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Review Article

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Mechanism of Mesenchymal Stem Cell Exosomes on Bone Remodeling/Repair

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Abstract

Pathologically, destructive bone disease is a global public health problem, which is closely related to bone remodeling imbalance. There are also adverse reactions in bone repair methods after bone defects, so it is urgent to find new therapeutic targets for bone diseases. Mesenchymal stem cell-based therapy is considered an effective approach to bone remodeling/repair, but it also has many drawbacks. Exosomes are extracellular vesicles with a particle size of 30-150 nm, which can transport their contents, such as mRNA, miRNA, DNA, lipids and proteins, to target cells, thus playing a role in cell-cell communication, influencing the cell microenvironment and changing cell differentiation/function, and achieving "cell-free therapy". Numerous experiments *in vivo* and vitro have also confirmed that exosomes can improve bone remodeling in osteoarthritis, osteoporosis and femur head necrosis. Bone marrow mesenchymal stem cells, umbilical cord mesenchymal stem cells and human-induced pluripotent stem cell exosomes can improve bone repair after bone defects. Exosomes as nanomaterials have a promising application in bone diseases, but there are still many unknown areas waiting for researchers to explore.

Keywords: Exosomes; Mesenchymal stem cells; Bone remodeling; Bone repair

Introduction

Bone is a highly organized, dynamic and vascularized connective tissue. Pathological destructive bone diseases **[1],** such as Osteoarthritis (OA), Osteoporosis (OP), Rheumatoid Arthritis (RA) and other common bone diseases, are global public health problems. The patient's quality of life continued to decline and the burden of life increased. Bone remodeling is a continuous and lifelong process of repairing the microdamage of bone structure and replacing

aging osteitis in the bone remodeling chamber, which is a prerequisite for maintaining bone mechanical strength and bone mass **[2].** In the process of bone remodeling, the destruction process of bone resorption by osteoclasts is combined with the formation of osteosynthesis by osteoblasts. Mature bone tissue is replaced by bone (osteoclasts), which is called bone resorption, and new bone tissue formation is called ossification or new bone formation. Imbalance in bone remodeling can lead to deterioration of bone microstructure, bone fragility, bone porosity, and increased risk of fracture **[3].** Osteoporosis, rheumatoid arthritis, osteoarthritis and delayed fracture healing are all characterized by an imbalance in bone remodeling, where bone formation and bone loss are unbalanced between aging and inflammatory states **[4].** Bone defects caused by trauma, infection, tumor resection and congenital malformations are widespread. Bone repair after injury is a complex and well-organized bone remodeling process that starts with injury and effectively restores bone function. The main methods of bone repair include autologous bone grafts, allografts, bone substitute material graft and tissue engineering bone graft in clinically, but they all have their own disadvantages, such as immune rejection and dysfunction **[5,6].** These problems have brought a great burden to patients' psychology and economy, so it is urgent to seek more safe and effective treatment. Treatment based on Mesenchymal Stem Cells (MSCs) is considered an effective approach for bone repair and remodeling **[7,8].** However, there are some problems with using mesenchymal stem cells directly, such as abnormal cell phenotype, low homing efficiency of transplanted cells and changes in differentiation and proliferation [9,10]. Therefore, one of the hotspots in current research is how to find substitutes for mesenchymal stem cells to achieve "cell-free therapy" to avoid the risks brought by the using of mesenchymal stem cells directly **[11].**

