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Review article

Exosomal non-coding RNAs in the regulation of bone metabolism homeostasis: Molecular mechanism and therapeutic potential

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ABSTRACT

Bone metabolism is a dynamic balance between bone formation and absorption regulated by osteoblasts/osteoclasts. Bone metabolic disorders can lead to metabolic bone disease. Osteoporosis (OP), osteoarthritis (OA) and femoral head necrosis (ONFH) are common metabolic bone diseases. At present, the treatment of metabolic bone disease is still mainly to relieve pain and improve joint function. However, surgical treatment does not apply to the vast majority of high-risk groups, including postmenopausal women, patients with diabetes, cirrhosis, etc. Exosomes (Exos) are nanoscale membrane vesicles that are released by almost all cells. Exos are rich in a variety of bioactive substances, such as non-coding RNAs, nucleic acids, proteins and lipids. In view of the structure of Exos, it can protect the biologically active molecules can be smoothly delivered to the target cells and involved in the regulation of cell function. In this review, we focus on the regulation mechanism and function of bone homeostasis mediated by exosomal ncRNAs (Exos-ncRNAs), including macrophage polarization, autophagy, angiogenesis, signal transduction and competing endogenous RNA (ceRNA). We summarized the therapeutic strategies and potential drugs of Exos-ncRNAs in metabolic bone disease. Moreover, we discussed the shortcomings and potential research directions of Exos as carrier to deliver ncRNAs to play a role.

1. Introduction

Bone is one of the largest organ systems with strong dynamic and metabolic activity [1,2]. Bone is mainly composed of calcium sulfate minerals and type I collagen [3]. In addition to providing necessary protection for important organs, it also provides mechanical support to maintain the body 's motor function [4]. Over the course of a person 's life, bone constantly reshapes the structure and composition to maintain the steady-state balance. Bone remodeling involves two distinct processes, in which osteoclasts remove old or damaged bones, while osteoblasts form new bones [5]. Osteoblasts are derived from mesenchymal stem cells (MSCs), which are mainly responsible for the synthesis, secretion and mineralization of bone matrix and promote the formation of new bone [6]. Osteoclasts are multinucleated giant cells formed by the fusion of monocytes and macrophages differentiated from myeloid progenitor cells [7]. Osteoclasts activate matrix metalloproteinases (MMPs) and cysteine proteases to degrade bone matrix [8]. Osteoblasts and osteoclasts are the key to bone metabolism.

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The pathogenesis of metabolic bone diseases is complex, involving metabolism, immunity, genetics and other aspects, but its specific molecular mechanism is still unclear. Bone metabolic diseases are a major challenge to human health. Osteoporosis (OP), osteoarthritis (OA) and osteonecrosis of the femoral head (ONFH) are common metabolic bone diseases [9,10]. OP is a bone degenerative disease characterized by a decrease in bone mass and an imbalance in the microstructure of bone tissue, leading to an increase in bone fragility and promoting the occurrence of fractures [11]. OP causes unbearable pain and even death. The clinical manifestations of OA are joint pain and decreased mobility. The main pathological features are cartilage degeneration and osteophyte formation [12]. ONFH is a common refractory disease in orthopedics. It is called "immortal cancer" because of its complex etiology, difficult treatment and high disability rate [13]. ONFH is also known as avascular necrosis of the femoral head. Its pathological feature is ischemia of the femoral head, often accompanied by progressive collapse of the femoral head and joint destruction [14]. In the late stage of metabolic bone disease, surgery has become the main treatment, such as artificial joint replacement, and the disadvantages of artificial joint replacement are also obvious, with limited life expectancy and the need for secondary replacement. Especially for young patients, the trauma caused by the surgery itself is inevitable. Therefore, we expect early interventions to prevent the progression of the disease. Current non-surgical treatments for OP include accurate nutritional diet, vitamin D supplementation, and regular physical activity [15]. The treatment of bisphosphonates is also common. For OA, oral non-steroidal anti-inflammatory drugs and intra-articular injection of drugs have become the mainstream treatment measures [16]. Non-surgical treatment of ONFH, including protective weight-bearing, drug therapy, physical therapy and rehabilitation exercise.

Exosomes (Exos), also known as extracellular vesicles (EVs), are secreted vesicles produced by cells that can bind to the membrane and promote intercellular information transmission [17]. Exos themselves carry a variety of bioactive substances, including proteins, lipids, nucleic acids, etc., which are involved in the regulation of cell function [18]. Exos act on target cells through autocrine, paracrine and distant secretion [19]. Based on the balance mechanism of bone formation and bone resorption, the Exos secreted by many bone metabolism-related cells are good regulators in the bone metabolism microenvironment. In particular, Exos released by mesenchymal stem cells (MSCs) may inhibit metabolic bone disease and contribute to the treatment of the disease [19].

