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

ZHICHAO LI¹, HAIPENG XUE², GUOQING TAN² and ZHANWANG XU²

¹First College of Clinical Medicine, Shandong University of Traditional Chinese Medicine; ²Department of Orthopaedics, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong 250011, P.R. China

Received March 22, 2021; Accepted August 25, 2021

DOI: 10.3892/mmr.2021.12428

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 micro RNAs (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.

Contents

1. Introduction
2. Mechanisms by which ncRNAs regulate BMSCs in osteoporosis
3. Mechanisms by which ncRNAs regulate OBs in osteoporosis
4. Mechanisms by which ncRNAs regulate OCs in osteoporosis
5. Conclusion and perspectives

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

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
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 BMS c osteogenic differentiation in vitro. Recently, Wu et al. (22) revealed 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

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 antagoniR-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 signaling. 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, acts 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 EPB4L4A-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 signaling pathways. The level of miR-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 1).

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...
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).

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 | (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 | HMG2 | 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 | (36) |
| 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 | Mobi1/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 IncRNA 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 IncRNA 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 IncRNA 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 IncRNA GAS5 plays a crucial role in negatively regulating lipoblast/adipocyte differentiation in humans and identified that GAS5 was down-regulated 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 IncSNHG5 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 IncRNAs in BMSC chondrogenic differentiation remains poorly studied. The IncRNA 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 IncRNA 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 IncRNA 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 IncRNA 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 adipogenic differentiation.

The IncRNA NORAD is 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 IncRNA 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 IncRNA 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 IncRNA 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 IncRNA 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...
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 M3T3-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-DA1 is upregulated during the osteogenic differentiation of BMSCs. Chia et al (83) later verified via RT-qPCR that circ-DA1 expression is significantly increased during the osteogenic differentiation of BMSCs. A mechanistic study revealed that circ-DA1 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 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 | (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.
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/P13K/AKT signalling pathway by inhibiting FTO (98).

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/   | Promote osteoblastic differentiation | (81)    |
| Chia et al, 2020   | circ-DAB1  | NOTCH/RBPJ     | Promote proliferation and            | (83)    |
|                    |           |                | osteoblastic differentiation         |         |
| Chen et al, 2020   | circ-CDR1  | miR-7-5p/      | Promote adipogenic and inhibit        | (84)    |
|                    |           | WNT5B          | osteoblastic differentiation          |         |
| Zhang et al, 2021  | circ_25487 | miR-134-3p/    | Promote apoptosis and inhibit         | (85)    |
|                    |           | p21            | proliferation                         |         |

circRNA, circular RNA; miR, microRNA.
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 H2O2 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 O Cs 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 DANCIR 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 DANCIR in patients with osteoporosis and an ovariectomy model, and DANCIR expression in BMSCs originating from osteoporosis patients was increased. In addition, DANCIR 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 CAT1 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 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.
Table V. Roles of lncRNAs in the regulation of osteoblasts.

| First author, year | lncRNA | Target gene | Role | (Ref.) |
|--------------------|--------|-------------|------|--------|
| Yin et al, 2021    | AK039312/ AK079370 | miR-199b-5p | Inhibit differentiation | (114) |
| Wang et al, 2020   | DANCRC | 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 miRNAs to 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. Moreover, some studies have suggested that the expression of 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 AFF4 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-kB, 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 cytidinomatosis, 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 IX, 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
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

| 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) |

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

circRNA, circular RNA; miR, microRNA.

| 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  | IncRNA Neat1 | miR-7 | Promote differentiation | (128) |
| Chang et al, 2020  | IncRNA-NONMUT037835.2 | RANK | Inhibit differentiation | (129) |
| Cong et al, 2020   | IncRNA GAS5 | miR-21 | Promote apoptosis | (131) |

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

| First author, year | lncRNA | 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  | IncRNA Neat1 | miR-7 | Promote differentiation | (128) |
| Chang et al, 2020  | IncRNA-NONMUT037835.2 | RANK | Inhibit differentiation | (129) |
| Cong et al, 2020   | IncRNA GAS5 | miR-21 | Promote apoptosis | (131) |

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

Acknowledgements

Not applicable.

Funding

Funding for the current study was provided by the Key Project of Natural Science Foundation of Shandong Province (grant no. ZR2020KH011), the Natural Science Foundation of Shandong Province (grant no. ZR2020MH362), the Cao Yixun National Famous Old Chinese Medicine Experts Inheritance Studio [Chinese Medicine Education Letter (2018) grant no. 134] and the Xu Zhanwang Shandong MingLao Traditional Chinese Medicine Experts Inheritance Studio [Shandong Provincial Health Commission, Lu Wei Han (2019) grant no. 92].

Availability of data and materials

Not applicable.