Exosomes and their Production Process

Extracellular Vesicles (EV) are membrane-bound particles shed by most cells, including exosomes and microvesicles, and increasingly considered as an important medium of cell-cell communication. Exosomes are the most widely studied **[12].** Exosomes were first discovered in reticulocytes in 1983 **[13]** and named "Exosomes" in 1987. Exosomes are small vesicles of a phospholipid bilayer with a diameter of about 30-150 nm. Exosomes can be secreted by a variety of cells, such as mesenchymal stem cells, dendritic cells, epithelial cells, adipocytes and B cells, and are widely found in blood, urine, saliva and other body fluids **[14].** Exosomes contain mRNA, miRNA, DNA, lipids and proteins, which can dock with target cells and transport their contents to target cells, thus playing a role in cell-cell communication, while influencing the cell microenvironment and changing cell differentiation/function **[15].** There is growing evidence that exosomes are essential for communication between cells, between organs, and throughout the body, and have pleiotropic effects on the function of cells, tissues, and organs adjacent or far away **[16-19].** For instance, exosomes released by cells in one tissue or organ can reach another tissue or organ through the humoral circulation and may bind to their cells through receptor-ligand interactions **[20].** They can also spread through the body and bind to cell membranes, transporting their contents to distant recipient cells **[21,22].** Therefore, the current proposed mechanism of exosomes interacting with target cells is mainly through antigen-antibody interaction or ligand-receptor interaction binding to the cell surface, and may trigger signal transduction through surface receptors **[23,24].** The most common modes of exosome uptake by target cells include endocytosis, micropinocytosis or phagocytosis, which mediated by clathrins, microvesicles, or lipid

rafts. Exosomes are derived from the sorting mechanism of endosomes. Early endosomes are formed by budding inward through the cell membranes. Later, the endosomal membrane undergoes a second inward (lumen) budding, producing smaller vesicles in the late endosomal lumen, forming Multivesicular Bodies (MVB). Then, some MVB fuses with lysosomes and is degraded, while the other part fuses with the plasma membrane and releases vesicles into the extracellular matrix, which are exosomes **[25].** Mitochondria-derived vesicles may also enter MVBs and contribute to eventual exosome formation. The formation of intracavitary vesicles is considered caused by microdomain enrichment of the Transmembrane 4 Superfamily (TM4SF) (e.g., CD9, CD63, CD81) on the late endosomal membrane, and the Endosomal Sorting Complex Required for Transport (ESCRT) protein family also plays a key role **[23,24,26].** ESCRT I and II are recruited to this site and may initiate endoluminal germination. Other ESCRT proteins, such as ESCRT III, are recruited through the helper proteins ALIX and TSG101 to complete the budding process **[12].**

Studies have shown that the function of MSCs is mainly through paracrine rather than direct differentiation into target tissues **[27,28].** As extracellular vesicles, exosomes have biological effects similar to those of their derived cells **[29,30].** A growing number of studies have shown that MSCs-derived exosomes can regulate cell-cell communication by delivering mRNA, miRNAs and proteins between cells, effectively promoting bone defect repair **[31,32].** Exosome implantation mediated balanced bidirectional signal transduction between osteoclasts and osteoblasts overcome bone loss due to pathologically destructive bone disease **[2].** Compared with direct cell transplantation, exosome-based therapy shows many advantages, such as high stability, low immunogenicity and intrinsic homing effect of exosomes **[33,34].** Bioinformatics analysis also showed that exosomes derived from bone marrow mesenchymal stem cells showed excellent regenerative ability, exosomes derived from adipose tissue mesenchymal stem cells play an important role in immune regulation, and exosomes derived from umbilical cord mesenchymal stem cells are more prominent in tissue injury repair, they share a common function in extracellular matrix receptors **[35].** Therefore, exosomes show great potential in bone remodeling and repair, enabling "cell-free therapy".

