Effects of miRNAs, lncRNAs and circRNAs on osteoporosis as regulatory factors of bone homeostasis (Review)

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Abstract. Osteoporosis is a common metabolic bone disorder typically characterized by decreased bone mass and an increased risk of fracture. At present, the detailed molecular mechanism underlying the development of osteoporosis remains to be elucidated. Accumulating evidence shows that non-coding (nc)RNAs, such as microRNAs (miRNAs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs), play significant roles in osteoporosis through the post-transcriptional regulation of gene expression as regulatory factors. Previous studies have demonstrated that ncRNAs participate in maintaining bone homeostasis by regulating physiological and developmental processes in osteoblasts, osteoclasts and bone marrow stromal cells. In the present review, the latest research investigating the involvement of miRNAs, lncRNAs and circRNAs in regulating the differentiation, proliferation, apoptosis and autophagy of cells that maintain the bone microenvironment in osteoporosis is summarized. Deeper insight into the aspects of osteoporosis pathogenesis involving the deregulation of ncRNAs could facilitate the development of therapeutic approaches for osteoporosis.

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Abbreviations: miRNAs, microRNAs; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; OB, osteoblast; OC, osteoclast; BMSCs, bone marrow stromal cells; PPARγ, peroxisome proliferator-activated receptor γ; Runx2, runt-related transcription factor 2; TGF-β, transforming growth factor-β; ROS, reactive oxygen species; YAP, yes-associated protein

Key words: osteoporosis, miRNA, lncRNA, circRNA, bone homeostasis

Contents

1. Introduction

Osteoporosis is a highly prevalent skeletal disorder associated with the ageing of the global population that imposes a considerable burden on health care and society, and is characterized by the deterioration of bone tissue and increased bone fragility due to the loss of bone mass and microstructure attributed to various factors, including menopause, ageing and related adverse reactions to medications (1). Bone and fat mass imbalance constitute a typical feature of the pathogenesis of osteoporosis (2). In Europe, an estimated 22 million women and 5.5 million men suffer from osteoporosis (3), and an estimated 10 million individuals over the age of 50 have osteoporosis in the USA (4). As the population of the world rapidly ages, an increasing number of individuals will suffer from osteoporosis.

Bone homeostasis is maintained mainly by intricate mechanisms synchronizing osteoblast (OB) activation with osteoclast (OC) activation, thus coupling bone formation with bone resorption (5). OBs, the cells responsible for bone formation, are believed to originate from bone marrow stromal cells (BMSCs). Osteoclasts are derived from mononuclear haematopoietic myeloid lineage cells that influence bone resorption. In addition to OBs and OCs, BMSCs, adipocytes and chondrocytes present in the microenvironment also participate in bone homeostasis (6). BMSCs, which are a key cause of osteoporosis, play an important role in maintaining the balance between bone formation and resorption. Previous findings have shown that BMSCs can normally differentiate into OBs, chondrocytes and adipocytes, but in the elderly, the differentiation of BMSCs into OBs decreases. Such changes

lead to a decrease in bone formation, which, in turn, leads to osteoporosis, and the underlying mechanism remains to be elucidated (7).

Non-coding (nc)RNAs, including microRNAs (miRNAs/miRs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs), play an important role as regulators in cellular processes, such as cell proliferation, differentiation, apoptosis and autophagy. miRNAs constitute a class of ncRNAs that are ~22 nucleotides in length, can recognize the 3'-untranslated regions (UTRs) of target mRNAs by means of complementary base pairing and degrade or repress the gene expression of target mRNAs at the post-transcriptional level (8). lncRNAs are a type of ncRNA with a length >200 nucleotides that can bind substrates through their own nucleotide sequence or folded secondary structure and regulate gene expression through multiple mechanisms at the transcriptional and post-transcriptional levels (9). circRNAs, which are formed mainly by reverse splicing, are endogenous covalent closed circRNA molecules that can act as miRNA sponges to regulate miRNA-related cellular processes (9).

Accumulating evidence has confirmed the crucial roles of ncRNAs in bone metabolism by regulating the differentiation, proliferation, apoptosis and autophagy of bone homeostasis-related cells. Jin *et al* (10) identified 260 circRNAs, 70 lncRNAs and 13 miRNAs that were differentially expressed between patients with postmenopausal osteoporosis and healthy controls using Illumina-based deep sequencing. Eskildsen *et al* (11) showed that miRNA-138 was related to the osteogenic differentiation of hMSCs and that the overexpression of miR-138 inhibited the OB differentiation of hMSCs. The lncRNA Xist was found to sponge miR-19a-3p to repress BMSC osteogenic differentiation in ageing-induced osteoporosis (12). Owing to the development of deep sequencing technology, an increasing number of biologically significant ncRNAs affecting bone metabolism and osteoporosis have been studied. Although the current therapies for osteoporosis, such as bisphosphonates, denosumab, teriparatide and selective oestrogen receptor modulators, are effective in restoring bone strength, they inadvertently reduce bone strain and are generally inadequate in preventing hip and non-vertebral fractures (13). Emerging evidence has indicated that ncRNAs play a crucial role in bone remodelling and degeneration in osteoporosis (9). In the present review, the latest studies are summarized to clarify the important role of miRNAs, lncRNAs and circRNAs involved in the regulation of OBs, OCs and BMSCs that affect bone metabolism in osteoporosis, which could provide a theoretical basis for exploring the pathogenesis and potential of clinical treatment for osteoporosis.

2. Mechanisms by which ncRNAs regulate BMSCs in osteoporosis

BMSCs have the capacity to differentiate into various bone-related cells, such as OBs, adipocytes and chondrocytes. Emerging studies have revealed that the abnormal differentiation capacities of BMSCs play a crucial role in this critical pathogenesis of osteoporosis (14). However, in the elderly, the degree of osteoblastic differentiation of BMSCs is lower than that of adipogenic differentiation, leading to a decrease in bone formation. Therefore, the number and function of BMSCs play a key role in osteoporosis, and the fine regulation of BMSCs plays an important role in maintaining bone homeostasis (7). Previous findings showed that peroxisome proliferator-activated receptor γ (PPARγ), core binding factor α1, osterix and runt-related transcription factor 2 (Runx2) are crucial regulators of differentiation towards adipogenesis or osteogenesis (15), and thus far, the most explored signalling pathway associated with OB differentiation is the Runx2 axis. Recent research indicates that epigenetic regulation is crucial and contributes to osteoporosis by regulating the differentiation, proliferation and apoptosis of BMSCs, and it is necessary to further study the role of ncRNA-mediated autophagy in osteoporosis (9).

Effects of miRNAs on BMSC regulation. miRNAs play crucial roles in regulating BMSC differentiation, proliferation and apoptosis. Several studies have proven the important roles of miRNAs in regulating the osteoclastic, osteoblastic, adipogenic and chondrogenic differentiation of BMSCs to maintain bone metabolic homeostasis (11,16). miRNAs involved in metabolic homeostasis and bone formation are novel targets for the treatment of bone-related diseases. As previously reported, miR-31a-5p derived from aged BMSCs reduced osteoblastogenesis via the SATB2 pathway and promoted osteoclastogenesis via the RhoA pathway in ageing bone tissue, leading to osteoporotic bone loss. The application of antagomiR-31a-5p reduced age-associated bone loss, suggesting that it is a potential biological therapy for age-related osteoporosis (17). Moura *et al* (18) reported that miR-99a-5p was significantly downregulated during the early stages of human primary MSC osteogenic differentiation and during MC3T3 osteogenic differentiation. It was found that the inhibition of miR-99a-5p promoted osteogenic differentiation and that the expression of miR-99a-5p was increased during OC differentiation, indicating that miR-99a-5p is a positive regulator of osteoclastogenic differentiation and a target candidate for osteoporosis (18). Zhou *et al* (19) found that the expression of miR-1286 in the serum of patients with osteoporosis was significantly higher than that in the serum of healthy controls. This level of expression decreased as the number of days of osteogenic differentiation of human amnion-derived mesenchymal stem cells increased, indicating that miR-1286 participates in the regulation of osteogenic differentiation and can inhibit the osteogenic differentiation of hMSCs by binding frizzled class receptor 4, leading to the development of osteoporosis. miR-199a-3p was documented as a biomarker of osteoporosis in a model of ovariectomized mice (20). A previous study highlighted the fact that miR-199a-3p plays a crucial role during adipocyte differentiation in ovariectomized mice (21). In addition, Chen *et al* (22) revealed that miR-199a-3p participates in the inhibition of cardiomyocyte differentiation in stem cells via the MEF2C pathway. Recently, Wu *et al* (23) found that miR-199a-3p expression was increased in ovariectomized mice and that the upregulation of miR-199a-3p inhibited the osteogenic differentiation of BMSCs *in vitro*. Furthermore, it was revealed that miR-199a-3p regulated the osteogenic differentiation of BMSCs mainly by targeting Kdm3a (23). miR-23 was found to be upregulated in osteoporosis patients compared with healthy populations, and downregulated in the

osteogenic differentiation of hBMSCs (24). Further experiments indicated that miR-23 could bind MEF2C to inhibit osteogenic differentiation (24). Yin *et al* (25) reported that the level of miR-129-5p expression in all osteoporosis models was changed and that the overexpression of miR-129-5p repressed OB differentiation in the MC3T3-E1 cell line and bone formation in an animal model. It was also found that miR-129-5p could regulate transcription factors in the Wnt/β-catenin pathway by binding Tcf4. Moreover, a miR-129-5p inhibitor could rescue the effect on osteoporosis, providing a novel target candidate for the condition.

In addition to mediating the inhibition of OB differentiation, miRNAs also play key regulatory roles in promoting OB differentiation. miR-218 has been reported to function as a specific suppressor in various types of cancer, such as nasopharyngeal and colorectal cancer (26,27). Recently, the role of miR-218 in postmenopausal osteoporosis was reported. miR-218-5p was found to be downregulated in BMSCs during OB differentiation, and miR-218-5p could regulate its target COL1A1 to promote OB differentiation, indicating that this miRNA may be a target for the treatment of postmenopausal osteoporosis (28). Similarly, Zhang *et al* (29) showed that miR-664a-5p expression was upregulated during the osteogenic differentiation of human BMSCs and that this miRNA could bind to the mRNA of HMGA2, a direct target of miR-664a-5p, to promote the osteogenic differentiation of BMSCs, which may provide new effective methods for osteoporosis therapy. Qi *et al* (30) reported that miR-199a-5p, which is upregulated during the induction of OB differentiation in hBMSCs, increased ALP activity and the calcification of hBMSCs, and promoted the OB differentiation of hBMSCs by targeting TET2 to downregulate its expression.

