteogenesis, increasing matrix mineralization and inorganic salt deposition and shortening the time of fracture healing. It has been shown that during fracture healing, miRNAs can transmit genetic materials between osteocytes and stem cells to realize the post-transcriptional regulation of fracture repair and reconstruction, thereby shortening the fracture healing cycle.[24] Some studies have shown that transforming growth factor βl and platelet-derived growth factor play an important role in osteogenic differentiation;[25] in addition, other studies have also demonstrated that the production of bone morphogenetic protein 2 is regulated by bone marrow stem cell-derived exosomes, and bone morphogenetic protein 2 contributes to the differentiation of stem cells into osteogenesis by the cascade activation of transcription factor 0SX.[26]

The miRNAs of stem cell-derived exosomes have the effects on activating target cells, promoting angiogenesis and osteogenic differentiation.[27] Encapsulated by lipid membranes, they can effectively evade the surveillance of the immune system and enter into the target cells by way of endocytosis to function; in addition, some studies have shown that stem cells can increase the ability to promote bone differentiation by selecting to carry different types of miRNAs.[28] The results from Furuta et al.[29] showed that miR-4332 and miR-21 of bone marrow stem cell-derived exosomes with a high expression could significantly shorten the time of fracture healing, and it was found through the experiments on the components regulating the skeletal muscle cell-derived exosomes that, the regulatory components had a positive effect on the functional improvement in both skeletal muscle stem cells and the microenvironment.

5. Role and mechanism of stem cell-derived exosomes in cardiac injury

The myocardial injury model experiments from Bilal et al.[30] showed that the paracrine pathway is the main mode of action after stem cell transplantation, and stem cell-derived exosomes can promote the recovery of damaged cardiomyocytes by accelerating the angiogenesis in damaged myocardium through anti-apoptosis and anti-fibrosis. During the process of cardiac injury, the increased blood troponin is one of the important biomarkers for the diagnosis, but Pereg et al.[31] found through the study that after the occurrence of myocardial infarction, the miRNA level of plasma exosomes can also be used as a diagnostic marker, of which the contents of miRNA-499 and miRNA-208b are significantly increased; in addition, in patients with acute myocardial infarction, various p53-related miRNAs such as miR-34a, miR-194 and miR-192 will also be increased significantly.[31] The implantation of human stem cell-derived into mice with acute myocardial infarction can significantly reduce the area of myocardial infarction and increase the cardiac contractility in mice.[32] Some experimental results have demonstrated that stem cell-derived exosomes can relieve the autophagy by regulating the levels of autophagy-related proteins and rapamycin target proteins in mammals;[33] in addition, the results have also shown that the activation of apoptosis executioners caspase 7 and caspase 3 can be inhibited by cardiac progenitor exosomes, thereby reducing myocardial apoptosis;[34] cardiac fibroblast-derived exosomes can protect damaged cardiomyocytes under the oxidative stress conditions, and the mechanism is probably to regulate the myocardial mitochondrial ATP-sensitive ion channel through the protein kinase C signaling pathway, thereby increasing the survival rate of damaged myocardial cells.[35]

6. Conclusion and prospect

With the continuous progress of research, the mechanism of communication between cells in stem cell-derived exosomes has gradually unveiled, and stem cell-derived exosomes play a positive role in wound healing, joint injury, fracture repair and cardiac injury. Stem cell-derived exosomes, working as information carriers, mainly realize the communication between cells by transmitting miRNAs; stem cell-derived exosomes will fuse with target cells after arriving at target cells and regulate the gene expression of target cells by degradation and re-expression. In addition, the proteins and RNAs carried by stem cell-derived exosomes can also limit the continued development of injury through cell homing. In future studies, it is feasible to deeply illustrate the specific mechanism of action of stem cell-derived exosomes in cell communication, so that exosomes can be further applied to provide new targets for clinical treatment.

Conflicts of Interest Disclosure

The authors declare they have no conflicts of interest.

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