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Research Progress on the Role of Exosomes and the PI3K/Akt Pathway in Osteoporosis

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Abstract: Osteoporosis (OP) is a metabolic bone disease characterized by decreased bone mineral density and microstructural deterioration, leading to an elevated risk of fragility fractures. Bone remodeling relies on the dynamic balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Exosomes, as key mediators of intercellular communication, regulate the differentiation and function of bone marrow mesenchymal stem cells (BMSCs), osteoblasts, and osteoclasts by delivering bioactive molecules (e.g., miRNAs), thereby playing a pivotal role in OP pathogenesis. Recent studies have revealed that the PI3K/Akt signaling pathway not only serves as a central regulator of BMSC osteogenic differentiation but also synergizes with exosomes to promote bone formation by activating downstream targets (e.g., RUNX2, BMP2). This review systematically summarizes the synergistic mechanisms of exosomes and the PI3K/Akt pathway in osteogenesis, focusing on how specific miRNAs (e.g., miR-19a-3p, miR-935) modulate key molecules (e.g., PTEN, STAT1) to restore bone metabolic homeostasis. These findings provide novel insights into the molecular mechanisms of OP and lay a theoretical foundation for developing targeted therapeutic strategies.

Keywords: Exosomes; PI3K/Akt; Osteoporosis; Bone marrow mesenchymal stem cells; Osteogenic differentiation

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1. Introduction

Osteoporosis (OP) is a disease that affects bone across the body and shows low mass in bone and damage to the structure of bone at a small scale, and this leads to bone that breaks more easily and shows a higher risk for breaks that occur [1]. The population across the world shows increasing age, and the rate of osteoporosis continues to increase. The most serious problem that results from this condition is fractures that occur with low force, and these fractures create a substantial burden in medical costs and economic impact on individuals who have the disease and on society in general [2,3]. This indicates that examination of the processes that produce osteoporosis in the body and investigation of approaches that provide prevention and treatment that work well are important to conduct.

The process that changes bone structure involves the balance between forming bone and removing bone. Bone formation occurs through cells that develop from bone marrow stem cells. These stem cells represent the main source for cells that form bone and play an important role in OP. When bone marrow stem cells show reduced potential for developing into cells that form bone or show an increased tendency for developing into fat cells, this produces insufficient bone formation. This represents a main factor in OP development [4]. In recent years, small particles that cells release have received significant attention in OP research. These particles that cells release can contain proteins, lipids, and miRNAs. The particles regulate the function and development of bone marrow stem cells, cells that form bone, and cells that remove bone. This affects the balance of the process that changes bone [5]. The PI3K/Akt pathway has received confirmation as a main pathway that regulates the development of cells forming bone and their function. However, the interaction between particles from bone marrow stem cells and the PI3K/Akt pathway remains unclear. The interaction between these particles and this pathway, and the combined regulation of OP development, requires systematic examination. This article examines the combined mechanisms of particles from bone marrow stem cells and the PI3K/Akt pathway in OP. This examination provides a basis for understanding OP development and developing treatment approaches.

2. Overview of BMSCs and exosomes

2.1. Bone marrow mesenchymal stem cells (BMSCs)

BMSCs are cells with multiple functions that occur in the bone marrow and show the capacity for division and development into different forms. These cells develop into cells forming bone, cells storing fat, cells in cartilage, and other types. The development of BMSCs follows regulation by factors that include aspects relating to biological processes, physical conditions, and chemical signals. The factor TAZ, which functions to activate processes in the cell, plays a major role in maintaining the balance between the development into bone-forming cells and the development into fat-storing cells in BMSCs. This factor promotes development into bone-forming cells and limits development into fat-storing cells. In the condition involving reduced bone density, BMSCs show decreased potential for development into bone-forming cells and increased development into fat-storing cells. This pattern produces insufficient formation of bone and an increase in fat in bone marrow, and these changes disrupt the balance that maintains bone structure. **Figure 1** shows the characteristics of mesenchymal stem cells.