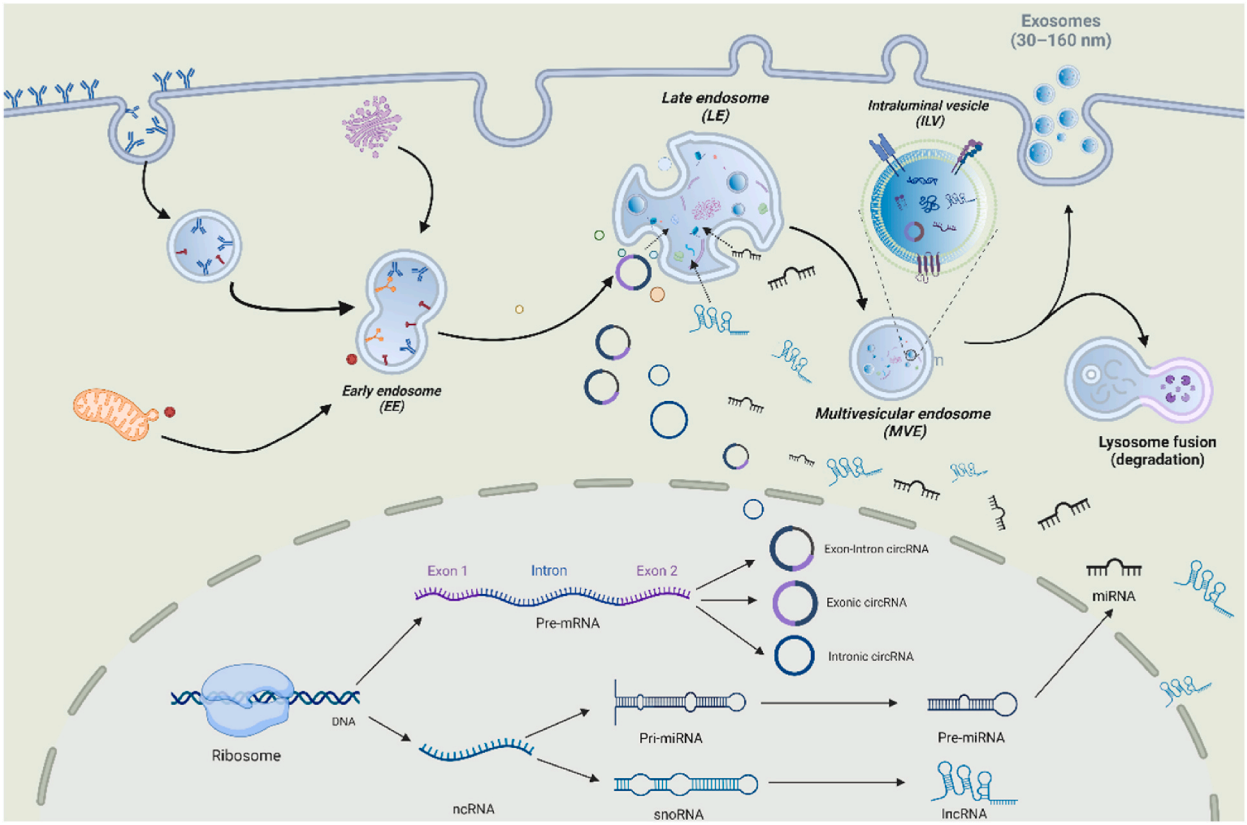

Fig. 1. The formation process of Exo-ncRNAs. DNA double strands form lncRNAs, miRNAs and circRNAs under the action of different enzymes. Early endosome (EE) exchanges material with other organelles or late endosome (LE) invagination can load ncRNAs into Exos. The cytoplasmic membrane is invaginated, and some extracellular components and cell membrane proteins are wrapped together to form early endosomes (EEs). EEs can exchange substances with other organelles, or fuse with different EEs to form late endosomes (LEs). The LEs invaginates and "absorbs" a variety of small biological molecules, and produces many intraluminal vesicles (ILVs). ILVs eventually form multivesicular endosome (MVE). MVEs can fuse with lysosomes or cell membranes to form exosomes (Exos). After secretion, Exos can directly fuse with cells or transmit active substances to target cells through receptor-mediated endocytosis. Various nucleic acid molecules carried by Exos, including lncRNAs, miRNAs and circRNAs, can be transmitted to a variety of bone cells to participate in the regulation of metabolic bone disease.

2. Exosomal ncRNAs: the occurrence and function

Exosomes were first discovered in 1981 [20]. Initially, this small vesicle in sheep reticulocytes cultured in vitro was considered to be a way for cells to release membrane proteins or remove cell debris during maturation [20]. Accumulating studies have confirmed that Exos act as an important medium for information transmission between cells. At present, the potential functions of Exos are still the focus of researchers.

Extensive genomic and transcriptome analyses have shown that 90 % of eukaryotic genomic DNA can be transcribed into RNA, of which only 2 % have protein-coding functions [21,22]. Most RNAs do not have protein-coding functions and are called ncRNAs. Accumulated studies have shown that "non-coding" is not equivalent to "non-essential" or "garbage" genes. NcRNAs play a wide range of regulatory roles in the life activities of organisms. The common types of ncRNAs include long non-coding RNA (lncRNA), microRNA (miRNA) and circular RNA (circRNA), which play a key role in various human diseases such as malignant tumors, nervous system diseases and bone metabolic diseases [23]. LncRNAs are defined as non-coding transcripts longer than 200 bp. Most lncRNAs are transcribed by RNA polymerase II (Pol II). Due to the limitation of processing, most lcRNAs show obvious nuclear localization [24]. MiRNAs play biological functions mainly by participating in the translation process of their downstream genes [25]. MiRNAs guide the silencing complex (RISC) to degrade mRNA or hinder its translation by pairing with the base of the target gene mRNA. Complete complementary pairing leads to mRNA degradation and incomplete complementary pairing acts on translation inhibition. CircRNA is a new type of non-coding RNA, which is produced by reverse splicing of pre-mRNA. Moreover, circRNA forms a closed ring structure with covalent bonds, does not have a 5′- cap and a3 ′- poly (A) tail, is not easily affected by RNA exonuclease, and is more stable in expression [25]. The formation of Exo-ncRNAs is a complex process (Fig. 1).

Studies have confirmed that Exo-ncRNAs play a role in various fields. Exo-ncRNAs in cervical cancer patients undergoing concurrent chemoradiotherapy may be markers for predicting early death (ED) [26]. The ncRNAs carried by mesenchymal stem cell-derived (MSC-Exos) exosomes have potential therapeutic effects in lung diseases [27]. Hepatocellular carcinoma-derived Exo--miR-21-5p is involved in cancer progression by promoting tumor cell-associated macrophage (TAM) polarization [28]. Exo-ncRNAs derived from adipocytes and immune cells also show effective regulatory effects in cardiovascular diseases [29]. In this review, we focus on the mechanism, function and potential therapeutic value of Exo-ncRNAs in metabolic bone disease.

3. Exosomal ncRNAs: the mechanism of action of in metabolic bone disease

In this review, we summarize the specific molecular mechanisms by which Exo-ncRNAs play a role in metabolic bone diseases. In view of the pathological mechanisms of different diseases, we highlight the research focus of Exo-ncRNAs in OA, OP and ONFH.