Zhang *et al* (31) identified that the expression of miR-199b-5p was increased during the transforming growth factor-β (TGF-β)-induced chondrogenic differentiation of MSCs, the latter of which was regulated by miR-199b-5p by targeting JAG1. In addition, miR-8485 derived from chondrocytes were able to activate the Wnt/β-catenin pathways to promote the chondrogenic differentiation of BMSCs (32). Shen *et al* (33) observed that the expression of miRNA-23c was significantly decreased during the process of chondrocyte differentiation of MSCs. The study found that miRNA-23c can regulate FGF2 expression to inhibit chondrogenic differentiation. SMADs are crucial mediators of canonical TGF-β. Similarly, SMADs are involved in the process of chondrogenesis. Recent findings have shown that miR-134 expression was downregulated during chondrogenesis and that miR-134, by interacting with SMAD6, acted as a negative regulator during the chondrogenic differentiation of BMSCs (34).

It has been reported that miR-149-3p inhibits the expression of fat mass- and obesity-associated genes by targeting the 3'-UTR of FTO mRNA. Additionally, miR-149-3p anti-miRNA oligonucleotides can promote the adipogenic differentiation of BMSCs and repress the osteoblastic differentiation of BMSCs, indicating that miR-149-3p, a prospective candidate target for the treatment of osteoporosis, can regulate the adipogenic differentiation of BMSCs through the miR-149-3p/FTO regulatory pathway (35). Several studies have shown that PPARγ, a key regulatory factor in adipocyte formation, is highly expressed in the early stage of adipogenesis (36,37). Lin *et al* (38) demonstrated that the expression level of miR-130a was decreased during ageing and that the decreased expression of miR-130 caused the upregulation of PPARγ, a direct target of miR-130, leading to the adipogenic differentiation of BMSCs. Jamali *et al* first reported the role of miR-100-3p, a regulatory factor of cellular apoptosis and proliferation in gastric cancer (39), in the regulation of the adipogenic differentiation of hMSCs and found that miR-100-3p plays an important role in regulating the adipogenic differentiation in hMSCs through the PI3K/AKT pathway by targeting PIK3R1 (40). Previous findings have shown that miRNAs also play a role in promoting the adipogenic differentiation of BMSCs. Zhu *et al* (41) reported that miR-20a-5p was upregulated during the adipogenic differentiation of BMSCs and could bind Klf3, an inhibitory factor of adipogenic differentiation, to promote adipocyte differentiation.

Emerging evidence has shown that miRNAs play a crucial role in BMSC proliferation. Cui *et al* (42) studied the regulatory role of miR-146a in BMSC proliferation for the first time. It was found that the knockdown of miR-146a could promote BMSC proliferation and that miR-146a could suppress the expression of SNHG7 and EPB41L4A-AS1, leading to the inhibition of BMSC proliferation. Kong *et al* (43) reported that miR-126 plays a key role in promoting the proliferation and migration of BMSCs through the PI3K/AKT and MEK1/ERK1 signalling pathways. The level of miP-144 in clinical serum samples obtained from patients with postmenopausal osteoporosis was found to be higher than that in normal populations, and further studies showed that miR-144 could promote proliferation and inhibit apoptosis in BMSCs to regulate osteoporosis via the Wnt/β-catenin pathway (44).

Accumulating studies indicate the crucial regulatory roles of exosomal miRNAs in various bone diseases. Yang *et al* (45) showed that miR-1263 derived from exosomes of HUCMSCs played a role in inhibiting apoptosis in BMSCs, and further experiments verified that miR-1263 directly targeted the 3'-UTR of Mob1 to suppress the expression of Mob1 to inhibit BMSC apoptosis in disuse osteoporosis by activating Yes-associated protein (YAP). Previous studies reported that miR-181c could regulate the viability of cancer cells under reactive oxygen species (ROS) stress by sustaining the function of mitochondria (46,47). Fan *et al* (48) revealed that miR-181c could reverse the effects of oxidative stress on BMSCs and attenuate oxidative stress-mediated BMSC apoptosis mainly through the AMPK-Mfn1 pathway. Increasing studies indicate that BMSCs are relatively radiosensitive. Ionizing radiation could induce BMSC apoptosis via ROS generation and accumulation in mitochondria. Liu *et al* (49) found that miR-22 was significantly upregulated in BMSCs after ionizing radiation exposure and that the overexpression of miR-22 in BMSCs accelerated the ionizing radiation-induced accumulation of mitochondrial ROS, thus resulting in cellular apoptosis. Furthermore, the study verified that the apoptosis of BMSCs induced by mitochondrial ROS generation is mainly dependent on the miR-22/Redd1 pathway (Table I).

Effects of lncRNAs on regulation of BMSCs. Numerous studies have concluded that lncRNAs play various vital roles in cell biology (50-52). Recent findings have indicated that lncRNAs are involved in BMSC differentiation and proliferation in

Table I. Roles of miRNAs in the regulation of bone marrow stromal cells.

First author, year	miRNA	Target gene	Role	(Refs.)
Xu *et al*, 2018	miR-31a-5p	SATB2, RhoA	Promote osteoclastic differentiation	(17)
Moura *et al*, 2020	miR-99a-5p	NA	Promote osteoclastic differentiation and inhibit osteoblastic differentiation	(18)
Zhou *et al*, 2020	miR-1286	FZD4	Inhibit osteoblastic differentiation	(19)
Wu *et al*, 2021	miR-199a-3p	Kdm3a	Inhibit osteoblastic differentiation	(23)
Jiang *et al*, 2020	miR-23	MEF2C/MAPK signalling pathway	Inhibit osteoblastic differentiation	(24)
Yin *et al*, 2020	miR-129-5p	Tcf4, Wnt/β-catenin pathway	Inhibit osteoblastic differentiation	(25)
Kou *et al*, 2020	miR-218-5p	COL1A1	Promote osteoblastic differentiation	(28)
Zhang *et al*, 2020	miR-664a-5p	HMGA2	Promote osteoblastic differentiation	(29)
Qi *et al*, 2020	miR-199a-5p	TET2	Promote osteoblastic differentiation	(30)
Zhang *et al*, 2020	miR-199b-5p	JAG1	Promote chondrogenic differentiation	(31)
Li *et al*, 2020	miR-8485	Wnt/β-catenin pathways	Promote chondrogenic differentiation	(32)
Shen *et al*, 2019	miRNA-23c	FGF2	Inhibit chondrogenic differentiation	(33)
Xu and Wu 2019	miR-134	SMAD6	Inhibit chondrogenic differentiation	(34)
Li *et al*, 2019	miR-149-3p	FTO	Inhibit adipogenic differentiation	(35)
Lin *et al*, 2019	miR-130	PPARγ	Inhibit adipogenic differentiation	(38)
Wang *et al*, 2020	miR-100-3p	PI3K/AKT pathway	Inhibit adipogenic differentiation	(40)
Zhu *et al*, 2018	miR-20a-5p	Klf3	Promote adipogenic differentiation	(41)
Cui *et al*, 2020	miR-146a	EPB41L4A-AS1/ SNHG7	Inhibit proliferation	(42)
Kong *et al*, 2020	miR-126	PI3K/AKT and MEK1/ERK1 pathway	Promote proliferation and migration	(43)
Tang *et al*, 2019	miR-144	Sfrp1/Wnt/ β-catenin	Promote proliferation and inhibit apoptosis	(44)
Yang *et al*, 2020	miR-1263	Mob1/Hippo signalling pathway	Inhibit apoptosis	(45)
Fan *et al*, 2020	miR-181c	AMPK-Mfn1	Inhibit apoptosis	(48)
Liu *et al*, 2019	miR-22	Redd1	Promote apoptosis	(49)

miRNA/miR, microRNA; NA, not applicable.

osteoporosis. The switch between the adipogenic and osteogenic differentiation of BMSCs plays an important role in ageing-induced osteoporosis. miR-19a-3p is able to regulate OB differentiation in BMSCs by regulating Hoxa5 expression, and lncRNA Xist, as a sponge of miR-19a-3p, plays a crucial role in OB differentiation by binding miR-19a-3p in BMSCs (12). Recently, Zhang *et al* (53) found that the expression of the lncRNA LOXL1-AS1 was high in the peripheral blood from patients with osteoporosis and that this gradually decreased during the process of osteogenic differentiation of hBMSCs. Furthermore, it was revealed that LOXL1-AS1 inhibited osteogenic differentiation but promoted adipocytic differentiation in hBMSCs, mainly by sponging miR-196a-5p to regulate Hmga2 expression (53). A report showed that the expression of the lncRNA HCG18 was increased in BMSCs from osteoporosis patients and that HCG18 expression was significantly decreased during the process of the differentiation of OB BMSCs, indicating that HCG18 plays an important role in BMSC differentiation (54). Subsequently, the study reported that HCG18, as a regulator of osteogenic differentiation, repressed the osteogenic differentiation of BMSCs induced by osteoporosis through the miR-30a-5p/NOTCH1 pathway (54).

Li *et al* (55) previously found that the lncRNA GAS5 plays a crucial role in negatively regulating lipoblast/adipocyte differentiation in humans and identified that GAS5 was downregulated in bones and BMSCs from osteoporosis patients. Specifically, the study concluded that GAS5 promotes OB differentiation in BMSCs by regulating the UPF1/SMAD7 pathway and protects against osteoporosis (55). Similarly,

Zheng *et al* (56) reported that lncSNHG5 promoted osteogenic differentiation in hBMSCs by competitively targeting miR-582-5p to regulate RUNX3 expression, indicating that SNHG5 may be a novel target candidate for osteoporosis therapy. MIR22HG expression was found to be significantly downregulated in BMSCs from osteoporotic mice and was increased during the process of human BMSC osteogenic differentiation. Mechanistically, MIR22HG promotes the osteogenic differentiation of BMSCs by downregulating phosphatase and tensin homologue and activating the AKT pathway, indicating that MIR22HG plays a crucial role in bone metabolism and may be a novel target for osteoporosis (57).

lncRNAs have emerged as crucial regulators of cell differentiation. However, the potential regulatory function of lncRNAs in BMSC chondrogenic differentiation remains poorly studied. The lncRNA ADAMTS9-AS2 was found to be upregulated during the chondrogenesis of hMSCs using microarray analysis, and ADAMTS9-AS2 acted as a ceRNA for miR-942-5p, thereby playing a crucial role in regulating chondrogenic differentiation, and promoted chondrogenic differentiation of hMSCs (58). Recent findings showed that ADAMTS9-AS2 can inhibit oesophageal cancer development by inducing CDH3 promoter methylation (59). Shu *et al* (60) reported that the lncRNA UCA1 was upregulated during the chondrogenic differentiation of BMSCs. Subsequently, it was found that the chondrogenic differentiation of BMSCs was promoted by UCA1 mainly through the miR-145-5p/SMAD5 and miR-124-3p/SMAD4 pathways. In another study, UCA1 was found to be significantly upregulated in patients with osteoporosis and was indicated to promote the proliferation and differentiation of OBs by regulating the BMP-2 pathway in OBs (61).