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

Not applicable.

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: 101989, 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: PPARY 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 CF: 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, Lihui Y, Ziqi G, Zhichen W, Zirui W and Shengwang W: The roles of miRNA, IncRNA 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 IncRNAs, 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: IncRNA Xist regulates osteoblast differentiation by sponging miR-19a-3p in aging-induced osteoporosis. Aging Dis 11: 1058-1068, 2020.
13. Meng XC, 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: 3795, 2019.
15. Tang QQ and Lane MD: Adipogenesis: From stem cell to adipocyte. Annu Rev Biochem 81: 715-736, 2012.
16. Frohatsou O, Zagoura D, Orfanos NK, Pappa KI, Marinou E, Anagnostou NP and Roubelakis MG: miR-26a mediates adipogenesis of amniotic fluid mesenchymal/stem/trial 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 HG, 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 IncRNAs, mRNAs and miRNAs 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-19a-5p 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-19a-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 osteoarthritic rats. Biochem Biophys Res Commun 521: 721-734, 2021.
24. Li J, Ayoub A, Xiu Y, Yin X, Sanders JO, Mesfin A, Xing L, Yao Z and Boyce BF: Brown adipocytes: From stem cell to adipocyte differentiation through mTOR signaling pathway. Mol Cell Endocrinol 476: 155-164, 2018.
31. Zhang M, Yuan SZ, Sun H, Sun L, Zhou D and Yan J: miR-199b-5p increases chemosensitivity of oxaliplatin-resistant colorectal cancer. Mol Cancer 18: 43, 2019.

32. Li Z, Wang Y, Xiang S, Zheng Z, Bian Y, Feng B and Weng X: NanoRNA-S4 promotes osteogenic differentiation of human bone marrow-derived mesenchymal stem cells by directly downregulating HMGAA2. Biochem Biophys Res Commun 522: 9-14, 2020.

33. Shen PF, Wang B, Qu YX, Zheng C, Xu JD, Xie ZK and Li Y: MicroRNA-126 promotes osteogenic differentiation of human bone marrow mesenchymal stem cells in postmenopausal osteoporosis through regulating the miR-196a-5p/Hmgaa2 axis. J Bone Miner Metab 38: 794-805, 2020.

34. Xu S and Wu X: miR-134 inhibits chondrogenic differentiation of human bone marrow mesenchymal stem cells by targeting TET2. Gene 726: 14493-2020.

35. Zhang M, Yuan SZ, Sun H, Sun L, Zhou D and Yan J: miR-199-5p promotes chondrogenic differentiation of C3H10T1/2 cells by regulating JAG1. J Tissue Eng Regen Med 14: 1618-1629, 2020.

36. Calvier L, Chouvarine P, Legchenko E, Hoffmann N, Geldner J, Calmon B and Yang T: MicroRNA-664a-5p promotes osteogenic differentiation of human bone marrow-derived mesenchymal stem cells. J Cell Biochem 121: 1216-1226, 2020.

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 lineage in diabetic patients. Diabetologia 55: S2-S268, 2012.

39. Jamali L, Toligt R, Tutunchi S, Panahi G, Borhani A, Akhavan S, Nourmohammadi P, Gheradian SMH, Rasouli M and Mirzaei H: MicroRNA-218 promotes osteogenic differentiation of bone marrow-derived mesenchymal stem cells in osteoporosis. J Cell Physiol: Oct 28, 2020 (Epub ahead of print). doi:10.1002/jcp.29527.

40. Cui P, Zhao X, Liu B, Hu F and Qiang L: Distinct functions of PPARγ isoforms in regulating adipocyte plasticity. Biochem Biophys Res Commun 481: 132-138, 2016.

41. Zhai B, 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 FTO. Mol Ther Nucleic Acids 17: 590-600, 2019.

42. Calvadar C, Chouvarine P, Legchenko E, Hoffmann N, Gheradian SMH, Rasouli M and Mirzaei H: MicroRNA-218 promotes osteogenic differentiation of bone marrow-derived mesenchymal stem cells. J Cell Physiol 235: 2857-2865, 2020.

43. Li Z, Li T, Zhu F, Deng SN, Li X and He Y: Regulatory roles of miR-22-Red1-mediated mitochondrial ROS and cellular autophagy in ionizing radiation-induced BMSC injury. Cell Death Dis 10: 227, 2019.

44. Yu D, Wang Y and Chen LL: Cellular functions of long noncoding RNAs. Nat Cell Biol 21: 542-551, 2019.

45. St Laurent G, Wahlestedt C and Kapranov P: The landscape of long noncoding RNA classification. Trends Genet 31: 239-251, 2015.