3.1. Macrophage polarization

Immune cell phenotype disorders may bring about inflammatory storms. OA is a typical inflammatory disease in bone diseases. Granulocyte-macrophage colony-stimulating factor (GM-CSF) can differentiate monocytes into two macrophages (Møs) with opposite functions. M1øs recruit immune cells in the early stage of inflammation and promote chronic inflammation. However, M2øs inhibits the secretion of immune cells and differentiates fibroblasts into myofibroblasts, promoting angiogenesis and repairing tissues. The formation of M1øs and M2øs should be balanced. M1øs causes cytokine storms and tissue damage. M2øs promotes collagen and angiogenesis, thereby promoting tumor development.

M1øs polarization has been shown to be a risk factor for synovial inflammation. A variety of cytokines, including LPS, IFN-γ, TNF-α and IL-12, promote the accumulation of M1øs and induce synovitis, cartilage loss, osteophyte formation and joint degeneration. Based on the pathological regulation mechanism of macrophages on OA, recent studies have reported some effective treatment strategies to alleviate OA. For example, TREM2, a signaling hub molecule expressed by myeloid immune cells, regulates CXCL3 expression and promotes M1øs to M2øs polarization through the NF-κB signaling pathway. The secretion of inflammatory factors such as TNF-α, IL-6 and IL-1β is reduced, and the inflammatory response is alleviated, thereby improving the progress of OA [30]. Transient receptor potential vanilloid type 1 receptor (TRPV1), a calcium-permeable non-selective cation channel, is widely expressed in neurons involved in pain perception. Lv et al. found that M1øs infiltration was increased and TRPV1 was highly expressed in the synovium of OA patients. Further mechanistic studies confirmed that TRPV1-induced Ca^{2+}influx promoted the phosphorylation of calcium and calmodulin-dependent protein kinase II (CaMKII), and promoted the nuclear translocation of Nrf2, ultimately inhibiting M1øs and inflammatory response and alleviating OA [31]. Based on TRPV1-mediated macrophage polarization regulation mechanism, Lv et al. developed a magnetocaloric modulator. Under the stimulation of alternating magnetic field (AMF), magnetic nanoparticles (MNP) coupled with TRPV1 monoclonal antibody (MNP-TRPV1) has been shown to effectively alleviate OA and improve knee pain sensitivity and limp gait in mice. TRPV1 is a potential target gene for clinical precision therapy [32]. In summary, the immune regulation strategy involving synovial macrophages is a potential treatment for OA. As one of the tools for intercellular communication, Exos also play a key role in regulating the inflammatory response activated by M1øs. Interestingly, macrophage-derived Exo-ncRNAs play an important role in regulating chondrocyte proliferation, differentiation, extracellular matrix synthesis, and synovial inflammation. TLR3 is expressed under the induction of a variety of inflammatory factors, which stimulates the conversion of M2øs to M1øs and further enhances innate immunity [33]. M2øs -derived Exo-miR-26b-5p repolarized M1øs into M2øs cells by targeting the TLR3 signaling pathway. In addition, Exo-miR-26b-5p inhibits articular cartilage hypertrophy by targeting $COL_{10}A_1$, improves gait abnormalities induced by pain, and alleviates OA [33]. Digoxin (DIG) inhibited M1øs polarization of macrophages in synovial fluid of OA patients [34]. Jia et al. confirmed that DIG controlled inflammation and promoted chondrogenesis in OA mice by down-regulating

M1øs-derived Exo-miR-146b-5p [34]. Exo-miR-146b-5p targeted inhibition of Usp3 and Sox5 expression levels may be the specific molecular mechanism of DIG in the treatment of OA [34]. In the progression of OA, various cells in the articular cavity can release Exos, including macrophages, chondrocytes, osteoblasts and fibroblasts. Different cell-derived Exos can produce different effects on OA [35]. Recent studies have found that BMSC- Exo has positive significance in regulating macrophage polarization and inflammatory levels. BMSCs-derived Exos-lncRNA TUC339 promotes the polarization of M1øs to M2øs, inhibits the inflammatory storm and improves OA [36]. This has laid a reliable foundation for the future application of stem cell transplantation in OA treatment.

The main mechanism of macrophage polarization in OP and ONFH is still to regulate local inflammatory response. Chronic inflammation is the main cause of OP, and M1øs release pro-inflammatory factors and promote bone resorption. M2øs inhibit excessive inflammation and secrete osteogenic factors. The proportion of M1øs/M2øs macrophage phenotype in OP patients is high, which may lead to the decrease of inflammatory microenvironment and bone mineral density. Therefore, regulating the balance between M1øs and M2øs is a potential treatment. Pseudolaric acid B (PAB) prevents OP by promoting the transformation of M1øs to M2øs and inhibiting the inflammatory response in ovariectomized (OVX) mice [37]. PPARβ/δ agonists alleviate high glucose-mediated macrophage imbalance and prevent OP by reducing M1øs polarization [38]. However, there is a gap in the research on the mechanism of Exos-mediated macrophage homeostasis in OP, which may be a new field worthy of further study. M2øs polarization is involved in inhibiting inflammation-mediated osteocyte apoptosis to reduce the bone pathology of ONFH. For example, Aucubin promotes M2øs polarization by inhibiting TLR4/NF-κB signal transduction, thereby reducing osteonecrosis [39]. Curcumin inhibits M1øs polarization and reduces osteocyte apoptosis by inhibiting the JAK1/2-STAT1 signaling pathway [40]. Similarly, the molecular mechanism and function of Exos in ONFH are very limited. Chen et al. constructed engineered Exos using exosomes derived from BMSCs and hydrogels. Engineered Exos can polarize M2øs and show significant effects in promoting bone formation and angiogenesis [41]. Exos have shown effective functions in the treatment of bone metabolic diseases, but the role of Exos-mediated macrophage polarization in OP and ONFH is still lacking.

3.2. Autophagy pathway

Autophagy is the use of lysosomes to degrade cellular components (defective organelles and misfolded proteins) under the regulation of autophagy-related genes in eukaryotic cells. Autophagy is a highly conserved biological process that prevents cell damage under physiological conditions, and excessive autophagy can lead to cell death. Accumulated studies have shown that autophagy plays a key role in various pathological processes such as cell homeostasis regulation, metabolism, immunity, tumorigenesis, and neurological diseases.