Pan *et al* (62) reported that the expression of lncRNA ROA, which promotes hnRNP A1 to target the PTX3 promoter, thereby activating the ERK1/2 signalling pathway and regulating BMSC adipogenic differentiation, was significantly decreased during the process of BMSC adipogenesis. The lncRNA Plnc1, which is derived from the PPAR-γ2 gene, was upregulated during the adipogenic differentiation of ST2 cells and BMSCs, and further investigation showed that Plnc1 decreased methylation of the CpG region in the PPAR-γ2 promoter, thereby promoting PPAR-γ2 transcription, indicating that Plnc1 plays an important role in promoting adipogenic differentiation (63). In addition, Zhang *et al* (53) showed that LOXL1-AS1 could also promote adipocytic differentiation.

The lncRNA NORAD iss decreased in steroid-induced osteonecrosis in femoral head tissues, and findings of a mechanistic study indicated that NORAD could target miR-26a-5p to promote the DEX-induced inhibition of proliferation in hBMSCs (64). However, numerous studies have concluded that NORAD also plays a crucial role in cellular processes involved in carcinogenesis, including cell proliferation, invasion and metastasis (65), indicating that the function of NORAD is complex and that further studies are needed. In another study, the inhibition of the lncRNA LINC01535 decreased the proliferation of hBMSCs, and the regulatory effect of LINC01535 on BMSCs was found to be mediated mainly by targeting miR-3619-5p (66). Gan *et al* (67) reported that the expression of the lncRNA H19 was significantly decreased in postmenopausal patients with osteoporosis and that the overexpression of H19 obviously inhibited BMSC proliferation by targeting miR-19b-3p, demonstrating the crucial role of H19/miR-19b-3p in osteoporosis for the first time and providing a novel target for osteoporosis. Recent evidence has indicated that autophagy has a critical effect on the pathogenesis of acute pancreatitis and that the overexpression of H19 in MSCs significantly inhibits autophagy via the FAK/PDK1/AKT/mTOR axis in rats with acute pancreatitis (68).

Li *et al* (69) identified that downregulated expression of the lncRNA LNC_000052 inhibited BMSC apoptosis through the PI3K/Akt pathway, and further investigations showed that LNC_000052 regulates BMSC apoptosis mainly by binding PIK3R1, which is also a target of miR-96-5p. In addition to the regulation of apoptosis, it was found that LNC_000052 plays a crucial role in BMSC proliferation and migration via the miR-96-5p-PIK3R1 axis (69). Knockdown of the lncRNA SNHG5 promoted apoptosis in hBMSCs, and further results demonstrated that SNHG5 inhibited apoptosis through the miR-582-5p/RUNX3 pathway (56). Similarly, SNHG5 has been reported to play an important role in human chronic myelogenous leukaemia by inhibiting cell apoptosis (70). Another study also reported that LINC01535 could inhibit hBMSC apoptosis by regulating miR-3619-5p (66) (Table II).

Effects of circRNAs on BMSC regulation. circRNAs are transcribed from exons that have a cell- or tissue-specific expression profile, and circRNA expression in tissues is highly stable due to their resistance to RNase degradation. Emerging studies have revealed that circRNAs play a crucial role in the regulation of cellular functions by sponging miRNAs or interacting with RNA-binding proteins (71,72). However, few studies have demonstrated the role of circRNAs in regulating BMSCs in osteoporosis. Wang *et al* (73) found that circ_0006393 expression was decreased in patients with glucocorticoid-induced osteoporosis, and further experiments revealed that the increased expression of circ_0006393 promoted the expression of osteogenesis-associated genes by targeting miR-145-5p. An abnormally low expression level of circ_0076906 was reported for the first time in osteoporosis; however, the roles of this circRNA in regulating osteoporosis are poorly understood (74). Wen *et al* (75) found that circ_0076906 promoted the osteogenic differentiation of hMSCs and relieved osteoporosis by binding miR-1305 to regulate osteoglycin expression. Shen *et al* (76) showed that circFOXP1 was significantly decreased in bone tissues from patients with osteoporosis, and *in vitro* and *in vivo* analyses indicated that circFOXP1 can sponge miR-33a-5p, promote the osteogenic differentiation of human adipose-derived mesenchymal stem cells and prevent osteoporosis by regulating FOXP1, revealing that circFOXP1 can be used as a novel candidate therapeutic target for osteoporosis. In another study, circFOXP1 was highly expressed in MSCs compared with differentiated mesodermal derivatives, and it was indicated to play a critical role in sustaining the identity of MSCs by regulating the Wnt and EGFR pathways (77). In addition, circFOXP1 was involved in the regulation of cancer cell proliferation (78). Liu *et al* (79) screened the differential expression of circRNAs in postmenopausal patients with

Table II. Roles of lncRNAs in regulation of bone marrow stromal cells.

First author, year	lncRNA	Target gene	Role	(Refs.)
Chen *et al*, 2020	Xist	miR-19a-3p	Inhibit osteoblastic differentiation	(12)
Zhang *et al*, 2020	LOXL1-AS1	miR-196a-5p	Inhibit osteoblastic differentiation promote adipogenic differentiation	(53)
Che *et al*, 2020	HCG18	miR-30a-5p/ NOTCH1	Inhibit osteoblastic differentiation	(54)
Li *et al*, 2020	GAS5	UPF1/SMAD7	Promote osteoblastic differentiation	(55)
Zheng *et al*, 2020	SNHG5	miR-582-5p/ RUNX3	Promote osteoblastic differentiation, inhibit apoptosis	(56)
Jin *et al*, 2020	MIR22HG	PTEN/AKT	Promote osteoblastic differentiation	(57)
Huang *et al*, 2019	ADAMTS9-AS2	miR-942-5p	Promote chondrogenic differentiation	(58)
Shu *et al*, 2019	UCA1	miR-145-5p/ miR-124-3p	Promote chondrogenic differentiation	(60)
Pan *et al*, 2020	ROA	hnRNP A1-PTX3-ERK	Inhibit adipogenic differentiation	(62)
Zhu *et al*, 2019	Plnc1	PPAR-γ2	Promote adipogenic differentiation	(63)
Fu *et al*, 2021	NORAD	miR-26a-5p	Promote proliferation	(64)
Zhao *et al*, 2020	LINC01535	miR-3619-5p	Promote proliferation, inhibit apoptosis	(66)
Gan *et al*, 2020	H19	miR-19b-3p	Inhibit proliferation	(67)
Li *et al*, 2020	LNC_000052	PIK3R1	Promote apoptosis, inhibit proliferation	(69)

lncRNA, long non-coding RNA; miR, microRNA.

osteoporosis using RNA-seq and found that circ_0007059 expression was increased in patients and during the OC differentiation of hBMSCs. Furthermore, circRNAs play a crucial role in OC differentiation by regulating the miR-378/BMP-2 pathway (79). In addition, circ_0007059 plays a critical role in lung cancer cell proliferation (80). Huang *et al* (81) found that YAP1 can promote BMSC and MC3T3-E1 osteogenic differentiation, and that circ_0024097, which is derived from YAP1, can target miR-376b-3p to regulate YAP1 expression, leading to increased osteogenic differentiation.

Zhang *et al* (82) documented for the first time that circ-DAB1 is upregulated during the osteogenic differentiation of BMSCs. Chia *et al* (83) later verified via RT-qPCR that circ-DAB1 expression is significantly increased during the osteogenic differentiation of BMSCs. A mechanistic study revealed that circ-DAB1 increases the proliferation and osteogenic differentiation of BMSCs through the NOTCH/RBPJ pathway (83). Chen *et al* (84) screened differentially expressed circRNAs in BMSCs from patients with steroid-induced osteonecrosis in the femoral head and found that the circRNA CDR1as was upregulated. It was revealed that circRNA CDR1as plays an important role in regulating the adipogenic and osteogenic differentiation of BMSCs (84). However, whether the circRNA CDR1as also participates in the regulation of BMSCs from patients with osteoporosis needs to be determined.

Recently (85), circRNA_25487 was found to be upregulated in the peripheral blood of patients with trauma-induced osteonecrosis of the femoral head (TIONFH), and the functions of circRNA_25487 in bone repair in TIONFH were studied using BMSCs. Zhang *et al* (85) revealed that circRNA_25487 promotes apoptosis and inhibits proliferation in BMSCs by binding miR-134-3p to promote p21 expression, which promotes bone repair in TIONFH. However, the role of circRNA_25487 in osteoporosis remains to be elucidated via further research.

Autophagy has pivotal functions in sustaining cell homeostasis by removing damaged macromolecules and organelles during oxidative stimulation or starvation (86). Autophagy is crucial for recycling cell components and promoting BMSC osteogenesis by eliminating ROS, which help maintain bone homeostasis (49). Previous findings have shown the relationship between circRNAs and autophagy in a number of conditions, such as sciatic nerve injury and thyroid cancer (87). However, the correlations between circRNAs and autophagy in osteoporosis remain unclear (Table III).

3. Mechanisms by which ncRNAs regulate OBs in osteoporosis

Osteoblasts, which are derived from multipotent mesenchymal stem cells, have an important function in maintaining bone microstructure and homeostasis, and the dysregulation of OB number or activity is related to the pathophysiology of bone disorders, such as osteoporosis (88). Numerous studies have revealed that miRNAs, lncRNAs and circRNAs are crucial factors involved in OB proliferation, differentiation, autophagy and apoptosis in osteogenesis.

Table III. Roles of circRNAs in the regulation of bone marrow stromal cells.

First author, year	circRNA	Target gene	Role	(Refs.)
Wang *et al*, 2019	circ_0006393	miR-145-5p	Promote osteoblastic differentiation	(73)
Wen *et al*, 2020	circ_0076906	miR-1305	Promote osteoblastic differentiation	(75)
Shen *et al*, 2020	circFOXP1	miR-33a-5p	Promote osteoblastic differentiation	(76)
Huang *et al*, 2020	circ-0024097	miR-376b-3p/ YAP1	Promote osteoblastic differentiation	(81)
Chia *et al*, 2020	circ-DAB1	NOTCH/RBPJ	Promote proliferation and osteoblastic differentiation	(83)
Chen *et al*, 2020	circ-CDR1	miR-7-5p/ WNT5B	Promote adipogenic and inhibit osteoblastic differentiation	(84)
Zhang *et al*, 2021	circ_25487	miR-134-3p/ p21	Promote apoptosis and inhibit proliferation	(85)

circRNA, circular RNA; miR, microRNA.