46. Hernandez SL, Nelson M, Sampedro GR, Bagrodia N, Defnet AM, Lee B, Emolo J, Kirscher R, Wu L, Biermann H, et al: Staphylococcus aureus alpha toxin activates Notch in vascular smooth muscle cells. J Cell Sci 123: 2857-2865, 2020.

47. Man S, Sanchez Duffhues G, Ten Dijker 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 Biochem: Sep 19, 2019 (Epub ahead of print). doi:10.1002/jcb.29527.

49. Li Z, Shi L, Liu J, Lin J, Zheng G, Liu W, Tang S, Cen S, Ye G, Li Z, et al: GASK protects against osteoporosis by targeting PUF1/SMAD7 axis in osteoblast differentiation. Elife 9: e59079, 2020.

50. Zheng J, Guo H, Qin Y, Liu Z, Ding Z, Zhang L and Wang W: SNHG5/miR-38-3p/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.

51. Li M, Xie Z, Li J, Liu J, Zheng G, Liu W, Tang S, Cen S, Ye G, Li Z, et al: GASK protects against osteoporosis by targeting PUF1/SMAD7 axis in osteoblast differentiation. Elife 9: e59079, 2020.

52. Li Z, Shi L, Liu J, Lin J, Zheng G, Liu W, Tang S, Cen S, Ye G, Li Z, et al: GASK protects against osteoporosis by targeting PUF1/SMAD7 axis in osteoblast differentiation. Elife 9: e59079, 2020.
67. Gan X, Liu S and Liang K: MicroRNA-19b-3p promotes cell proliferation and osteogenic differentiation of BMSCs by interacting with IncRNA H19. BMC Med Genet 21: 143, 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-214-3p. Gene 788: 4812-4825, 2018.

69. Li M, Cong R, Yang L, Yang L, Zhang Y and Fu Q: A novel IncRNA LNC_0000552 leads to the dysfunction of osteoporotic BMSCs via the miR-96-5p-PIK3R1 axis. Cell Death Dis 11: 795, 2020.

70. Guo B, Li S and Li G: Long noncoding RNA (IncRNA) small nuclear RNA Host Gene 5 (SNHG5) regulates proliferation, differentiation, and apoptosis of K562 cells in chronic Myeloid 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_LARP1 inhibits cell proliferation and invasion of gastric cancer by sponging miR-424-5p and regulating LATSI expression. Mol Cancer 16: 151, 2017.

72. Wang R, Zhang S, Chen X, Li N, Li J, Ria P and Liang H: CircNTSE acts as a sponge of miR-422a to promote glialbloma cell migration and invasion. Canc Lett 378: 4812-4825, 2018.

73. Wang XQ, Li PB, Guo SF, Yang QS, Chen ZX, Wang D and Shi SB: circRNA_0063935 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_0063924 could sponging miR-98 to regulate BMP2 expression in postmenopausal osteoporosis. Biochem Biophys Res Commun 516: 546-550, 2020.

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 binding site to alleviate the progression of osteoporosis. Int J Biochem Cell Biol 122: 105710, 2020.

76. Shen W, Sun B, Zhou C, Ming W, Zhang S and Wu X: CircFOX1P/FOX1P promotes osteogenic differentiation in adipose-derived mesenchymal stem cells and bone regeneration in vivo via miR-33a-5p. J Cell Mol Med 24: 12513-12524, 2020.

77. Cherubini A, Barilani M, Rossi RL, Jalal MMK, Rossini F, Buono G, Ragni E, Cantarella G, Simpson HarW, Péault B and Grazzi A: FoXP1 circular RNA sustains mesenchymal stem cell identity via micro RNA inhibition. Nucleic Acids Res 47: 12754-12763, 2019.

78. Liu F, Zhang J, Qin L, Yang Z, Xiong J, Zhang Y, Li S, Buono G, Ragni E, Cantarella G, Simpson HarW, Péault B and Grazzi A: IncRNA CYTOR promotes pancreatic cancer cell migration and proliferation by sponging miR-21. J Cell Mol Med 25: 32-40, 2021.

79. Garcia J and Delany AM: MicroRNAs regulating TGFβ and BMP signaling in the osteoblast lineage. Bone 143: 115791, 2021.

80. Chen Y and Yang C: miR-197-3p-induced downregulation of lym-63 deubiquitase promotes cell proliferation and inhibits cell apoptosis in lung adenocarcinoma cell lines. Mol Med Rep 17: 3921-3927, 2018.

81. You M, Zhang L, Zhang X, Fu Y and Dong X: MicroRNA-197-3p inhibits the osteogenic differentiation in osteoblasts via down-regulating KLF 10. Clin Investig 101: 167-171, 2021.

82. Seeliger C, Karpinski K, Haug AT, Vester H, Schmitt A, Bauer JS and van Gerven M: Five freely circulating miRNAs and bone tissue miRNAs are associated with osteoporotic fractures. J Bone Miner Res 29: 1718-1728, 2014.