In bone metabolic diseases, the regulation of autophagy pathway mediated by Exo-ncRNAs has only been confirmed in OA. Excessive decomposition of cell matrix and accumulation of inflammation lead to imbalance of chondrocyte homeostasis. Cartilage homeostasis disorder is a key initiating factor for osteoarthritis. In the occurrence of OA, Exo-miRNAs play a role as autophagy activators. Exos isolated from synovial fluid of degenerative knee joints release miR-182-5 to promote chondrocyte repair [42]. TNFAIP8 is down-regulated by miR-182-5p, which is involved in the activation of autophagy pathway [42]. TNFAIP8 is a tumor-promoting gene regulated by cellular immunity. Recent studies have confirmed that TNFAIP8 interacts with autophagy-related proteins ATG3 and ATG7 [43–45]. The interaction between TNFAIP8 and ATG3 mediated by Exo-miR-182-5p in synovial fluid may be a potential molecular mechanism to alleviate osteoarthritis. Metabolic disorders lead to excessive autophagy and induce cell death, which is a signal to stimulate chondrocyte damage. mTORC1 promotes autophagy inactivation by phosphorylating the autophagy regulatory complex. mTORC1 is a key regulator of autophagy pathway inactivation. PI3K/Akt is the central mediator of the signal transduction pathway and the upstream pathway of mTOR. PI3K/Akt/mTOR is of great significance in excessive autophagy in OA. Wen et al. established an IL-1β-induced excessive autophagy model of chondrocytes [46]. However, mesenchymal stem cell-derived Exo-lncRNA KLF3-AS1 targets YBX1 and activates PI3K/Akt/mTOR, which effectively inhibits excessive autophagy of chondrocytes and improves the progression of OA [46].

The main causes of OP are aging and estrogen deficiency. Autophagy regulates the balance between bone formation and bone resorption, and inducing autophagy activation is the protective mechanism of OP [47,48]. Activation of OPTN (an autophagy receptor) can enhance the degradation of the autophagy substrate FABP3, reduce adipogenesis and promote the osteogenesis of MSC [49]. The lack of RUBCN (a negative regulator of autophagy) can accelerate the degradation of the intracellular domain of the receptor NOTCH by autophagy and further promote osteogenic differentiation [48]. Liu et al. found that the gene LRRc17 expressed in BMSCs was highly positively correlated with age. The down-regulation of LRRc17 gene induces autophagy activation by inhibiting mTOR/PI3K signaling pathway, thereby effectively improving ovarian resection-induced bone flow and restoring the viability of senescent MSCs [50]. However, some researches have shown that activation of the autophagy degradation pathway inhibits osteogenic differentiation and accelerates bone loss. TP53INP2 was lowly expressed in BMSCs of OP patients and OVX-mice. Oxidative stress induced degradation of TP53INP2 in an autophagy-dependent manner and inhibited osteogenic differentiation of BMSCs [51]. Mul-A (Mulberroside A) improves estrogen deficiency-induced bone loss and OP by inhibiting the expression and nuclear transfer of autophagy activator Mitf [52]. Interestingly, Pueraria lobata-derived exosome-like nanovesicles (PELNs) further effectively promoted bone formation by degrading the intestinal flora-derived metabolite TMAO and activating autophagy [53]. Exos were extracted from mouse plasma exposed to low temperature. These Exos can inhibit autophagy and promote OP by targeting the miR-25-3p/SATB2 axis [54]. At present, there is a lack of research on the mechanism of Exos-mediated autophagy activation in OP.

Most studies have confirmed that autophagy is a protective mechanism in the pathogenesis of ONFH. On the one hand, the ischemic and hypoxic microenvironment of ONFH induces HIF-α expression. HIF-α promotes the expression of downstream target gene BNIP3 and blocks the inhibition of hypoxia-induced mitophagy [55]. The hypoxic microenvironment causes damaged mitochondria to

release excessive reactive oxygen species (ROS). The transplanted BMSCs have a large number of apoptosis and aging due to oxidative stress in the femoral head necrosis area, which is not conducive to the early repair of ONFH. Down-regulation of p53 in transplanted BMSCs can effectively relieve the inhibition of Parkin expression, promote Parkin transfer to mitochondria to activate autophagy and promote ONFH repair [56]. On the other hand, PI3K/AKT/mTOR is a known autophagy inhibition pathway. Current studies have confirmed that inhibition of this pathway can induce autophagy activation, but the role of this pathway in the pathogenesis of ONFH is still controversial. For example, oral lithium reduced the degree of femoral head necrosis in GC-ONFH rats. The specific molecular mechanism is that lithium inhibits excessive autophagy of osteoblasts and alleviates ONFH by activating the PI3K/AKT/mTOR pathway [57]. Pinocembrin attenuates GA-ONFH by inhibiting PI3K/Akt/mTOR pathway and activating autophagy to reduce osteocyte apoptosis [58]. There are few studies on the mechanism of Exos-mediated autophagy in ONFH. The latest research focuses on the molecular mechanism and function of Exo-miRNAs derived from BMSCs in ONFH. By inhibiting the GREM1/NF-κB signaling pathway and activating autophagy, Exo-miR-150 helps to alleviate the pathological features of ONFH [59]. We summarized the molecular mechanism and function of Exo-ncRNAs-mediated autophagy pathway involved in the regulation of bone metabolism homeostasis (Table 1).