Exosomes and Bone Remodeling in Pathologically Destructive Bone Diseases

Exosomes and osteoarthritis

Osteoarthritis (OA) is a common degenerative joint disease characterized by progressive articular cartilage degeneration, subchondral bone thickening, osteophyte formation, synovial inflammation, and ligament calcification **[36],** and is associated with physical disability, mortality, morbidity, and increasing health care expenditures in the middle-aged and elderly **[37,38].** To investigate the effects of exosomes derived from Bone Marrow Mesenchymal Stem Cells (BMSCs) on cartilage injury and pain relief in osteoarthritis, Lei He **[39]** research team established OA models *in vitro* and *in vivo*, and detected chondrocyte proliferation and migration by using CCK-8 and Transwell methods, and the rat model of osteoarthritis was established by sodium iodoacetate injection. The results showed that exosomes can be endocytosed by chondrocytes *in vitro*. Treatment with exosomes significantly reduced the inhibitory effect of IL-1β on chondrocyte proliferation and migration, and significantly reduced the downregulation of COL2A1 and ACAN induced by IL-1β, as well as the upregulation of MMP13 and ADAMTS5. *In vivo*, exosome

treatment significantly upregulated COL2A1 protein and downregulated MMP13 protein in cartilage tissue of OA rats, and PWL value of OA rats treated with exosomes was significantly higher than that of untreated rats. In conclusion, BMSCs-derived exosomes can effectively promote cartilage remodeling and extracellular matrix synthesis in OA rats, and alleviate knee pain in OA rats.

Jin et al. **[40]** extracted exosomes from Human Bone Mesenchymal Stem Cells (hBMSCs), identified differentially expressed genes related to OA through microarray analysis, then elevated or silenced miR-26a-5p and PTGS2, and co-cultured hBMSCs exosomes with fibroblasts. To explore the effect of hBMSCs-derived exosomes carrying miR-26a-5p on synovial fibroblast injury. The results showed that miR-26a-5p expression was low and PTGS2 expression was high in OA patients and IL-1β treated synovial fibroblasts. miR-26a-5p was identified as specifically targeting PTGS2 and its overexpression could reduce synovial fibroblast injury by inhibiting PTGS2. In addition, hBMSCs-derived exosomes overexpressing miR-26a-5p delayed synovial fibroblast injury *in vitro* and alleviated OA injury *in vivo*. In conclusion, hBMSCs-derived exosomes overexpressing miR-26a-5p can inhibit the damage of synovial fibroblasts in OA through PTGS2, which is of great significance for the treatment of OA in rats.

Exosomes and osteoporosis

Osteoporosis remains a major medical and socio-economic problem, characterized by systemic damage to bone mass and microstructure that ultimately increases the propensity for brittle fractures **[41].** MSCs can differentiate into osteoblasts, chondrocytes, bone marrow stromal cells, adipocytes, tendon cells and muscle cells **[42].** BMSCs-derived exosomes containing miRNAs mediate the development of bone formation **[43]**. Exosomes were extracted from BMSCs of osteoporosis patients, and the level of miR-424-5p in exosomes was detected by qRT-PCR, the expression of WIF1/Wnt/β-catenin was detected by Western blot, and the binding correlation between miR-424-5p and WIF1 was detected by double luciferase reporter gene. The function enhancement assay confirmed the role of miR-424-5p and WIF1/Wnt/β-catenin carried by exosomes in osteoblast differentiation. ALP staining and qRT-PCR were used to detect the related indexes of osteoblast differentiation. The results showed that exosomes inhibited osteoblast differentiation by upregulating miR-424-5p, resulting in the inhibition of WIF1/Wnt /β-catenin. These results may provide evidence for the exosome miR-424-5p as a new biomarker for the treatment of osteoporosis **[44].** miRNAs in exosomes also regulate bone development, inhibit osteoclast activity, and improve fracture repair, which may be a promising therapeutic target for osteoporosis **[45,46].**

In vitro, Human Osteoblasts (hFOB1.19) were co-cultured with the extracted primary BMSCs. It was found that BMSCs-derived exosomes promoted the expression of SATB2 in osteoblasts, while SATB2 silencing decreased the ALP activity of osteoblasts and mineralized nodules. BMSCs exosome MALAT1 can promote the activity of osteoblasts. Ovariectomized mice experiments showed that miR-34c reversed the action of MALAT1 and SATB2 reversed the action of miR-34c in. In conclusion, this study indicated that BMSCs-derived exosome MALAT1 enhanced osteoblast activity in osteoporotic mice by mediating the miR-34c/SATB2 axis **[47].**

