Biomedicine & Pharmacotherapy 142 (2021) 111942

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Contribution of miRNAs and lncRNAs in osteogenesis and related disorders

Soudeh Ghafouri-Fard [a], Atefe Abak [b], Shiva Tavakkoli Avval [c], Shayan Rahmani [d], Hamed Shoorei [e], Mohammad Taheri [f,*], Mohammad Samadian [g,*]

[a] Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Tabriz Dental School, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Department of Anatomical Sciences, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[f] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[g] Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
lncRNA
miRNA
Osteogenesis

ABSTRACT

Non-coding RNAs have been found to regulate several developmental processes among them is osteogenesis. Although these transcripts have several distinct classes, two classes i.e. microRNAs and long non-coding RNAs have attained more attention. These transcripts regulate intramembranous as well as endochondral ossification processes. The effects of microRNAs on osteogenesis are mostly mediated through modulation of Wnt/β-catenin and TGFβ/BMP pathways. Long non-coding RNAs can directly affect expression of these pathways or osteogenic transcription factors. Moreover, they can serve as a molecular sponge for miRNAs. MALAT1/miR-30, MALAt1/miR-214, LEF1-AS1/miR-24-3p, MCF2L-AS1/miR-33a, MSC-AS1/miR-140-5p and KCNQ1OT1/miR-214 are examples of such kind of interaction between lncRNAs and miRNAs in the context of osteogenesis. In the current paper, we explain these two classes of non-coding RNAs in the osteogenesis and related disorders.

1. Introduction

Bones are produced from the paraxial mesoderm through finely tuned mechanisms. In fact, the skeleton can be generated from three distinctive lineages. The somites and lateral plate produce axial and limb skeletons, respectively; and the cranial neural crest generates branchial arch and craniofacial bones and cartilage [1]. Osteogenesis is accomplished through two main ways, both of them leading to conversion of formerly established mesenchymal tissues into bone tissue. Yet, this process can be achieved directly through intramembranous ossification process or indirectly through primary formation of cartilages and their replacement by bone cells which is termed endochondral ossification. The former is involved in the formation of skull bones, while the latter contributes in the osteogenesis in other regions [1]. A number of morphogenetic proteins, namely BMP2, BMP4, and BMP7 as well as CBFA1 transcription factors contribute in the intramembranous ossification process [2]. On the other hand, endochondral ossification comprises five distinct stages through which mesenchymal cells produce cartilage tissue which is then replaced by bone. The first stage is commitment to mesenchymal cells to cartilage cells which is induced by paracrine molecules that stimulate expression of Pax1 and Scleraxis transcription factors in the mesodermal cells. Then, the committed mesenchyme cells are converted into compact nodules and differentiated chondrocytes. This stage is facilitated by N-cadherin and N-CAM. The subsequent stage involves rapid proliferation of chondrocytes and secretion of cartilage-specific extracellular matrix by these cells, subsequent hypertrophy of chondrocytes and their mineralization by calcium carbonate. Finally, this process is completed by the invasion of the cartilage model by blood vessels, induction of apoptosis in the hypertrophic chondrocytes, differentiation of a group of cells around the cartilage model into osteoblasts and construction of bone matrix by the osteoblasts [1].

An important signaling pathway in the development, preservation and osteogenic differentiation of mesenchymal stem cells is Wnt signaling pathway. Activation of this pathway enhances bone formation, whereas its inactivation results in osteopenic conditions [3]. Activation of canonical Wnt signaling results in the stabilization of β catenin in the cytoplasm. In the absence of Wnt ligands, a protein degradation complex containing GSK3β, axin and APC phosphorylates β catenin, facilitating its ubiquitination and subsequent degradation in the proteasome [4]. In

* Corresponding authors.
E-mail addresses: mohammad_823@yahoo.com (M. Taheri), mdsamadian@hotmail.com (M. Samadian).

https://doi.org/10.1016/j.biopha.2021.111942
Received 12 June 2021; Received in revised form 7 July 2021; Accepted 14 July 2021

the presence of Wnt 1, 3a, and 8 as the canonical Wnt ligands, these ligands bind to the Fzd receptors and one of the coreceptors, leading to phosphorylation of Dvl and subsequent inhibition of phosphorylation of β catenin by GSK3β. These events enhance stabilization of β catenin and its translocation into the nucleus. Therapeutic targeting of Wnt signaling is a possible route for treatment of osteogenic disorders [3].

Several non-coding RNAs (ncRNAs), particularly long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) have been found to affect osteogenesis process and contribute in the pathobiology of the related disorders. The effects of these non-coding RNAs are exerted through modulation of signaling pathways controlling osteogenesis. Fig. 1 illustrates the role of ncRNAs in regulating the developmental processes of skeletal patterning and a variety of bone diseases via modulating the Wnt signaling cascade.

Another important mechanism of bone formation relies on the parathyroid hormone (PTH). This hormone regulates calcium homeostasis and induces bone remodeling through directly influencing the function of osteoblasts and osteocytes, and indirectly affecting osteoclasts. Depending on the dose and periodicity of PTH administration, PTH can stimulate both bone resorption and bone formation [6]. Function of PTH, Wnt and BMP in the osteogenic process can be regulated by ncRNAs. Fig. 2 depicts the cross-talk between Wnt, PTH and BMP signaling pathways in endochondral bone formation and intramembranous bone formation and the role of miRNAs and lncRNAs in the regulation of this cross-talk.