3.3. Angiogenesis

Bone is an organ with abundant blood supply, which plays a key role in bone regeneration and homeostasis. The regulation of angiogenesis mediated by Exo-ncRNAs can alleviate the progression of ONFH and OP. Compared with healthy individuals, BMSCs-derived Exos from traumatic ONFH patients have low expression of miR-224-3p, which targets up-regulation of FIP200 and promotes angiogenesis [62]. BMSCs may be an effective method for the treatment of traumatic ONFH. Another study of stem cell therapy for ONFH focused on CD34 stem cells. Exos produced by paracrine of $CD43^{+}$ stem cells have the effect of promoting angiogenesis [63,64]. Recent studies have confirmed that $CD43^{+}$ stem cell Exos, as a carrier of miR-26 a, can enhance angiogenesis and protect the femoral head from damage caused by glucocorticoids (GC) [65,66]. ONFH is avascular necrosis of the femoral head. Promoting angiogenesis and osteogenic repair is one of the most important mechanisms of stem cell therapy for ONFH. There is still a lack of research on the molecular mechanism and function of Exo-ncRNAs in angiogenesis. In addition, only one study reported the regulatory effect of Exo-ncRNAs on OP angiogenesis. Wang et al. explored the changes of angiogenesis and bone remodeling in OVX-mice under mechanical load stimulation [67]. Mechanical stimulation promotes VEGF expression by inhibiting the expression of BMMSC-miR-214-3p, thereby promoting angiogenesis and alleviating OP [67]. Unfortunately, the specific molecular mechanism is not clear. Interference in bone angiogenesis will inevitably increase the risk of low bone mass diseases. The molecular mechanism of Exo-ncRNAs in OP needs to be further studied. Unlike ONFH and OP, angiogenesis is beneficial to the progress of OA. Under normal physiological conditions, human cartilage does not contain blood vessels and has the ability to resist angiogenesis [68]. However, in the pathological process of OA, there is a phenomenon of microfracture at the osteochondral junction, which leads to the invasion of a large number of cytokines, pro-angiogenic factors and inflammatory factors [68]. Increased angiogenesis in cartilage, synovium and meniscus of OA patients ultimately enhances cartilage damage. In the OA mouse model, osteoclast-Exos were transferred to chondrocytes. The expression of osteoclast-Exo-miRNA was up-regulated and secreted to chondrocytes, which reduced the resistance of chondrocytes to angiogenesis by inhibiting the expression of tissue inhibitors of metalloproteinase TIMP-2 and TIMP-3 [69]. Based on the regulation of osteoclast-Exo-miRNA, the application of targeted exosome inhibitors can effectively alleviate the progress of OA [69].

3.4. Competing endogenous RNA (ceRNA) mechanism

Competing endogenous RNA (ceRNA) mechanism is that ncRNAs (lncRNAs/circRNAs) compete with miRNA to bind to target genes, thereby preventing miRNA from inhibiting the translation of target genes. The ceRNA mechanism is ubiquitous in cell growth and participates in basic physiological metabolic regulation. Abnormally expressed lncRNAs/circRNAs are involved in a variety of physiological processes as ceRNAs. We summarize the molecular mechanism of Exo-lncRNAs/circRNAs as ceRNAs regulating bone metabolism, in order to further understand potential biomarkers and therapeutic targets (Table 2).

CeRNA is ubiquitous in various metabolic bone diseases. In view of the clinical characteristics of patients with OP, promoting

Table 1
Exo-ncRNAs regulate autophagy in metabolic bone disease.

Source of exosomes	NcRNAs	Autophagy pathway	Molecular mechanism	Function	References
Fucoidan-pretreated MSC	miR-146b-5p	Activation	Target TRAF6 gene	Inhibit the inflammatory response of chondrocytes and degrade of ECM	[34].
Synovial fluid	miR-182-5p	Activation	Target TNFAIP8/ATG/LC3 axis	Promote chondrocyte proliferation, migration and invasion	[42]
Subcutaneous fat	miR-199a-3p	Activation	Target mTOR pathway	Inhibition of chondrocyte injury and ECM degradation	[60]
Adipose tissue	miR-429	Activation	Target FEZ2 gene	Promote chondrocyte proliferation	[61]
MSC	LncKLF3-AS1	Inactivation	Target YBX1/PI3K/AKT/mTOR axis	Inhibit chondrocyte apoptosis	[46]

osteoblast formation is the key to prevent the occurrence of brittle fractures. Bone marrow mesenchymal stem cells (BMSCs) -derived Exos lncRNA MALAT1, as a ceRNA, activates osteoblast formation by targeting down-regulation of miR-34c and promoting SATB2 expression [71]. The transcription factor Runx2 determines the osteogenic fate of MSCs [74]. SATB2 enhances the transcriptional activity of Runx2 gene and plays a crucial role in promoting osteogenic differentiation [71]. Postmenopausal women are the main population suffering from osteoporosis. Serum Exo-circ_0006859 from postmenopausal women with OP acts as a ceRNA, targeting the miR-431-5p/ROCK1 axis to inhibit OP [70]. Circ_0006859 is a potential serological marker for assessing the risk and treatment prognosis of postmenopausal OP [70]. The role of CeRNAs in OA is still focused on understanding the molecular mechanism of excessive decomposition of ECM in chondrocytes. SOX9 is a key gene that inhibits ECM degradation and promotes cartilage repair [75]. MSCs-derived Exo-circ_0001236 reduces the catabolism of ECM by adsorbing miR-3677-3p and promoting Sox9 expression, and ultimately effectively alleviates the progression of OA [73]. Circ_0001236 is a potential target for the treatment of OA [73]. The mechanism of lncRNAs/circRNAs as ceRNAs in the occurrence of ONFH is still unclear and needs to be studied. The occurrence of ONFH is mainly due to the femoral head artery blood supply interruption, bone cells and bone marrow components caused by partial death of bone tissue necrosis. The clinical effect of surgical treatment of ONFH is not satisfactory. Promoting angiogenesis may be one of the promising studies of Exo-lncRNAs/circRNAs as ceRNAs to prevent ONFH.

3.5. Signal transduction pathways

3.5.1. Signaling pathways regulated by Exo-ncRNAs in OP

3.5.1.1. PI3K/Akt signaling pathway. PI3K/AKT is a classical intracellular signal transduction pathway that corresponds to extracellular signals and promotes metabolism, cell proliferation and angiogenesis. PTEN is a negative regulator of the PI3K/AKT signaling pathway. Studies have confirmed that PI3K/AKT signaling pathway is involved in the regulation of bone metabolism and has the effect of alleviating OP. Specifically, mechanical stimulation directly acts on bone tissue or promotes muscle cells to secrete growth factors to regulate bone metabolism. Xu et al. confirmed that Exos induced by mechanical stimulation can resist the inhibitory effect of dexamethasone on osteogenic differentiation by secreting miR-92a-3p and regulating PTEN/AKT pathway [76]. Exos produced by muscle cells induced by mechanical stimulation are potential clinical indicators of bone remodeling and valuable prognosis in OP patients. In addition, the adaptability of bone to mechanical stimulation and the production and function of Exos deserve further study to maximize the improvement of bone mineral density, trabecular structure and accelerate osteogenic differentiation.