Exosomes and femoral head necrosis

Osteonecrosis of the Femoral Head (ONFH) is caused by long-term use of glucocorticoids and usually affects young patients between 30 and 50 years old. If not treated promptly and inappropriately, approximately 75% of affected hips will develop femoral head collapse and many patients will require total hip replacement. However, the

exosomes of BMSCs obtained by hypoxia treatment can exert the potential of osteogenic proliferation and differentiation and improve the therapeutic effect of ONFH transplantation **[48].** Yuan et al. **[49]** found *in vitro* that rat BMSCs-derived exosomes pretreated with hypoxia could significantly promote the proliferation and migration of Human Umbilical Vein Endothelial Cells (HUVECs), the expression of Vascular Endothelial Growth Factor (VEGF) and the formation of tube. *In vivo* results showed that hypoxic pretreated BMSCs exosomes could play a role in angiogenesis and protection of osteonecrosis, prevent femoral head loss and increase blood vessel volume in the rat ONFH model, and play a better role in the treatment of steroid-induced ONFH by promoting angiogenesis and preventing bone loss. Exosomes overexpressing miR-122-5p downregulated SPRY2 through the RTK/Ras/ Mitogen-Activated Protein Kinase (MAPK) pathway, thereby alleviating femoral head necrosis **[50].**

Exosome and Bone Repair after Bone Defect

BMSCs exosomes can promote bone repair. Inflammation after tendon-bone junction injury leads to excessive scar tissue formation and poor biomechanical properties. To retain exosomes to play their biological functions in the defective site, a hydrogel containing BMSCs exosomes was implanted into the damaged site by establishing a mouse tendon-bone reconstruction model. Then, macrophage polarization and tendon-bone healing were analyzed by histology, immunofluorescence and qRT-PCR. It was found that the local application of BMSCs exosomes improved the biomechanical properties of bone by increasing the polarization of M2 macrophages in the tendon to bone healing and promoting the formation of fibrocartilage **[11].** BMSCs exosomes were prepared by stimulation of magnetic nanoparticles and/or Static Magnetic Field (SMF). Osteogenic differentiation, cell proliferation, cell migration and tube formation were measured *in vitro*. A critical size skull defect rat model was established *in vivo*, and the miRNA expression profile in exosomes was compared. It has been found that magnetic field-stimulated exosomes can promote osteogenesis and angiogenesis *in vitro* and *in vivo*. Exosomal miR-1260a targeting HDAC7 and COL4A2 played a key role in this process, providing a new approach for tissue-engineered bone repair and bone regeneration **[51].**

Umbilical Cord Mesenchymal Stem Cell (UMSCs) exosomes can play the same role. Zhang et al. **[52]** encapsulated UMSCs-derived exosomes in Hyaluronic Acid Hydrogel (HA-GEL) and combined them with customized nano-hydroxyapatite/poly-ε-caprolactone (nHP) scaffold folds to repair critical size skull defect models in rats. The results showed that UMSCs-EXOs/Gel/nHP composites significantly promoted skull regeneration in rats, and MSC-EXOs may play a key role in this process. *In vitro* experiments also showed that UMSCs-EXOs promoted the proliferation, migration, angiogenesis and differentiation of Endothelial Progenitor Cells (EPCs). The mechanism revealed that exosome miR-21 was a potential intercellular messenger that promoted angiogenesis through upregulation of NOTCH1/DLL4 pathway. In conclusion, these results suggested that UMSCs exosomes repaired large bone defects by promoting angiogenesis, possibly mediated by miR-21/NOTCH1/DLL4 signaling axis. Exosomes (hiPSC-MSC-Exos) secreted from Mesenchymal Stem Cells (MSCs) derived from Human-Induced Pluripotent Stem Cells (hiPSCs) combine the advantages of MSCs and iPSCs without immunogenicity. To investigate the effect of hiPSC-MSC-Exos on the proliferation and osteogenic differentiation of Bone Marrow Mesenchymal Stem Cells (rBMSCS-OVX) in Ovariectomized Rats (OVX) *in vitro*, we found that hiPSC- MSC-Exos could promote the alkaline