Effects of miRNAs on OB regulation. miRNAs have been documented to play pivotal roles in the regulation of OB biology. Numerous studies have concluded that miRNAs are involved in the regulation of the osteogenic differentiation of mesenchymal precursor cells. One previous study found that miR-197-3p expression was significantly increased in a number of cancer types, including lung cancer, indicating that miR-197-3p plays an important role in the development of tumours by promoting cell proliferation (89). You *et al* (90) demonstrated that miR-197-3p expression was upregulated in a rat model of osteoporosis, and further research revealed that miR-197-3p inhibits OB differentiation by regulating KLF10 in osteoporosis. Emerging evidence has elucidated that miR-122 is a diagnostic and prognostic biomarker for osteoporosis. Seeliger *et al* (91) reported that miR-122 expression was significantly increased in serum samples from patients with osteoporosis. A recent study reported that miR-122 was upregulated in OBs originating from ovariectomized rats, and further investigation revealed that miR-122 could inhibit OB proliferation and differentiation by activating the JNK pathway and suppressing PCP4 expression (13). Recent studies have shown that miR-205-5p is involved in regulating the proliferation of various cells, such as retinal pigment epithelial cells, thymic epithelial cells and pancreatic cancer cells (92-94). Recently, Huang *et al* (95) revealed that miR-205-5p expression was increased in samples from patients with osteoporosis and then was gradually downregulated during osteogenic differentiation. Moreover, it was concluded that miR-205-5p could inhibit osteogenic differentiation by regulating RUNX2 expression. Previous findings showed that miR-22-3p expression was high in extracellular vesicles originating from BMSCs, and that the abundance of miR-22-3p was also high in extracellular vesicles derived from plasma (96,97). A current study revealed that miR-22-3p, which is delivered by BMSC-derived extracellular vesicles, promotes osteogenic differentiation in BMSCs via the MYC/PI3K/AKT signalling pathway by inhibiting FTO (98).

Previously, it was revealed that miR-150-3p is a regulatory factor of inflammatory signalling pathways and that the osteogenic differentiation of hBMSCs may play an important role in modulating inflammation during bone formation (99). The latest research highlighted that miR-150-3p can promote OB proliferation in osteoporosis and identified it as a novel clue for osteoporosis therapy (100). Ma *et al* (101) documented that the expression of miR-497-5p, which is considered a clinically significant biomarker for osteoporosis, was downregulated in bone tissues from ageing mice and played an important role in the metabolism of bone. In addition, it was reported that miR-497 was decreased in breast cancer (102). Recently, Gu *et al* (103) declared that miR-497 expression is decreased in osteoporosis and that increased miR-497 promotes OB proliferation by regulating the TGF-β1/Smad signalling pathway, alleviating the progression of osteoporosis. miR-214 was previously reported to play a role in osteoporosis by regulating the expression of osterix in bones (104). Another study indicated that miR-214 could protect MC3T3-E1 OBs against apoptosis by repressing oxidative stress (105). Yang *et al* (106) demonstrated that the expression of miR-214 in femoral tissues from osteoporosis rats was low and that the overexpression of miR-214 could promote OB proliferation by repressing TXNIP, which could provide a novel therapeutic target for osteoporosis. miR-15b is known to participate in the occurrence of osteoporosis and plays a role in OB differentiation in bone diseases (20,107). Recent findings indicated that the expression of miR-15b was upregulated in mice with osteoporosis and that miR-15b can suppress OB proliferation, which could aggravate osteoporosis by targeting USP7 and regulating KDM6B expression, providing a new target for osteoporosis treatment (108).

The dysregulation of miR-142 has been identified in numerous diseases. miR-142 is related to malignancy in breast cancer stem cells via the WNT pathway (109). In addition, miR-142 plays a role in regulating the growth and apoptosis of airway smooth muscle cells. Importantly, miR-142 promotes the osteoclastogenesis of bone marrow-originated macrophages by regulating PTEN and the PI3K/Akt/FoxO1 axis, indicating the regulatory function of miR-142 in osteoporosis (110). Recently, Luo *et al* (111) revealed that miR-142 could promote apoptosis and inhibit proliferation in MC3T3-E1 cells by targeting the

Table IV. Roles of miRNAs in the regulation of osteoblasts.

First author, year	miRNA	Target gene	Role	(Refs.)
You *et al*, 2021	miR-197-3p	KLF10	Inhibit differentiation	(90)
Meng *et al*, 2020	miR-122	PCP4/JNK	Inhibit differentiation and proliferation	(13)
Huang *et al*, 2020	miR-205-5p	RUNX2	Inhibit differentiation	(95)
Zhang *et al*, 2020	miR-22-3p	FTO/MYC/PI3K/AKT	Promote differentiation	(98)
Qiu *et al*, 2021	miR-150-3p	NA	Promote proliferation and differentiation	(100)
Gu *et al*, 2020	miR-497	TGF-β1/Smads	Promote proliferation	(103)
Yang *et al*, 2021	miR-214	TXNIP	Promote proliferation	(106)
Lu *et al*, 2021	miR-15b	USP7/KDM6B	Inhibit autophagy, proliferation, and differentiation	(108)
Luo *et al*, 2020	miR-142	BMP/Smad	Promote apoptosis	(111)
Hu *et al*, 2020	miR-491-3p	CTSS	Inhibit apoptosis	(112)
Zhang *et al*, 2020	miR-708	PTEN	Inhibit apoptosis	(113)

miRNA/miR, microRNA; NA, not applicable.

BMP/Smad signalling pathway. miR-491-3p expression was found to be downregulated in postmenopausal osteoporosis, and the overexpression of miR-491-3p enhanced the viability and suppressed the apoptosis of hFOB1.19 cells by regulating cathepsin S (CTSS) (112). Similarly, Zhang *et al* (113) revealed that miR-708 plays a role in protecting MC3T3-E1 cells by inhibiting apoptosis induced by H_2O_2 by targeting PTEN expression.

Autophagy is a stress-responsive catabolic process that plays a critical role in maintaining cellular and tissue homeostasis. In addition, autophagy can facilitate osteogenic differentiation to preserve bone homeostasis. However, dysregulation of autophagy in bone cells can cause a series of bone diseases, such as osteoporosis, and the activation of autophagy in OCs is related to bone loss. Recently, Lu *et al* (108) disclosed that the overexpression of miR-15b could depress USP7 expression, which could inhibit the autophagy, proliferation and differentiation of OBs, and lead to osteoporosis by suppressing KDM6B expression (Table IV).

Effects of lncRNAs on regulation of OBs. The inhibition of OB differentiation has been confirmed to be a crucial regulator of osteoporosis, and emerging evidence has indicated that lncRNAs may be treated as targets for osteoporosis treatment. Yin *et al* (114) recently revealed that the lncRNAs AK039312 and AK079370 are involved in inhibiting OB differentiation and bone formation by targeting miR-199b-5p, and that upregulated GSK-3β further suppresses the Wnt/β-catenin signalling pathway. Moreover, it was revealed that small interfering RNAs targeting AK039312 and AK079370 could relieve postmenopausal osteoporosis in mice, providing a novel direction for the treatment of osteoporosis. The lncRNA DANCR was previously found to be deregulated in human circulating monocytes and to play a key role in osteoporosis (115). Wang *et al* (116) reported the dysregulation of DANCR in patients with osteoporosis and an ovariectomy model, and DANCR expression in BMSCs originating from osteoporosis patients was increased. In addition, DANCR can suppress osteogenic differentiation in osteoporosis by suppressing the Wnt/β-catenin signalling pathway by regulating CTNNB1 expression (116).

The lncRNA MEG3 has previously been reported to inhibit the osteogenic differentiation of BMSCs in postmenopausal osteoporosis (117). Yang *et al* (106) suggested that the downregulation of MEG3 can promote the differentiation and proliferation of OBs in osteoporosis by targeting miR-214 and depressing TXNIP expression. The dysregulation of lncRNA CCAT1 is involved in a number of human diseases. Recently, Hu *et al* (118) revealed that the suppression of CCAT1 improved pathology and inhibited osteocyte apoptosis in bone tissues from ovariectomized rats with osteoporosis, promoted differentiation and proliferation, and depressed apoptosis in OBs derived from ovariectomized rats by promoting miR-34a-5p expression by downregulating SMURF2. Mulati *et al* (119) suggested that the lncRNA CRNDE, which was previously reported as a cancer-related RNA, plays a crucial role in OB proliferation and differentiation. Additionally, mechanistically, the upregulation of CRNDE can promote OB proliferation and regulate bone formation via the Wnt/β-catenin pathway (119).

Recent results have shown that iron accumulation (IA), which is a pathological risk factor among postmenopausal women, is related to postmenopausal osteoporosis and that iron accumulation leads to BMSC apoptosis by activating the caspase 3 pathway. The latest study reported that the expression of the lncRNA XIST was increased in IA mouse and cell models, indicating that XIST may play an important role in osteoporosis (120). Furthermore, knockdown of XIST can suppress OB apoptosis induced by IA via the regulation of caspase 3. Similarly, Niu *et al* (121) revealed that XIST, which was found to be upregulated in plasma, also promoted

Table V. Roles of lncRNAs in the regulation of osteoblasts.

First author, year	lncRNA	Target gene	Role	(Refs.)
Yin *et al*, 2021	AK039312/ AK079370	miR-199b-5p	Inhibit differentiation	(114)
Wang *et al*, 2020	DANCR	CTNNB1	Inhibit differentiation	(116)
Yang *et al*, 2021	MEG3	miR-214	Inhibit proliferation and differentiation	(117)
Hu *et al*, 2021	CCAT1	miR-34a-5p	Inhibit proliferation and differentiation and promote apoptosis	(118)
Mulati *et al*, 2020	CRNDE	Wnt/β-catenin	Promote proliferation	(119)
Liu *et al*, 2021	XIST	miR-758-3p/ miR-203-3p	Promote apoptosis	(120)
Niu *et al*, 2020	XIST	miR-758-3p/ miR-203-3p	Promote apoptosis	(121)

lncRNA, long non-coding RNA; miR, microRNA.

OB apoptosis through the miR-203-3p/ZFPM2 pathway. In addition, XIST plays a role in regulating OB differentiation by modulating the expression of miR-19a-3p, indicating that XIST performs various important regulatory functions in bone-related diseases (12). The effect of lncRNA-mediated autophagy on OBs in osteoporosis has rarely been reported and needs further exploration (Table V).