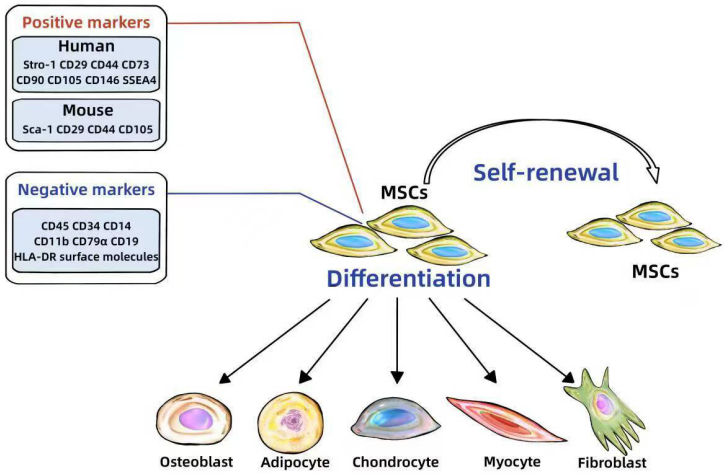

Figure 1. Schematic diagram of the characteristics of mesenchymal stem cells (MSCs). There are both positive markers and negative markers for identifying MSCs. MSCs possess the characteristics of self-renewing and differentiating into multiple cell types, including osteoblast, adipocyte, chondrocyte, myocyte, and fibroblast [10]

2.2. Exosomes

Cells produce small structures that move outside the cell, and these structures show a size of approximately 30 to 150 units in measure. The structures appear in different fluids in the body. These small structures contain various molecules that provide biological activity, and the molecules include specific forms of proteins, lipids, and genetic material. The structures function as important means for communication between cells, and this communication involves the process of control in different conditions relating to normal function and disease [6]. In the area of examining bone change and development, research shows that the small structures can change the activity of cells that form bone and cells that break down bone. The structures affect this activity through molecules that provide signals, and specific genetic material represents one form of these molecules. The process influences the relationship between bone loss and bone formation. The small structures show a significant role in the development and occurrence of the condition involving bone weakness [5,7].

2.3. Exosomes derived from BMSCs (BMSCs-Exos)

Small structures from bone marrow stem cells show characteristics that these cells demonstrate and indicate important roles in tissue repair and regulation of immune processes. These structures also show potential in promoting tissue development. Studies indicate that small structures from stem cells of different tissue sources, such as bone marrow and fat tissue, show effects that promote bone development, and research examining structures from bone marrow stem cells provides the most extensive data. For example, small structures that originate from human stem cells of a particular type show significant effects in promoting blood vessel formation and bone formation processes [8]. Liu and other researchers found that structures from stem cells showed effects that limited bone loss and promoted blood vessel formation in a rat model examining hormone effects on bone tissue death in the upper leg bone [9]. These structures also affected a particular signaling pathway involving specific factors to promote bone cell development. Additionally, these small structures from bone marrow stem cells provide a means for carrying specific small molecules. For example, structures enriched with a particular small molecule designated miR-196a promoted bone healing in rat skull defects, and this finding suggests possible applications in treating diseases that affect bone processes [10].

3. The role of BMSCs-Exos in bone metabolism

3.1. The effect of BMSCs-Exos on osteoblasts

The main cells that produce new bone are called osteoblasts. Studies show that small particles released by these cells, or by cells from bone marrow, can affect how osteoblasts develop and form mineral deposits. This occurs through signals between cells. Cui *et al.* found that small molecules in particles from osteoblasts that already contain minerals can increase the development of bone-forming cells [10]. These molecules increase levels of RUNX2 and alkaline phosphatase. Other studies report that miR-30d-5p, miR-133b-3p, and miR-140-3p show higher levels in particles from osteoblasts. These molecules may increase osteoblast development and function through multiple pathways. The pathways include Wnt, insulin, TGF-β, and calcium signaling [10]. Evidence indicates that these particles use a complex network of signaling molecules to control osteoblast development in a

precise manner.