phosphatase (ALP) activity and proliferation of rBMSCs-OVX cells *in vitro*, upregulated mRNA and protein expression of osteogenic genes. In the ovariectomized rat experiments, hiPSC-MSC-Exos were implanted into critical size bone defects, and angiogenesis and bone regeneration were observed by Microcomputed Tomography (micro-CT), sequential fluorescence labeling analysis, micropore perfusion, histological and immunohistochemical analysis. The results confirmed that hiPSC- MSC-Exos could significantly stimulate angiogenesis and bone regeneration in ovariectomized rat skull defects, and the effect was enhanced with the increase of exosome concentration. In conclusion, the application of the hiPSC-MSC-Exos +β-TCP scaffold promoted bone repair and regeneration of critical size skull defects by enhancing angiogenesis and bone formation in ovariectomized rats **[52].** Critical size bone defects of the skull were repaired with Mesenchymal Stem Cell Exosomes (hiPSC-MSC-Exos) from human-induced pluripotent stem cells combined with tricalcium phosphate (β-TCP). Compared with pure β-TCP, exosomes /β-TCP composite scaffolds could promote bone formation. The mechanism is through the activation of PI3K/Akt signaling pathway to enhance β-TCP osteogenic induction ability. *In vitro* experiments also showed that exosomes can significantly enhance the proliferation, migration and osteogenic differentiation of hBMSCs **[3].**

Application Prospect and Prospect

Exosomes are used in bone remodeling and repair, which is a very promising "cell-free therapy". Exosomes, nanoscale vesicles secreted by cells, are important carriers of gene therapy and drug delivery, and key regulators of cellular interactions **[54].** Nanomedicine is a new type of medicine that uses nanoscale objects or nanotechnology as a tool for disease diagnosis or treatment. Nanoparticles have unique advantages in targeting drug delivery systems, tumor region accumulation, crossing biological barriers, improving drug solubility, and promoting the stability of drug resistance to enzyme degradation **[55].** Exosomes point out a new development direction for the clinical application of nanomaterials in bone diseases. However, most studies on exosomes are in the preclinical stage, and the traditional methods of exosomes isolation and characterization are not applicable to clinical applications. In addition, the current extraction methods of exosomes are nothing more than ultra-high-speed centrifugation (time-consuming, small extracted exosomes with low purity) and kits (high economic cost). Therefore, one of the biggest challenges in the future is to improve the production technology of exosomes, and to design and produce high-purity exosomes with large volume for clinical application. This requires the development of more efficient and accurate exoteric experience and quantification methods. An alternative strategy to produce exosomes with high yield and improved regenerative capacity has been reported, which is to accumulate Exosome Mimics (EMs) from human Mesenchymal Stem Cells (hMSCs) by extrusion. Compared with hMSCs-derived exosomes, the proportion of exosomal specific CD63 marker-positive vesicles collected by EMs was significantly increased. Combined application of the extruded hMSCs-EMs and injectable chitosan hydrogel to the unhealed skull defect in mice showed strong bone regeneration ability **[56].** More efficient methods will need to be developed in the future.

There are still many unexplored areas regarding exosomes, such as the specific mechanisms controlling the release of exosomes by mesenchymal stem cells and the uptake of exosomes by recipient cells. Many studies have not really isolated exosomes and microvesicles in extracellular vesicles (EVs), so it is not clear whether exosomes are

responsible. Moreover, large numbers of exosomes have been used in cell experiments or injected into experimental animals, while producing cells can continuously release small amounts of exosomes under complete physiological conditions. How to translate the results into clinical applications remains a challenge.

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