Effects of circRNAs on OB regulation. circRNAs are known to play crucial roles in osteoporosis by binding miRNAs to modulate the expression of target genes at the transcriptional or post-transcriptional level. However, few studies and reports related to circRNAs regulating OB differentiation in osteoporosis, especially OB proliferation, apoptosis and autophagy, are available. Further systematic studies are needed to clarify the role of circRNAs in regulating OBs during osteoporosis. Mi *et al* (122) suggested that the expression of the circRNA AFF4, which is located in the cytoplasm, was upregulated during the few days after fracture *in vivo*, and mechanistic studies revealed that circRNA AFF4 promotes OB proliferation and suppresses apoptosis by regulating the miR-7223-5p/PIK3R1 signalling pathway. However, whether circRNA AFF4A plays a role in osteoporosis remains to be determined. A recent study reported that the expression of circ8500 was obviously increased during mineralization processes, and further experiments showed that circ8500 can facilitate OB matrix mineralization by inhibiting miR-1301-3p to promote PADI4 expression (123). Recently, Ji *et al* (124) revealed that circ_0026827 promotes OB differentiation via the Beclin-1-mediated autophagy pathway. Mechanistically, circ_0026827 regulates the autophagy signalling pathway by targeting miR-188-3p, suggesting novel therapeutics for osteoporosis (Table VI).

4. Mechanisms by which ncRNAs regulate OCs in osteoporosis

Osteoclasts, which are derived from the mononuclear haematopoietic lineage, are multinucleated giant cells after fusion that are regulated mainly by various cytokines, which play a crucial role in the formation of functional OCs (88). The process of osteoclastic bone resorption is related to the dysregulation of miRNA, lncRNA and circRNA expression, which, in turn, regulates the differentiation, proliferation, apoptosis and autophagy of OCs by modulating target genes.

Previously, miR-128 was reported to be involved in ageing, inflammatory signalling and inflammatory diseases. Additionally, miR-128 was involved in osteogenic/adipogenic differentiation (125). Recently, miR-128 was found to be upregulated in bone tissues from patients with postmenopausal osteoporosis, and the expression level of miR-128 was positively correlated with the expression level of nuclear factor of activated T cells 1 (125). Mechanistically, miR-128 knockdown can inhibit osteoclastogenesis by targeting sirtuin 1 and regulating the activity of NF-κB, which, in turn, markedly depresses ovariectomy-induced osteoclastogenesis and alleviates bone loss in mice (125). Similarly, miR-301-b expression was upregulated in bone tissues derived from postmenopausal patients with osteoporosis. Results of mechanistic studies showed that miR-301-b could promote osteoclastogenesis by post-transcriptionally regulating the expression of cylindromatosis, a target of miR-301-b (126). Huang *et al* (127) suggested that miR-25-3p plays an important role in inhibiting OC proliferation by suppressing the expression of nuclear factor I X, which is involved in the regulation of OC proliferation and differentiation.

Zhang *et al* (128) showed that the expression of the lncRNA Neat1 was increased during osteoclastic differentiation and that Neat1 knockdown suppressed OC formation, whereas Neat1 overexpression promoted it. Further evidence revealed that upregulated Neat1 can facilitate osteoclastogenesis in mice, providing a novel therapeutic target for osteoporosis (128). Mechanistic studies revealed that Neat1 targets miR-7 and regulates the expression of protein tyrosine kinase 2 (128). Chang *et al* (129) analysed lncRNA expression levels using a microarray during the process of OC differentiation and fusion, and found that the overexpression of lncRNA-NONMMUT037835.2 suppressed osteoclastic differentiation, whereas the inhibition of lncRNA-NONMMUT037835.2 facilitated OC formation and

Table VI. Roles of circRNAs in the regulation of osteoblasts.

First author, year	circRNA	Target gene	Role	(Refs.)
Mi *et al*, 2019	circ AFF4	miR-7223-5p	Promote proliferation and inhibit apoptosis	(122)
Zhai *et al*, 2020	circ-0008500	miR-1301-3p	Promote matrix mineralization	(123)
Ji *et al*, 2020	circ_0026827	miR-188-3p	Promote differentiation	(124)

circRNA, circular RNA; miR, microRNA.

Table VII. Roles of ncRNAs in the regulation of osteoclasts.

First author, year	ncRNA	Target gene	Role	(Refs.)
Shen *et al*, 2020	miR-128	SIRT1	Promote differentiation	(125)
Zhu *et al*, 2020	miR-301-b	CYLD	Promote differentiation	(126)
Huang *et al*, 2020	miR-25-3p	NFIX	Inhibit proliferation	(127)
Zhang *et al*, 2020	lncRNA Neat1	miR-7	Promote differentiation	(128)
Chang *et al*, 2020	lncRNA-NONMMUT037835.2	RANK	Inhibit differentiation	(129)
Cong *et al*, 2020	lncRNA GAS5	miR-21	Promote apoptosis	(131)

ncRNA, non-coding RNA; lncRNA, long ncRNA; miR, microRNA.

fusion. it was also revealed that lncRNA-NONMMUT037835.2 modulated osteoclastogenesis by targeting RANK and repressing the NF-κB/MAPK pathway (129). Previous findings suggested that miR-21 plays crucial roles in osteoporosis by targeting reversion-inducing cysteine-rich protein with Kazal motifs to depress the process of osteoporosis (130). A recent study indicated that miR-21 expression was decreased in plasma from patients with osteoporosis, and further evidence showed that the overexpression of miR-21 could inhibit OC apoptosis (131). In addition, the expression of GAS5 was increased in plasma from patients with osteoporosis, and GAS5 could decrease miR-21 expression to promote OC apoptosis, which, in turn, plays a protective role in osteoporosis (131) (Table VII).

5. Conclusion and perspectives

In this review, the latest evidence concerning the regulatory roles of miRNAs, lncRNAs and circRNAs involved in the modulation of BMSCs, OBs and OCs in osteoporosis was summarized. Recently, emerging studies have shown that ncRNAs are related to bone homeostasis and play essential roles in the occurrence and development of osteoporosis. In addition, some ncRNAs have therapeutic potential for osteoporosis treatment.

Although various anabolic drugs are applied in osteoporosis treatment, these agents have side effects and unwanted limitations that interrupt the quality of life of patients. Thus, it is imperative to identify the therapeutic potential of ncRNAs in osteoporosis. To the best of our knowledge, research related to the regulatory function of miRNAs in the differentiation, proliferation, apoptosis and autophagy of BMSCs, OBs and OCs has markedly increased. However, only a few studies were conducted *in vivo*, and functional investigations of miRNAs in bone homeostasis *in vivo* are needed. Both lncRNAs and circRNAs can influence the process of osteoporosis by directly binding miRNAs as sponges. Compared with miRNAs, which have been studied extensively, the lncRNAs and circRNAs involved in osteoporosis are relatively new. In particular, the role of circRNAs in maintaining bone homeostasis requires further investigation. For instance, data related to the regulation of circRNAs in OBs and OCs in osteoporosis are limited. The potential use of circRNAs as treatment options for osteoporosis is undoubtedly promising. Differentiation, proliferation, apoptosis and autophagy are important physiological processes in cells that play crucial roles in the regulation of BMSCs, OBs and OCs in the bone microenvironment. However, few studies have investigated apoptosis and autophagy in the aforementioned cells, and the importance of ncRNAs in the regulation of apoptosis and autophagy of BMSCs, OBs, and OCs needs to be further elucidated. In addition, some ncRNAs simultaneously play a specific regulatory role in various diseases and can simultaneously participate in the occurrence and development of tumours and the progression of osteoporosis. Therefore, it is necessary to explore the precise mechanism underlying the links between ncRNAs and osteoporosis and other organ diseases, which could be of great significance for the therapeutic application of ncRNA-related drugs in osteoporosis.

Although numerous recent studies have investigated the mechanisms of ncRNAs in the progression of osteoporosis, limited research concerning the important ncRNAs has been

clinically translated. In addition, *in vivo* studies investigating differentially expressed ncRNAs in bone tissue at different stages of osteoporosis are currently insufficient. Therefore, identifying more consequential ncRNAs related to osteoporosis and carrying out meaningful clinical translational research are of great importance for understanding the pathological mechanism, prevention and treatment of osteoporosis.