3.2. The effect of BMSCs-Exos on osteoclasts

Large cells with multiple internal structures that function in removing bone material develop from cells in the blood-forming system. The process that produces these cells and the process that makes these cells active involve factors that cells supporting bone formation provide. Small structures that cells release show effects in both directions on the process of forming these large bone-removing cells. Studies indicate that structures from cells developing into bone-removing cells appear to support the formation process, but structures from cells that complete development contain a factor that binds to a signal molecule. This factor competes with the signal molecule for binding sites on cells forming bone-removing structures, and this competition limits the formation process. Also, a molecule that modifies other molecules gets released in these small structures. This molecule changes a factor important for bone-removing cell function by adding specific modifications. The modifications increase on a factor that controls the process in these cells, and this increase reduces the activity that removes bone material. The findings provide an approach for affecting the process that removes bone.

4. PI3K/Akt signaling pathway

4.1. Overview of the PI3K/Akt pathway

The pathway involving enzymes that change lipid molecules in cell membranes plays a major role in regulating different activities in cells, including processes relating to cell growth, development, cell death, use of energy, and survival. The enzyme that changes lipid molecules is a group of related enzymes that can be divided into three forms based on structure and how activation occurs. The first form of this enzyme, particularly one type in this form, is associated with receptors on cell surfaces that respond to signals and is activated by factors that promote growth, causing conversion of one lipid molecule in the membrane to a different molecule that provides signals. The enzyme that follows in the pathway is a key enzyme that changes proteins at specific sites and contains a region at one end that binds to the signal molecule, bringing it to the membrane. At the membrane, one site in this enzyme is changed by a different enzyme, and a second site is typically changed by a complex of proteins, leading to full activation. The activated enzyme regulates what happens to cells and how cells function by changing a series of target proteins that follow, such as proteins that control gene activity, proteins that regulate cell growth, and proteins that affect energy use.

4.2. The PI3K/Akt pathway and bone metabolism

The pathway involving PI3K and Akt shows important effects in processes relating to bone. Studies indicate that Akt and factors that follow in signaling function as main elements in the development of bone and in changes occurring in bone over time. Work using the removal of specific genes reveals that animals lacking both Akt1 and Akt2 show formation of bone that occurs more slowly than in other cases, and animals lacking Akt1 show bones that differ in length and centers for later bone formation that develop with delay [11]. In cells that produce bone, processes that increase activity in the pathway involving PI3K and Akt show effects on genes that indicate bone formation, such as BMP2 and ALP, and these effects support changes in cells that produce bone and an increase in the number of these cells [12]. The pathway also works together with BMP2 in processes that guide cells of a particular type to develop into cells that produce bone [13]. Akt also adds phosphate groups to a factor that controls

other genes, the FoxO factor, and this leads to the factor remaining in the part of the cell outside the central structure, and these processes support the continued function of cells that produce bone and the formation of bone.

In osteoclasts, the PI3K/Akt signaling pathway is also indispensable for their generation. Lee *et al.* confirmed that inhibiting PI3K activity using LY294002 significantly reduces osteoclastogenesis induced by RANKL and M-CSF [14]. Although Akt is not absolutely essential for osteoclast survival, it is crucial for the proliferation and differentiation of osteoclasts. The Akt signaling pathway may regulate osteoclast differentiation by affecting the DNA-binding activity of NF-κB.

PTEN, the element that removes phosphate groups from position ten on the chromosome, provides important control that limits activity in the pathway involving PI3K and Akt. This element functions by removing phosphate groups from PIP3, and the process terminates signals that increase Akt activity. In cells that form bone, the loss of PTEN results in phosphorylation of Akt that remains at high levels for extended periods. This condition produces increased differentiation in these cells and also produces reduced rates of cell death [15]. The findings suggest that control of activity in the pathway involving PI3K and Akt requires specific regulation. This regulation appears important for maintaining the balance in bone tissue that supports normal function.