83. Yang C, Wang X, Li J, Lu R, Zhao K, Li B, Ma Y and Li Y: miR-205-5p inhibits thymin epithelial cell proliferation via FA2H-TPAP2A feedback regulation in age-associated thymus involution. Mol Immunol 122: 173-185, 2020.

84. Otra 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.

85. Zhu H, Shan Y, Ge K, Lu J, Kong W and Jia C: IncRNA CYTOR promotes pancreatic cancer cell migration and proliferation by sponging miR-205-5p. Pancreatology 20: 1139-1148, 2020.

86. Huang M, Li X, Zhou C, Si M, Zheng H, Chen L and Ding H: Noncoding RNA miR-205-5p mediates osteopathogenesis and osteosynthesis and osteoblast differentiation by regulating RUNX2. J Cell Biochem 121: 4196-4203, 2020.

87. Baglio SR, Rooijiers K, Koppers-Lalic D, Verweij FJ, Perez Lanzon M, Zini N, Naajkens B, Perut F, Niessen HW, Bader N and Plevy SE: Human peripheral blood mononuclear cell-derived mesenchymal stem cells secrete exosomes enriched in distinctive miRNA and iRNA species. Stem Cell Res Ther 5: 2021.

88. Sunder IK, Li D and Rahman J: 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.

89. 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.

90. Wang N, Zhou Z, Wu T, Liu W, Yin P, Pan C and Yu X: TFN-a-induced NF-kB activation upregulates microRNA-150-3p and inhibits osteogenesis of mesenchymal stem cells by targeting β-catenin. Open Biol 6: 210056, 2016.

91. 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.

92. Mao X, Lin X, Chen G, 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.

93. 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.

94. Gu Z, Xie D, Huang C, Ding R, Zhang R, Li Q, Lin C and Qiu Y: MicroRNA-497 elevation or LRG1 knockdown promotes osteosclerosis and collagen synthesis in osteoporosis via TGF-beta1/Smads signalling pathway. J Cell Mol Med 24: 12553-12564, 2020.

95. Mohamad N, Nabib ES, Zakaria ZM, Nagaty MM and Metwaly RG: Insight into the possible role of miR-214 in primary osteoporosis via osteoster. J Cell Biochem 120: 15518-15526, 2019.

96. Lu XZ, Yang ZH, Zhang HJ, Zhu LL, Mao XL and Yuan Y: miR-214 protects MC3T3-E1 osteoblasts against H2O2-induced apoptosis by suppressing oxidative stress and targeting ATF4. Eur Rev Med Pharmacol Sci 21: 4762-4770, 2017.

97. Yang C, Gu Z, Ding R, Huang C, Li Q, Xie D and Qiu R: Long non-coding RNA MEG3 silencing and microRNA-214 restoration elevates the osteogenic expression to ameliorate osteoporosis by limiting TNXIP. J Cell Mol Med 25: 2025-2039, 2021.

98. Vimalraj S, Saravanan S, Vairamani M, Gopalakrishnan C, Sastry TP and Selvamurugan N: A Combinatorial effect of carboxymethyl cellulose base scaffold and microRNA-15b on osteoblast differentiation. Int J 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. Nasiri Z, Oskuee RK, Jaafari MR and Forouzandeh Moghadam M: Exosomes-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 osteoporosis by directly inhibiting the Wnt/β-catenin signaling pathway. exp Aging 15: 255, 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-DANCRA regulates miR-21 to promote apoptosis of osteoclasts. c lin interv Aging 15: 1163-1169, 2020.

116. Wang CG, Hu YH, Su SL and Zhong D: IncRNA DANCRA 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: IncRNA 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: 115072, 2020.

120. Liu H, Wang YW, Chen WD, Dong HH and Xu YJ: Iron accumulation regulates osteoblast apoptosis through IncRNA 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 IncRNA 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 osteoblasts proliferation and inhibits apoptosis via the Mir-7223-5p/PIK3R1 axis. Aging (Albany NY) 11: 11988-12001, 2019.

123. Zhao 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 CYD/ 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, Shen Z, Lv J, Shen S and Ma J: MicroRNA-25-3p regulates osteoclasts through nuclear factor Χ. Biochem Biophys Res Commun 522: 74-80, 2020.

128. Zhang Y, Chen XF, Li J, He F, Li X and Guo Y: IncRNA Nett1 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: IncRNA expression profiles and the negative regulation of IncRNA-NOMMTU037835.2 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: IncRNA GASS is upregulated in osteoporosis and downregulates miR-21 to promote apoptosis of osteoclasts. Clin Interv Aging 15: 1163-1169, 2020.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.