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Authors' contributions

ZL and ZX wrote the manuscript. HX and GT edited and proofread the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Li X, Xu J, Dai B, Wang X, Guo Q and Qin L: Targeting autophagy in osteoporosis: From pathophysiology to potential therapy. Ageing Res Rev 62: 101098, 2020.
2. de Paula FJA and Rosen CJ: Marrow adipocytes: Origin, structure, and function. Annu Rev Physiol 82: 461-484, 2020.
3. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B and Kanis JA: Osteoporosis in the European Union: Medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 8: 136, 2013.
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A and Tosteson A: Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 22: 465-475, 2007.
5. Wan Y: PPARγ in bone homeostasis. Trends Endocrinol Metab 21: 722-728, 2010.
6. Zhao W, Shen G, Ren H, Liang D, Yu X, Zhang Z, Huang J, Qiu T, Tang J, Shang Q, *et al*: Therapeutic potential of microRNAs in osteoporosis function by regulating the biology of cells related to bone homeostasis. J Cell Physiol 233: 9191-9208, 2018.
7. Infante A and Rodríguez CI: Osteogenesis and aging: Lessons from mesenchymal stem cells. Stem Cell Res Ther 9: 244, 2018.
8. Feng Q, Zheng S and Zheng J: The emerging role of microRNAs in bone remodeling and its therapeutic implications for osteoporosis. Biosci Rep 38: BSR20180453, 2018.
9. Yang Y, Yujiao W, Fang W, Linhui Y, Ziqi G, Zhichen W, Zirui W and Shengwang W: The roles of miRNA, lncRNA and circRNA in the development of osteoporosis. Biol Res 53: 40, 2020.
10. Jin D, Wu X, Yu H, Jiang L, Zhou P, Yao X, Meng J, Wang L, Zhang M and Zhang Y: Systematic analysis of lncRNAs, mRNAs, circRNAs and miRNAs in patients with postmenopausal osteoporosis. Am J Transl Res 10: 1498-1510, 2018.
11. Eskildsen T, Taipaleenmäki H, Stenvang J, Abdallah BM, Ditzel N, Nossent AY, Bak M, Kauppinen S and Kassem M: MicroRNA-138 regulates osteogenic differentiation of human stromal (mesenchymal) stem cells in vivo. Proc Natl Acad Sci USA 108: 6139-6144, 2011.
12. Chen S, Li Y, Zhi S, Ding Z, Huang Y, Wang W, Zheng R, Yu H, Wang J, Hu M, *et al*: lncRNA Xist regulates osteoblast differentiation by sponging miR-19a-3p in aging-induced osteoporosis. Aging Dis 11: 1058-1068, 2020.
13. Meng YC, Lin T, Jiang H, Zhang Z, Shu L, Yin J, Ma X, Wang C, Gao R and Zhou XH: miR-122 exerts inhibitory effects on osteoblast proliferation/differentiation in osteoporosis by activating the PCP4-mediated JNK pathway. Mol Ther Nucleic Acids 20: 345-358, 2020.
14. Li J, Ayoub A, Xiu Y, Yin X, Sanders JO, Mesfin A, Xing L, Yao Z and Boyce BF: TGFβ-induced degradation of TRAF3 in mesenchymal progenitor cells causes age-related osteoporosis. Nat Commun 10: 2795, 2019.
15. Tang QQ and Lane MD: Adipogenesis: From stem cell to adipocyte. Annu Rev Biochem 81: 715-736, 2012.
16. Trohatou O, Zagoura D, Orfanos NK, Pappa KI, Marinos E, Anagnou NP and Roubelakis MG: miR-26a mediates adipogenesis of amniotic fluid mesenchymal stem/stromal cells via PTEN, Cyclin E1, and CDK6. Stem Cells Dev 26: 482-494, 2017.
17. Xu R, Shen X, Si Y, Fu Y, Zhu W, Xiao T, Fu Z, Zhang P, Cheng J and Jiang H: MicroRNA-31a-5p from aging BMSCs links bone formation and resorption in the aged bone marrow microenvironment. Aging Cell 17: e12794, 2018.
18. Moura SR, Bras JP, Freitas J, Osório H, Barbosa MA, Santos SG and Almeida MI: miR-99a in bone homeostasis: Regulating osteogenic lineage commitment and osteoclast differentiation. Bone 134: 115303, 2020.
19. Zhou JG, Hua Y, Liu SW, Hu WQ, Qian R and Xiong L: MicroRNA-1286 inhibits osteogenic differentiation of mesenchymal stem cells to promote the progression of osteoporosis via regulating FZD4 expression. Eur Rev Med Pharmacol Sci 24: 1-10, 2020.
20. Hao L, Fu J, Tian Y and Wu J: Systematic analysis of lncRNAs, miRNAs and mRNAs for the identification of biomarkers for osteoporosis in the mandible of ovariectomized mice. Int J Mol Med 40: 689-702, 2017.
21. Gao Y, Cao Y, Cui X, Wang X, Zhou Y, Huang F, Wang X, Wen J, Xie K, Xu P, *et al*: miR-199a-3p regulates brown adipocyte differentiation through mTOR signaling pathway. Mol Cell Endocrinol 476: 155-164, 2018.
22. Chen HP, Wen J, Tan SR, Kang LM and Zhu GC: miR-199a-3p inhibition facilitates cardiomyocyte differentiation of embryonic stem cell through promotion of MEF2C. J Cell Physiol 234: 23315-23325, 2019.
23. Wu JC, Sun J, Xu JC, Zhou ZY and Zhang YF: Down-regulated microRNA-199a-3p enhances osteogenic differentiation of bone marrow mesenchymal stem cells by targeting Kdm3a in ovariectomized rats. Biochem J 478: 721-734, 2021.
24. Jiang K, Teng GD and Chen YQ: MicroRNA-23 suppresses osteogenic differentiation of human bone marrow mesenchymal stem cells by targeting the MEF2C-mediated MAPK signaling pathway. J Gene Med 22: e3216, 2020.
25. Yin C, Tian Y, Yu Y, Yang C, Su P, Zhao Y, Wang X, Zhang K, Pei J, Li D, *et al*: miR-129-5p inhibits bone formation through TCF4. Front Cell Dev Biol 8: 600641, 2020.

26. Alajez NM, Lenarduzzi M, Ito E, Hui AB, Shi W, Bruce J, Yue S, Huang SH, Xu W, Waldron J, *et al*: miR-218 suppresses nasopharyngeal cancer progression through downregulation of survivin and the SLIT2-ROBO1 pathway. Cancer Res 71: 2381-2391, 2011.
27. Liu T, Zhang X, Du L, Wang Y, Liu X, Tian H, Wang L, Li P, Zhao Y, Duan W, *et al*: Exosome-transmitted miR-128-3p increase chemosensitivity of oxaliplatin-resistant colorectal cancer. Mol Cancer 18: 43, 2019.
28. Kou J, Zheng X, Guo J, Liu Y and Liu X: MicroRNA-218-5p relieves postmenopausal osteoporosis through promoting the osteoblast differentiation of bone marrow mesenchymal stem cells. J Cell Biochem 121: 1216-1226, 2020.
29. Zhang Y, Liu Y, Wu M, Wang H, Wu L, Xu B, Zhou W, Fan X, Shao J and Yang T: MicroRNA-664a-5p promotes osteogenic differentiation of human bone marrow-derived mesenchymal stem cells by directly downregulating HMGA2. Biochem Biophys Res Commun 521: 9-14, 2020.
30. Qi XB, Jia B, Wang W, Xu GH, Guo JC, Li X and Liu JN: Role of miR-199a-5p in osteoblast differentiation by targeting TET2. Gene 726: 144193, 2020.
31. Zhang M, Yuan SZ, Sun H, Sun L, Zhou D and Yan J: miR-199b-5p promoted chondrogenic differentiation of C3H10T1/2 cells by regulating JAG1. J Tissue Eng Regen Med 14: 1618-1629, 2020.
32. Li Z, Wang Y, Xiang S, Zheng Z, Bian Y, Feng B and Weng X: Chondrocytes-derived exosomal miR-8485 regulated the Wnt/β-catenin pathways to promote chondrogenic differentiation of BMSCs. Biochem Biophys Res Commun 523: 506-513, 2020.
33. Shen PF, Wang B, Qu YX, Zheng C, Xu JD, Xie ZK and Ma Y: MicroRNA-23c inhibits articular cartilage damage recovery by regulating MSCs differentiation to chondrocytes via reducing FGF2. Eur Rev Med Pharmacol Sci 23: 941-948, 2019.
34. Xu S and Wu X: miR-134 inhibits chondrogenic differentiation of bone marrow mesenchymal stem cells by targetting SMAD6. Biosci Rep 39: BSR20180921, 2019.
35. Li Y, Yang F, Gao M, Gong R, Jin M, Liu T, Sun Y, Fu Y, Huang Q, Zhang W, *et al*: miR-149-3p regulates the switch between adipogenic and osteogenic differentiation of BMSCs by targeting FTO. Mol Ther Nucleic Acids 17: 590-600, 2019.
36. Calvier L, Chouvarine P, Legchenko E, Hoffmann N, Geldner J, Borchert P, Jonigk D, Mozes MM and Hansmann G: PPARγ Links BMP2 and TGFβ1 pathways in vascular smooth muscle cells, regulating cell proliferation and glucose metabolism. Cell Metab 25: 1118-1134.e7, 2017.
37. Li D, Zhang F, Zhang X, Xue C, Namwanje M, Fan L, Reilly MP, Hu F and Qiang L: Distinct functions of PPARγ isoforms in regulating adipocyte plasticity. Biochem Biophys Res Commun 481: 132-138, 2016.
38. Lin Z, He H, Wang M and Liang J: MicroRNA-130a controls bone marrow mesenchymal stem cell differentiation towards the osteoblastic and adipogenic fate. Cell Prolif 52: e12688, 2019.
39. Jamali L, Tofigh R, Tutunchi S, Panahi G, Borhani F, Akhavan S, Nourmohammadi P, Ghaderian SMH, Rasouli M and Mirzaei H: Circulating microRNAs as diagnostic and therapeutic biomarkers in gastric and esophageal cancers. J Cell Physiol 233: 8538-8550, 2018.
40. Wang T, Zhong D, Qin Z, He S, Gong Y, Li W and Li X: miR-100-3p inhibits the adipogenic differentiation of hMSCs by targeting PIK3R1 via the PI3K/AKT signaling pathway. Aging (Albany NY) 12: 25090-25100, 2020.
41. Zhu E, Zhang J, Zhou J, Yuan H, Zhao W and Wang B: miR-20a-5p promotes adipogenic differentiation of murine bone marrow stromal cells via targeting Kruppel-like factor 3. J Mol Endocrinol 60: 225-237, 2018.
42. Cui P, Zhao X, Liu J, Chen X, Gao Y, Tao K, Wang C and Zhang X: miR-146a interacting with lncRNA EPB41L4A-AS1 and lncRNA SNHG7 inhibits proliferation of bone marrow-derived mesenchymal stem cells. J Cell Physiol 235: 3292-3308, 2020.
43. Kong R, Gao J, Ji L and Zhao D: MicroRNA-126 promotes proliferation, migration, invasion and endothelial differentiation while inhibits apoptosis and osteogenic differentiation of bone marrow-derived mesenchymal stem cells. Cell Cycle 19: 2119-2138, 2020.
44. Tang L, Lu W, Huang J, Tang X, Zhang H and Liu S: miR-144 promotes the proliferation and differentiation of bone mesenchymal stem cells by downregulating the expression of SFRP1. Mol Med Rep 20: 270-280, 2019.
45. Yang BC, Kuang MJ, Kang JY, Zhao J, Ma JX and Ma XL: Human umbilical cord mesenchymal stem cell-derived exosomes act via the miR-1263/Mob1/Hippo signaling pathway to prevent apoptosis in disuse osteoporosis. Biochem Biophys Res Commun 524: 883-889, 2020.
46. Hernandez SL, Nelson M, Sampedro GR, Bagrodia N, Defnet AM, Lec B, Emolo J, Kirschner R, Wu L, Biermann H, *et al*: Staphylococcus aureus alpha toxin activates Notch in vascular cells. Angiogenesis 22: 197-209, 2019.
47. Man S, Sanchez Duffhues G, Ten Dijke P and Baker D: The therapeutic potential of targeting the endothelial-to-mesenchymal transition. Angiogenesis 22: 3-13, 2019.
48. Fan L, Wang J and Ma C: miR125a attenuates BMSCs apoptosis via the MAPK-ERK pathways in the setting of craniofacial defect reconstruction. J Cell Physiol 235: 2857-2865, 2020.
49. Liu Z, Li T, Zhu F, Deng SN, Li X and He Y: Regulatory roles of miR-22/Redd1-mediated mitochondrial ROS and cellular autophagy in ionizing radiation-induced BMSC injury. Cell Death Dis 10: 227, 2019.
50. Yao RW, Wang Y and Chen LL: Cellular functions of long noncoding RNAs. Nat Cell Biol 21: 542-551, 2019.
51. St Laurent G, Wahlestedt C and Kapranov P: The landscape of long noncoding RNA classification. Trends Genet 31: 239-251, 2015.
52. Chen LL: Linking long noncoding RNA localization and function. Trends Biochem Sci 41: 761-772, 2016.
53. Zhang L, Xie H and Li S: lncRNA LOXL1-AS1 controls osteogenic and adipocytic differentiation of bone marrow mesenchymal stem cells in postmenopausal osteoporosis through regulating the miR-196a-5p/Hmga2 axis. J Bone Miner Metab 38: 794-805, 2020.
54. Che M, Gong W, Zhao Y and Liu M: Long noncoding RNA HCG18 inhibits the differentiation of human bone marrow-derived mesenchymal stem cells in osteoporosis by targeting miR-30a-5p/NOTCH1 axis. Mol Med 26: 106, 2020.
55. Li M, Xie Z, Li J, Lin J, Zheng G, Liu W, Tang S, Cen S, Ye G, Li Z, *et al*: GAS5 protects against osteoporosis by targeting UPF1/SMAD7 axis in osteoblast differentiation. Elife 9: e59079, 2020.
56. Zheng J, Guo H, Qin Y, Liu Z, Ding Z, Zhang L and Wang W: SNHG5/miR-582-5p/RUNX3 feedback loop regulates osteogenic differentiation and apoptosis of bone marrow mesenchymal stem cells. J Cell Physiol: Oct 28, 2020 (Epub ahead of print). doi:10.1002/jcp.29527.
57. Jin C, Jia L, Tang Z and Zheng Y: Long non-coding RNA MIR22HG promotes osteogenic differentiation of bone marrow mesenchymal stem cells via PTEN/AKT pathway. Cell Death Dis 11: 601, 2020.
58. Huang MJ, Zhao JY, Xu JJ, Li J, Zhuang YF and Zhang XL: lncRNA ADAMTS9-AS2 controls human mesenchymal stem cell chondrogenic differentiation and functions as a ceRNA. Mol Ther Nucleic Acids 18: 533-545, 2019.
59. Liu D, Wu K, Yang Y, Zhu D, Zhang C and Zhao S: Long noncoding RNA ADAMTS9-AS2 suppresses the progression of esophageal cancer by mediating CDH3 promoter methylation. Mol Carcinog 59: 32-44, 2020.
60. Shu T, He L, Wang X, Pang M, Yang B, Feng F, Wu Z, Liu C, Zhang S, Liu B, *et al*: Long noncoding RNA UCA1 promotes chondrogenic differentiation of human bone marrow mesenchymal stem cells via miRNA-145-5p/SMAD5 and miRNA-124-3p/SMAD4 axis. Biochem Biophys Res Commun 514: 316-322, 2019.
61. Zhang RF, Liu JW, Yu SP, Sun D, Wang XH, Fu JS and Xie Z: lncRNA UCA1 affects osteoblast proliferation and differentiation by regulating BMP-2 expression. Eur Rev Med Pharmacol Sci 23: 6774-6782, 2019.
62. Pan Y, Xie Z, Cen S, Li M, Liu W, Tang S, Ye G, Li J, Zheng G, Li Z, *et al*: Long noncoding RNA repressor of adipogenesis negatively regulates the adipogenic differentiation of mesenchymal stem cells through the hnRNP A1-PTX3-ERK axis. Clin Transl Med 10: e227, 2020.
63. Zhu E, Zhang J, Li Y, Yuan H, Zhou J and Wang B: Long noncoding RNA Plnc1 controls adipocyte differentiation by regulating peroxisome proliferator-activated receptor γ. FASEB J 33: 2396-2408, 2019.
64. Fu D, Yang S, Lu J, Lian H and Qin K: lncRNA NORAD promotes bone marrow stem cell differentiation and proliferation by targeting miR-26a-5p in steroid-induced osteonecrosis of the femoral head. Stem Cell Res Ther 12: 18, 2021.
65. Soghli N, Yousefi T, Abolghasemi M and Qujeq D: NORAD, a critical long non-coding RNA in human cancers. Life Sci 264: 118665, 2021.
66. Zhao Y, Chen Y, Hu X, Zhang N and Wang F: lncRNA LINC01535 upregulates BMP2 expression levels to promote osteogenic differentiation via sponging miR-3619-5p. Mol Med Rep 22: 5428-5435, 2020.