5. The impact of BMSCs-Exos synergizing with the PI3K/Akt pathway on osteoporosis

Multiple studies show the main role of BMSCs-Exos in bone remodeling. The mechanisms that these factors use relate to the PI3K/Akt signaling pathway. BMSCs-Exos contain high levels of miRNAs. These miRNAs show different patterns during the process of forming bone. For example, miR-218, let-7a, and miR-135b increase in level. However, miR-155 and miR-320c decrease in level. These miRNAs provide possible targets for the treatment of osteoporosis, also called OP [16].

Recent work shows more small structures in cells that relate to forming bone. For example, miR-144 increases the process where cells with multiple possible forms produce more cells and develop into bone forms by reducing SFRP1 levels through the pathway using Wnt signals. miR-27a-3p supports the formation of bone by reducing the factor ATF3, which increases the production of other factors. miR-935 produces effects relating to bone by reducing STAT1 levels in cells [17]. In contrast, miR-1297 reduces the process where cells develop into bone forms and increases the progression of the condition involving reduced bone strength by limiting the Wnt pathway and reducing levels of Runx2 and Osterix.

Data show that bone formation effects from small particles released by bone cells relate in part to activation of one particular process involving PI3K and Akt. Kawamura and other researchers indicate that this PI3K and Akt process provides important control for both bone breakdown and bone formation. The studies that follow provide direct confirmation of these patterns. In these studies, researchers use substances that block the PI3K and Akt process, such as LY294002, before treatment with the small particles. Results show that the small particles from bone cells produce less promotion of bone cell development and mineral formation when this blocking occurs. The difference appears significant. These findings suggest that the small particles released by bone cells produce their effects through a process involving PI3K and Akt signaling. This process appears to provide the main means for the observed changes in bone cell function and bone formation that the studies examine [18].

At the level of molecular mechanisms, particles that cells release carry specific forms of small molecules that can affect and change important factors in the pathway involving PI3K and Akt. Zhou *et al.* found that PTEN

is a direct target that miR-19a-3p affects. The particles carrying miR-19a-3p can reduce PTEN in cells, and this reduces the limiting effect that PTEN provides on the pathway involving PI3K and Akt. This process makes Akt more active and increases the development of cells that form bone [19]. The work that Burger *et al.* present also indicates the limiting role that PTEN provides in the pathway involving PI3K and Akt and in the processes relating to bone [20].

In conclusion, BMSCs-Exos deliver specific functional miRNAs that target and regulate key nodes in the PI3K/Akt signaling pathway (such as PTEN), activating downstream osteogenic gene expression, and thereby synergistically promoting the osteogenic differentiation and bone formation of BMSCs. This provides new theoretical insights and potential strategies for targeted therapy of osteoporosis.

6. Conclusion and outlook

This review systematically summarizes the synergistic regulatory effects of BMSCs-derived exosomes and the PI3K/Akt signaling pathway in osteoporosis. Existing studies show that BMSCs-Exos, as important information carriers, can regulate the PI3K/Akt pathway through molecules such as miRNAs (e.g., miR-19a-3p, miR-935) that they carry, influencing osteoblast differentiation and bone formation, and playing a key role in the pathophysiological process of osteoporosis.

Progress in the field shows significant development, but challenges remain. The mechanisms that underlie the interaction between exosomes and the pathway involving PI3K and Akt are not fully understood. Research requires further work to reveal the complete picture of these mechanisms. Issues in delivery to specific targets, stability of exosomes, and possible responses from the system that provides protection in the body present major obstacles. These factors limit the use of exosomes in treatment. Strategies that modify exosomes through design need development to address these issues. The pathway involving PI3K and Akt shows complexity in structure and function. This pathway interacts with other pathways that provide signals in the body. These interactions complicate efforts to regulate the pathway with precision.

Looking ahead, further elucidating the detailed map of the synergistic interaction between BMSCs-Exos and the PI3K/Akt pathway, optimizing the exosome preparation process and targeted delivery systems, and exploring their safety and efficacy in large animal models and preclinical studies, will strongly promote the translation of exosome- and signaling pathway-based therapies for osteoporosis from basic research to clinical application.

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Disclosure statement

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