3.5.1.2. MAPK signaling pathway. MAPK signaling pathway plays a key role in regulating the balance of osteogenic and adipogenic differentiation of BMSCs [77]. Adipocyte-derived Exo-miR-122-5p binds to the target gene SPY2 and mediates the activation of the MAPK signaling pathway, thereby reducing the accumulation of bone marrow fat [77]. At present, the drugs for the treatment of OP are mainly estrogen receptors, and long-term use can bring many adverse reactions to patients [78]. Wang et al. emphasized that Wen-Shen-Tong-Luo-Zhi-Tong (WSTLZT), as a traditional Chinese medicine prescription, is involved in inducing adipocyte-derived Exos to secrete miR-122-5p, thereby alleviating bone marrow adipose tissue accumulation and promoting osteogenic differentiation [79].

3.5.1.3. Hippo pathway. The key molecules of the Hippo signaling pathway are a pair of kinases (MST1/2 and LATS1/2) and a transcriptional coactivator (YAP/TAZ) [80]. Integrin, glycogen, inflammation and oxidative stress activate the activity of key kinase MST1/2 and further phosphorylate LATS1/2 [81,82]. YAP/TAZ has a nuclear localization sequence, which assists it to enter the nucleus and binds to the transcription factors of the TEAD family to exert transcriptional activation [83]. Activation of the Hippo signaling pathway promotes YAP/TAZ phosphorylation. The activation of Hippo signaling pathway can promote the phosphorylation of YAP/TAZ complex. The phosphorylated YAP/TAZ complex was bound by cytoplasmic protein 14-3-3 and retained in the cytoplasm or degraded [84].

The inactivation of Hippo plays a protective role in the progression of OP [85–88]. Most studies have focused on the regulatory role of transcription coactivator YAP/TAZ in the development of OP. For example, myoblast-derived Exo-Prrx2 activates the Hippo signaling pathway and reduces bone loss in OVX mice by regulating the lncRNA-MIR22 HG/miR-128/YAP axis [89]. Current studies have shown that the inactivation of the Hippo signaling pathway mainly relies on non-phosphorylated YAP to maintain the balance of

Table 2
The molecular mechanism and functions of Exo-lncRNAs/circRNAs as ceRNAs regulating metabolic bone disease.

Source of exosomes	NcRNAs	miRNAs	Target gene	Functions	References
Patient serum-Exo	Circ_0006859	miR-431-5p	ROCK1	Inhibit osteoblast differentiation and promote adipogenic differentiation of hBMSC	[70]
BMSC-Exo	LncRNA MALAT1	miR-34c	SATB2	Promote osteoblast activity	[71]
CHON-001 cell-Exo	Circ_0001846	miR-149-5p	WNT5	Modulate IL-1β-induced chondrocyte cell damage	[72]
MSC-Exo	Circ_0001236	miR-3677-3p	Sox9	Enhance cartilage formation and inhibit cartilage degradation	[73]

bone metabolism and alleviate OP. The specific effects include: (1) the promotion of MSCs proliferation and osteogenic differentiation [90]; (2) the promotion of proliferation of osteoblasts and chondrocytes [90]; (3) the inhibition of osteoclast proliferation; (4) the weakening effect of immune cells such as inflammatory cells and macrophages on the adverse effects of osteoblasts [91]; (5) Enhance the blood perfusion and nutrition supply of new bone.

The resereach of Exo-ncRNAs-mediated Hippo signaling pathway inactivation focuses on the regulation of kinases. The kinase activator Mob1 acts as a targeted inhibitor gene of Exo-miRNAs, thereby inhibiting the activation of the Hippo signaling pathway to alleviate OP. For example, BMSCs-Exo-miR-186 and human umbilical cord mesenchymal stem cells (HUCMSCs) -*Exo*-miR-1263 target Mob1, participate in bone formation [89,92]. There is still a lack of research on the mechanism of Exo-ncRNAs-mediated Hippo signaling pathway regulation in maintaining bone metabolism and OP. Future studies can pay more attention to other unreported regulatory factors in the Hippo signaling pathway.

3.5.2. *Signaling pathways regulated by Exo-ncRNAs in OA*

3.5.2.1. Wnt/β-Catenin signaling pathway. Wnt/β-Catenin signaling pathway can regulate the pluripotency of stem cells and determine the fate of cell differentiation. Adipose mesenchymal stem cell-derived Exo-miR-376c-3p is highly expressed, which reduces chondrocyte degradation by targeting WNT3/9a and inhibiting the Wnt/β-Catenin signaling pathway [93]. Interestingly, synovial mesenchymal stem cell-derived Exo-miR-320c inhibits Wnt signaling pathway activity to reduce ECM degradation and alleviate OA progression [94]. Different sources of mesenchymal stem cell Exo-miRNAs targeting Wnt signaling pathway help to enhance the function of chondrocyte repair, which is a promising method for mesenchymal stem cells combined with Exo-miRNAs to treat OA.

3.5.2.2. TGF-β signaling pathway. Aging or dysfunction of articular chondrocytes is a key pathological factor of OA. TGF-β is essential for cartilage repair. Excessive activation of TGF-β can lead to cartilage degradation, and supplementation of TGF-β may be an effective treatment for OA [95]. Dai et al. confirmed that osteoclast-Exo-miR-212-3p was transferred to chondrocytes, which inhibited the anabolism of chondrocytes and accelerated the decomposition of cell matrix by inhibiting the TGF-β signaling pathway [96]. This finding reveals that Exo-miRNA is one of the effective ways for osteoclasts to play a role.