67. Gan X, Liu S and Liang K: MicroRNA-19b-3p promotes cell proliferation and osteogenic differentiation of BMSCs by interacting with lncRNA H19. BMC Med Genet 21: 11, 2020.
68. Song G, Zhou J, Song R, Liu D, Yu W, Xie W, Ma Z, Gong J, Meng H, Yang T and Song Z: Long noncoding RNA H19 regulates the therapeutic efficacy of mesenchymal stem cells in rats with severe acute pancreatitis by sponging miR-138-5p and miR-141-3p. Stem Cell Res Ther 11: 420, 2020.
69. Li M, Cong R, Yang L, Yang L, Zhang Y and Fu Q: A novel lncRNA LNC_000052 leads to the dysfunction of osteoporotic BMSCs via the miR-96-5p-PIK3R1 axis. Cell Death Dis 11: 795, 2020.
70. Gao B, Li S and Li G: Long noncoding RNA (lncRNA) small nucleolar RNA Host Gene 5 (SNHG5) regulates proliferation, differentiation, and apoptosis of K562 cells in chronic Myeliod Leukemia. Med Sci Monit 25: 6812-6819, 2019.
71. Zhang J, Liu H, Hou L, Wang G, Zhang R, Huang Y, Chen X and Zhu J: Circular RNA_LARP4 inhibits cell proliferation and invasion of gastric cancer by sponging miR-424-5p and regulating LATS1 expression. Mol Cancer 16: 151, 2017.
72. Wang R, Zhang S, Chen X, Li N, Li J, Jia R, Pan Y and Liang H: CircNT5E acts as a sponge of miR-422a to promote glioblastoma tumorigenesis. Cancer Res 78: 4812-4825, 2018.
73. Wang XB, Li PB, Guo SF, Yang QS, Chen ZX, Wang D and Shi SB: circRNA_0006393 promotes osteogenesis in glucocorticoid-induced osteoporosis by sponging miR-145-5p and upregulating FOXO1. Mol Med Rep 20: 2851-2858, 2019.
74. Yu L and Liu Y: circRNA_0016624 could sponge miR-98 to regulate BMP2 expression in postmenopausal osteoporosis. Biochem Biophys Res Commun 516: 546-550, 2019.
75. Wen J, Guan Z, Yu B, Guo J, Shi Y and Hu L: Circular RNA hsa_circ_0076906 competes with OGN for miR-1305 biding site to alleviate the progression of osteoporosis. Int J Biochem Cell Biol 122: 105719, 2020.
76. Shen W, Sun B, Zhou C, Ming W, Zhang S and Wu X: CircFOXP1/FOXP1 promotes osteogenic differentiation in adipose-derived mesenchymal stem cells and bone regeneration in osteoporosis via miR-33a-5p. J Cell Mol Med 24: 12513-12524, 2020.
77. Cherubini A, Barilani M, Rossi RL, Jalal MMK, Rusconi F, Buono G, Ragni E, Cantarella G, Simpson HARW, Péault B and Lazzari L: FOXP1 circular RNA sustains mesenchymal stem cell identity via microRNA inhibition. Nucleic Acids Res 47: 5325-5340, 2019.
78. Luo Y, Liu F, Ma J, Fu Y and Gui R: A novel epigenetic regulation of circFoxp1 on Foxp1 in colon cancer cells. Cell Death Dis 11: 782, 2020.
79. Liu S, Wang C, Bai J, Li X, Yuan J, Shi Z and Mao N: Involvement of circRNA_0007059 in the regulation of postmenopausal osteoporosis by promoting the microRNA-378/BMP-2 axis. Cell Biol Int 45: 447-455, 2021.
80. Gao S, Yu Y, Liu L, Meng J and Li G: Circular RNA hsa_circ_0007059 restrains proliferation and epithelial-mesenchymal transition in lung cancer cells via inhibiting microRNA-378. Life Sci 233: 116692, 2019.
81. Huang Y, Xiao D, Huang S, Zhuang J, Zheng X, Chang Y and Yin D: Circular RNA YAP1 attenuates osteoporosis through up-regulation of YAP1 and activation of Wnt/β-catenin pathway. Biomed Pharmacother 129: 110365, 2020.
82. Zhang M, Jia L and Zheng Y: circRNA expression profiles in human bone marrow stem cells undergoing osteoblast differentiation. Stem Cell Rev Rep 15: 126-138, 2019.
83. Chia W, Liu J, Huang YG and Zhang C: A circular RNA derived from DAB1 promotes cell proliferation and osteogenic differentiation of BMSCs via RBPJ/DAB1 axis. Cell Death Dis 11: 372, 2020.
84. Chen G, Wang Q, Li Z, Yang Q, Liu Y, Du Z, Zhang G and Song Y: Circular RNA CDR1as promotes adipogenic and suppresses osteogenic differentiation of BMSCs in steroid-induced osteonecrosis of the femoral head. Bone 133: 115258, 2020.
85. Zhang Y, Jia S, Wei Q, Zhuang Z, Li J, Fan Y, Zhang L, Hong Z, Ma X, Sun R, *et al*: circRNA_25487 inhibits bone repair in trauma-induced osteonecrosis of femoral head by sponging miR-134-3p through p21. Regen Ther 16: 23-31, 2020.
86. Kim KH and Lee MS: Autophagy-a key player in cellular and body metabolism. Nat Rev Endocrinol 10: 322-337, 2014.
87. Liu F, Zhang J, Qin L, Yang Z, Xiong J, Zhang Y, Li R, Li S, Wang H, Yu B, *et al*: Circular RNA EIF6 (Hsa_circ_0060060) sponges miR-144-3p to promote the cisplatin-resistance of human thyroid carcinoma cells by autophagy regulation. Aging (Albany NY) 10: 3806-3820, 2018.
88. Garcia J and Delany AM: MicroRNAs regulating TGFβ and BMP signaling in the osteoblast lineage. Bone 143: 115791, 2021.
89. Chen Y and Yang C: miR-197-3p-induced downregulation of lysine 63 deubiquitinase promotes cell proliferation and inhibits cell apoptosis in lung adenocarcinoma cell lines. Mol Med Rep 17: 3921-3927, 2018.
90. You M, Zhang L, Zhang X, Fu Y and Dong X: MicroRNA-197-3p inhibits the osteogenic differentiation in osteoporosis by down-regulating KLF 10. Clin Interv Aging 16: 107-117, 2021.
91. Seeliger C, Karpinski K, Haug AT, Vester H, Schmitt A, Bauer JS and van Griensven M: Five freely circulating miRNAs and bone tissue miRNAs are associated with osteoporotic fractures. J Bone Miner Res 29: 1718-1728, 2014.
92. Gong B, Wang X, Li B, Li Y, Lu R, Zhang K, Li B, Ma Y and Li Y: miR-205-5p inhibits thymic epithelial cell proliferation via FA2H-TFAP2A feedback regulation in age-associated thymus involution. Mol Immunol 122: 173-185, 2020.
93. Oltra M, Vidal-Gil L, Maisto R, Sancho-Pelluz J and Barcia JM: Oxidative stress-induced angiogenesis is mediated by miR-205-5p. J Cell Mol Med 24: 1428-1436, 2020.
94. Zhu H, Shan Y, Ge K, Lu J, Kong W and Jia C: lncRNA CYTOR promotes pancreatic cancer cell proliferation and migration by sponging miR-205-5p. Pancreatology 20: 1139-1148, 2020.
95. Huang M, Li X, Zhou C, Si M, Zheng H, Chen L and Ding H: Noncoding RNA miR-205-5p mediates osteoporosis pathogenesis and osteoblast differentiation by regulating RUNX2. J Cell Biochem 121: 4196-4203, 2020.
96. Baglio SR, Rooijers K, Koppers-Lalic D, Verweij FJ, Pérez Lanzón M, Zini N, Naaijkens B, Perut F, Niessen HW, Baldini N and Pegtel DM: Human bone marrow- and adipose-mesenchymal stem cells secrete exosomes enriched in distinctive miRNA and tRNA species. Stem Cell Res Ther 6: 127, 2015.
97. Sundar IK, Li D and Rahman I: Small RNA-sequence analysis of plasma-derived extracellular vesicle miRNAs in smokers and patients with chronic obstructive pulmonary disease as circulating biomarkers. J Extracell Vesicles 8: 1684816, 2019.
98. Zhang X, Wang Y, Zhao H, Han X, Zhao T, Qu P, Li G and Wang W: Extracellular vesicle-encapsulated miR-22-3p from bone marrow mesenchymal stem cell promotes osteogenic differentiation via FTO inhibition. Stem Cell Res Ther 11: 227, 2020.
99. Wang N, Zhou Z, Wu T, Liu W, Yin P, Pan C and Yu X: TNF-α-induced NF-κB activation upregulates microRNA-150-3p and inhibits osteogenesis of mesenchymal stem cells by targeting β-catenin. Open Biol 6: 150258, 2016.
100. Qiu M, Zhai S, Fu Q and Liu D: Bone marrow mesenchymal stem cells-derived exosomal MicroRNA-150-3p promotes osteoblast proliferation and differentiation in osteoporosis. Hum Gene Ther 32: 717-729, 2021.
101. Ma J, Lin X, Chen C, Li S, Zhang S, Chen Z, Li D, Zhao F, Yang C, Yin C, *et al*: Circulating miR-181c-5p and miR-497-5p are potential biomarkers for prognosis and diagnosis of osteoporosis. J Clin Endocrinol Metab 105: dgz300, 2020.
102. Shen L, Li J, Xu L, Ma J, Li H, Xiao X, Zhao J and Fang L: miR-497 induces apoptosis of breast cancer cells by targeting Bcl-w. Exp Ther Med 3: 475-480, 2012.
103. Gu Z, Xie D, Huang C, Ding R, Zhang R, Li Q, Lin C and Qiu Y: MicroRNA-497 elevation or LRG1 knockdown promotes osteoblast proliferation and collagen synthesis in osteoporosis via TGF-beta1/Smads signalling pathway. J Cell Mol Med 24: 12619-12632, 2020.
104. Mohamad N, Nabih ES, Zakaria ZM, Nagaty MM and Metwaly RG: Insight into the possible role of miR-214 in primary osteoporosis via osterix. J Cell Biochem 120: 15518-15526, 2019.
105. Lu XZ, Yang ZH, Zhang HJ, Zhu LL, Mao XL and Yuan Y: miR-214 protects MC3T3-E1 osteoblasts against H_2O_2-induced apoptosis by suppressing oxidative stress and targeting ATF4. Eur Rev Med Pharmacol Sci 21: 4762-4770, 2017.
106. Yang C, Gu Z, Ding R, Huang C, Li Q, Xie D, Zhang R and Qiu Y: Long non-coding RNA MEG3 silencing and microRNA-214 restoration elevate osteoprotegerin expression to ameliorate osteoporosis by limiting TXNIP. J Cell Mol Med 25: 2025-2039, 2021.
107. Vimalraj S, Saravanan S, Vairamani M, Gopalakrishnan C, Sastry TP and Selvamurugan N: A Combinatorial effect of carboxymethyl cellulose based scaffold and microRNA-15b on osteoblast differentiation. Int J Biol Macromol 93: 1457-1464, 2016.

108. Lu X, Zhang Y, Zheng Y and Chen B: The miRNA-15b/USP7/KDM6B axis engages in the initiation of osteoporosis by modulating osteoblast differentiation and autophagy. J Cell Mol Med 25: 2069-2081, 2021.
109. Naseri Z, Oskuee RK, Jaafari MR and Forouzandeh Moghadam M: Exosome-mediated delivery of functionally active miRNA-142-3p inhibitor reduces tumorigenicity of breast cancer in vitro and in vivo. Int J Nanomedicine 13: 7727-7747, 2018.
110. Lou Z, Peng Z, Wang B, Li X, Li X and Zhang X: miR-142-5p promotes the osteoclast differentiation of bone marrow-derived macrophages via PTEN/PI3K/AKT/FoxO1 pathway. J Bone Miner Metab 37: 815-824, 2019.
111. Luo B, Yang J, Yuan Y, Hao P and Cheng X: MicroRNA-142 regulates osteoblast differentiation and apoptosis of mouse pre-osteoblast cells by targeting bone morphogenetic protein 2. FEBS Open Bio 10: 1793-1801, 2020.
112. Hu WX, Li H and Jiang JZ: miR-491-3p is down-regulated in postmenopausal osteoporosis and affects growth, differentiation and apoptosis of hFOB1.19 cells through targeting CTSS. Folia Histochem Cytobiol 58: 9-16, 2020.
113. Zhang W, Cui SY, Yi H, Zhu XH, Liu W and Xu YJ: miR-708 inhibits MC3T3-E1 cells against HO-induced apoptosis through targeting PTEN. J Orthop Surg Res 15: 255, 2020.
114. Yin C, Tian Y, Yu Y, Li D, Miao Z, Su P, Zhao Y, Wang X, Pei J, Zhang K and Qian A: Long noncoding RNA AK039312 and AK079370 inhibits bone formation via miR-199b-5p. Pharmacol Res 163: 105230, 2021.
115. Tong X, Gu PC, Xu SZ and Lin XJ: Long non-coding RNA-DANCR in human circulating monocytes: A potential biomarker associated with postmenopausal osteoporosis. Biosci Biotechnol Biochem 79: 732-737, 2015.
116. Wang CG, Hu YH, Su SL and Zhong D: lncRNA DANCR and miR-320a suppressed osteogenic differentiation in osteoporosis by directly inhibiting the Wnt/β-catenin signaling pathway. Exp Mol Med 52: 1310-1325, 2020.
117. Wang Q, Li Y, Zhang Y, Ma L, Lin L, Meng J, Jiang L, Wang L, Zhou P and Zhang Y: lncRNA MEG3 inhibited osteogenic differentiation of bone marrow mesenchymal stem cells from postmenopausal osteoporosis by targeting miR-133a-3p. Biomed Pharmacother 89: 1178-1186, 2017.
118. Hu F, Jiang C, Bu G, Fu Y and Yu Y: Silencing long noncoding RNA colon cancer-associated transcript-1 upregulates microRNA-34a-5p to promote proliferation and differentiation of osteoblasts in osteoporosis. Cancer Gene Ther: Jan 5, 2021 (Epub ahead of print). doi: https://doi.org/10.1038/s41417-020-00264-7.
119. Mulati M, Kobayashi Y, Takahashi A, Numata H, Saito M, Hiraoka Y, Ochi H, Sato S, Ezura Y, Yuasa M, *et al*: The long noncoding RNA Crnde regulates osteoblast proliferation through the Wnt/β-catenin signaling pathway in mice. Bone 130: 115076, 2020.
120. Liu H, Wang YW, Chen WD, Dong HH and Xu YJ: Iron accumulation regulates osteoblast apoptosis through lncRNA XIST/miR-758-3p/caspase 3 axis leading to osteoporosis. IUBMB Life 73: 432-443, 2021.
121. Niu S, Xiang F and Jia H: Downregulation of lncRNA XIST promotes proliferation and differentiation, limits apoptosis of osteoblasts through regulating miR-203-3p/ZFPM2 axis. Connect Tissue Res 62: 381-392, 2021.
122. Mi B, Xiong Y, Chen L, Yan C, Endo Y, Liu Y, Liu J, Hu L, Hu Y, Sun Y, *et al*: circRNA AFF4 promotes osteoblast cells proliferation and inhibits apoptosis via the Mir-7223-5p/PIK3R1 axis. Aging (Albany NY) 11: 11988-12001, 2019.
123. Zhai Q, Zhao Y, Wang L, Dai Y, Zhao P, Xiang X, Liu K, Du W, Tian W, Yang B, *et al*: circRNA hsa_circ_0008500 Acts as a miR-1301-3p sponge to promote osteoblast mineralization by upregulating PADI4. Front Cell Dev Biol 8: 602731, 2020.
124. Ji F, Zhu L, Pan J, Shen Z, Yang Z, Wang J, Bai X, Lin Y and Tao J: hsa_circ_0026827 promotes osteoblast differentiation of human dental pulp stem cells through the Beclin1 and RUNX1 signaling pathways by sponging miR-188-3p. Front Cell Dev Biol 8: 470, 2020.
125. Shen G, Ren H, Shang Q, Zhang Z, Zhao W, Yu X, Tang J, Yang Z, Liang D and Jiang X: miR-128 plays a critical role in murine osteoclastogenesis and estrogen deficiency-induced bone loss. Theranostics 10: 4334-4348, 2020.
126. Zhu J, Wang H and Liu H: Osteoclastic miR-301-b knockout reduces ovariectomy (OVX)-induced bone loss by regulating CYDR/NF-κB signaling pathway. Biochem Biophys Res Commun 529: 35-42, 2020.
127. Huang Y, Ren K, Yao T, Zhu H, Xu Y, Ye H, Chen Z, Lv J, Shen S and Ma J: MicroRNA-25-3p regulates osteoclasts through nuclear factor I X. Biochem Biophys Res Commun 522: 74-80, 2020.
128. Zhang Y, Chen XF, Li J, He F, Li X and Guo Y: lncRNA Neat1 stimulates osteoclastogenesis via sponging miR-7. J Bone Miner Res 35: 1772-1781, 2020.
129. Chang Y, Yu D, Chu W, Liu Z, Li H and Zhai Z: lncRNA expression profiles and the negative regulation of lncRNA-NOMMUT037835.2 in osteoclastogenesis. Bone 130: 115072, 2020.
130. Zhao W, Dong Y, Wu C, Ma Y, Jin Y and Ji Y: miR-21 overexpression improves osteoporosis by targeting RECK. Mol Cell Biochem 405: 125-133, 2015.
131. Cong C, Tian J, Gao T, Zhou C, Wang Y, Cui X and Zhu L: lncRNA GAS5 is upregulated in osteoporosis and downregulates miR-21 to promote apoptosis of osteoclasts. Clin Interv Aging 15: 1163-1169, 2020.