3.5.2.3. NF-κB signaling pathway. NF-κB signal transduction is directly or indirectly related to almost all embryonic development and physiological processes. NF-κB plays an important regulatory role in osteoblast differentiation, mesenchymal stem cell proliferation and other processes. However, only one study reported that mesenchymal stem cell-derived Exo-miR-361-5p inactivates the NF-κB signaling pathway and reduces chondrocyte damage by targeting DDX20 [97]. At present, there is still a lack of research on the mechanism and function of Exo-ncRNAs-mediated NF-κB signaling pathway in the development of osteoarthritis.

3.5.3. *Signaling pathways regulated by Exo-ncRNAs in ONFH*

3.5.3.1. Sonic hedgehog signaling pathway. The role of Exo-ncRNAs-mediated signal transduction in ONFH still focuses on

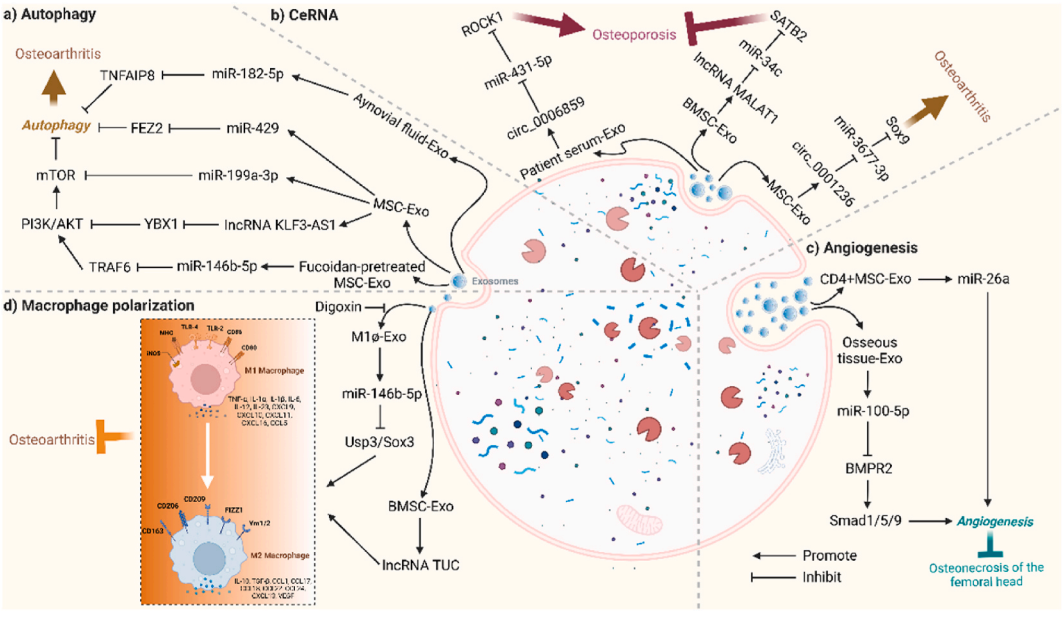

Fig. 2. The key mechanisms in metabolic bone disease.

angiogenesis. The Shh signaling pathway is highly conserved in evolution and plays an important role in regulating development and various physiological processes, including normal stem cell proliferation and differentiation. Shh signaling pathway plays an active role in angiogenesis. For example, activation of the Shh signaling pathway promotes angiogenesis in cerebral ischemia, skeletal muscle ischemia, and skin expansion [98–100]. In the occurrence of ONFH, Exo-miR-378 activates the shh signaling pathway by targeting Sufu and promotes angiogenesis [101]. Nan et al. focused on the angiogenesis and osteogenesis of shh signaling pathway in ONFH [102]. They found that adipose-derived stem cells (ASCs)-*Exo*-miR-378 activates the shh signaling pathway by targeting Sufu (a negative regulator of the shh signaling pathway), thereby promoting bone formation and angiogenesis [102]. The activation of Shh signaling pathway is of great significance for the establishment of bone vascular system.

Here, we summarized the key mechanisms of Exo-ncRNAs in different metabolic bone diseases (Fig. 2).

4. The therapeutic potential of Exo-ncRNAs in bone metabolic diseases

At present, the commonly used drug therapy for bone metabolic diseases is usually used to relieve the pain of patients. The mechanism of these drugs is to resist bone resorption, regulate hormone levels and supplement calcium [103–105]. In addition, drug treatment has side effects and cannot be taken for a long time. By summarizing the mechanism of action of Exo-ncRNAs in metabolic bone disease, we can understand that the treatment focus of different types of metabolic bone disease is inconsistent. However, the key to fundamentally solving the problem is still to regulate bone metabolism and promote bone tissue repair.

Recently, Exos have received extensive attention as extracellular vesicles. Exos are considered to be miniature versions of parental cells, mainly because parental cells determine the diversity of Exos structure and transport special active substances [106]. For example, macrophage-derived Exos contribute to anti-infection and inflammation, while BMSCs-derived Exos contribute to osteoblast formation [107–109]. In the metabolic microenvironment, long-distance regulation of Exos is a promising therapeutic alternative. Exo-miRNAs that regulate glucose and lipid metabolism have shown advantages in the treatment of diabetes [110].

In the mechanism study, a variety of drugs have shown good therapeutic effects in metabolic bone diseases. Wen-Shen-Tong-Luo-Zhi-Tong (WSTLZT), a traditional Chinese medicine with less toxic effect, induces adipocyte-derived Exos to promote osteoblast differentiation of BMSC and alleviate OP in mice [79]. Another classic cardiac glycoside drug, digoxin (DIG), has potential anti-inflammatory effects. DIG stimulates M1-like øs-derived Exos to secrete miR-146b-5p targeting Usp3 and Sox5 to control the inflammatory microenvironment of OA. It is still difficult to achieve precise delivery and targeting of drug-stimulated Exos in vivo. Improving the targeting of Exos can achieve efficient delivery.

Engineered Exos can selectively deliver exosomes to target cells for precise regulation. Combining the multi-differentiation function of MSC with exosomes is the focus of regenerative medicine. The research on the application of engineered exosomes in the treatment of metabolic bone disease is relatively novel. Subcutaneous fat (SC) contains a large number of MSC-Exos, which are called $MSCs^{SC}$-Exos. Zhao et al. modified the surface of Exos with chondrocyte affinity peptide (CAP) [60]. CAP- $MSCs^{SC}$-Exos can specifically deliver miR-199a-3p to chondrocytes and inhibit cell matrix degradation of chondrocytes [60]. Compared with natural exosomes, CAP- $MSCs^{SC}$-Exos can be preserved in the joint cavity for a long time [60]. On the other hand, CAP- $MSCs^{SC}$-Exos can also pass through the dense cartilage matrix and deliver miR-140 to the deep cartilage tissue area [60]. This study developed a new and efficient engineered exosome, CAP-MSCsSC-Exos, which showed excellent therapeutic effect in OA mouse model [60]. The development of engineering exosomes is a research gap in the field of OP treatment. However, other studies have shown that the combination of tissue engineering and regenerative medicine has beneficial effects on bone formation and angiogenesis. For example, multifunctional hydrogels loaded with M2Dø-Exo and stromal cell-derived factor-1α (SDF-1α) are involved in bone formation and angiogenesis. Engineering Exos derived from MSC are expected to become a feasible treatment in bone tissue repair. However, other studies have shown that the combination of tissue engineering and regenerative medicine has beneficial effects on bone formation and angiogenesis. For example, multifunctional hydrogels loaded with M2Dø-Exo and stromal cell-derived factor-1α (SDF-1α) are involved in bone formation and angiogenesis [111]. Multifunctional hydrogel loaded with BMSCs-Exo-miR-29a promotes osteogenesis and angiogenesis. Similar hydrogel-exosome systems are widely used in the treatment of various diseases [112]. A variety of bioactive molecules carried by exosomes play a major regulatory role. On the other hand, the combined application of exosomes and hydrogels helps to protect bioactive molecules from degradation and promote the sustained role of exosomes. Some hydrogels themselves can also promote tissue repair and reduce inflammatory response. To a certain extent, engineered exosomes have potential application value in alleviating OP and ONFH.

5. Discussion

The imbalance of bone metabolism will lead to specific changes in the abundance of ncRNAs in exosomes, which indicates that the loading of ncRNAs into Exos is not a passive process. Insight into the differential expression and function of Exo-ncRNAs in metabolic bone diseases can promote the development of engineered exosomes. Early reviews have focused more on the mechanisms and functions of Exos or ncRNAs (mainly miRNAs) in bone diseases. In particular, there is a lack of research on the regulatory mechanism and function of Exo-ncRNAs in the development of OP & ONFH. The previous article mainly describes the pathological changes of OP & ONFH & OA and the regulatory mechanism mediated by Exo-ncRNAs. Here, we further discuss the latest on the selective packaging of ncRNAs into Exos and the challenges of applying Exo-ncRNAs to metabolic bone diseases.

A specific mechanism must exist in order to sort ncRNAs into Exos. By extracting exosomes from five different cells, the relative abundance and sequence structure differences between cells and Exos were analyzed. Researchers have cracked specific sequences of miRNA release or retention. Adding or deleting these EXOmotifs (secretion-related sequences) or CELLmotifs (retention-related

sequences) to miRNAs will determine whether miRNAs will eventually be loaded into exosomes [113]. Moreover, studies have confirmed that two specific RNA binding proteins Alyref and Fus are involved in promoting the entry of EXOmotifs (CGGGAG) miRNAs into exosomes [113]. Other RBPs, Syncrip are also involved in the regulation of miRNA sorting. The amino terminal domain of Syncrip (named NURR) has a high affinity with miRNAs [114]. The NURR domain can achieve the sorting of miRNAs and distribute them to specific exosomes [114]. Another study confirmed that hnRNPA2B1 (intracellularly expressed RBP) controls the secretion of ncRNAs by binding to specific motifs of miR-503 [115]. Some RBPs have high affinity with ncRNAs. The Exo-ncRNAs sorting mechanism may improve the delivery efficiency of target ncRNAs, thereby enhancing the regulation of target genes in distant cells.

Exo-ncRNAs have been shown to be potential therapeutics for metabolic bone disease. However, there are still two obstacles to the application of Exo-ncRNAs in clinical treatment. First, we must solve the problem of efficient production of Exos. Most mammalian cells release a little natural exosomes, but the culture cell cycle is very long and expensive. It has been reported that mechanical loading, tangential flow filtration (TFF), 3D cultures, hypoxia, and small molecule regulators can effectively increase exosome production [116–119]. Nevertheless, many aspects need to be addressed to ensure the safety, efficiency and robustness of such technologies. For example, the strength of mechanical load needs to meet the threshold of secretion and protect cells from excessive stress. Environmental factors, such as hypoxia and glucose content, must still be tested in clinically relevant cell types.

In order to apply Exo-ncRNAs to clinical treatment, another problem to be solved is how to deliver Exo-ncRNAs to target cells stably and efficiently. Engineering Exo-ncRNAs provides a new idea for clinical transformation. Genetic engineering methods add specific motifs to ncRNAs to enhance the affinity of RBPs to ncRNAs [120,121]. RBPs-ncRNA complexes are fused with Exos membrane proteins and selectively deliver ncRNAs to Exos. Furthermore, the addition of peptides targeting receptor cells to the Exos membrane further improved the targeting effect of Exo-ncRNAs. However, there are very few studies on engineered Exo-ncRNAs in regulating bone metabolism disorders. The therapeutic significance of the interaction between RBPs and Exo-ncRNAs in metabolic bone disease is worthy of further study.

6. Conclusion

Exo-ncRNAs have not been widely used in the clinical treatment of metabolic bone diseases. Thus, it is necessary to further study the specific molecular mechanism and function of Exo-ncRNAs in bone metabolism. The development of Exo-ncRNAs targeted delivery system is helpful to fundamentally regulate the balance of bone metabolism and provide a new solution for metabolic bone disease.

CRediT authorship contribution statement

Chengxiong Huang: Writing – review & editing. **Yu Xiao:** Data curation. **Liming Qing:** Writing – review & editing. **Juyu Tang:** Writing – review & editing, Funding acquisition. **Panfeng Wu:** Writing – review & editing, Writing – original draft, Funding acquisition.

Data and code availability statement

No data was used for the research described in the article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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