Development of cranial bones can be also affected by miRNAs. Fig. 3 represents the potential role of miRNAs on function of osteogenic factors and modulation of the osteoblast differentiation and bone formation in the development of cranial sutures.

In the following sections, we describe the role miRNAs and lncRNAs in osteogenesis and related disorders.

2. Contribution of miRNAs in the osteogenesis

Differential expression of miRNAs during the osteogenic differentiation has suggested indispensable role of these transcripts in bone formation. miR-128 has been found to be up-regulated in the course of osteogenic differentiation of rat bone marrow stem cells (rBMSCs). Up-regulation of this miRNA has enhanced osteogenic differentiation of these stem cells through inducing expression of ALP, increasing

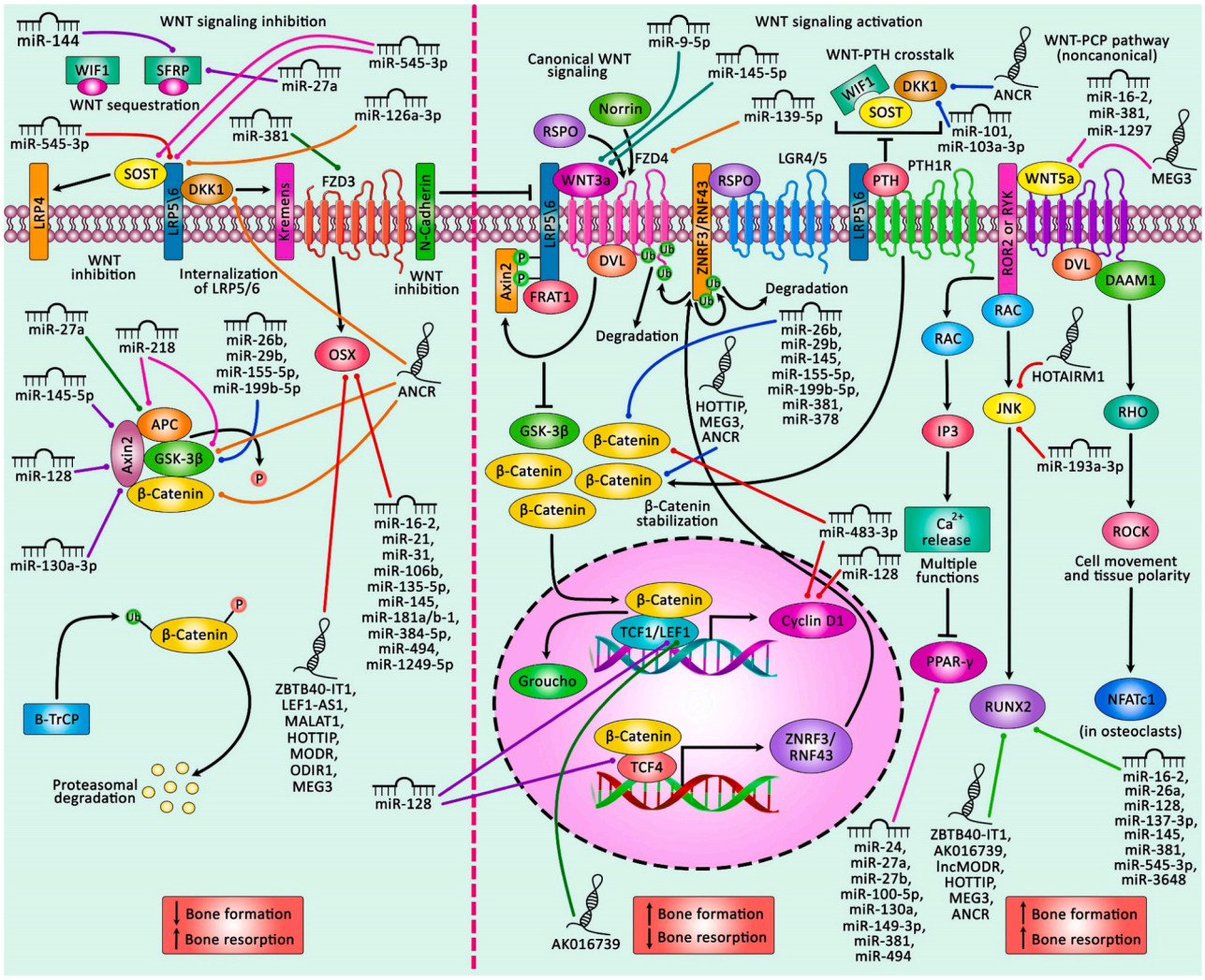

Fig. 1. A schematic representation of the crosstalk between non-coding RNAs and the Wnt/β-catenin pathway in the regulation of osteogenesis. In the absence of WNT signaling, destruction complex phosphorylates cytosolic β-catenin. The phosphorylated β-catenin could be targeted for polyubiquitination, thus the amounts of β-catenin are reduced by the proteasome degradation. Following activation of Wnt signaling, the function of destruction complex which contains FRAT1 and GSK-3β is suppressed. Then, unphosphorylated β-catenin could be accumulated in the cytoplasm and translocate into the nucleus, and thereby could activate the expression of WNT target genes such as members of the TCF/LEF family of transcription factors whilst displacing Groucho to control target gene transcription [5]. Accumulating evidence has illustrated that aberrant expression of various miRNAs as well as lncRNAs affects the Wnt/β-catenin signaling cascade, thus being involved in causing several bone diseases including osteoporosis, osteopenia, osteonecrosis, atrophic nonunion, and peri-implantitis.

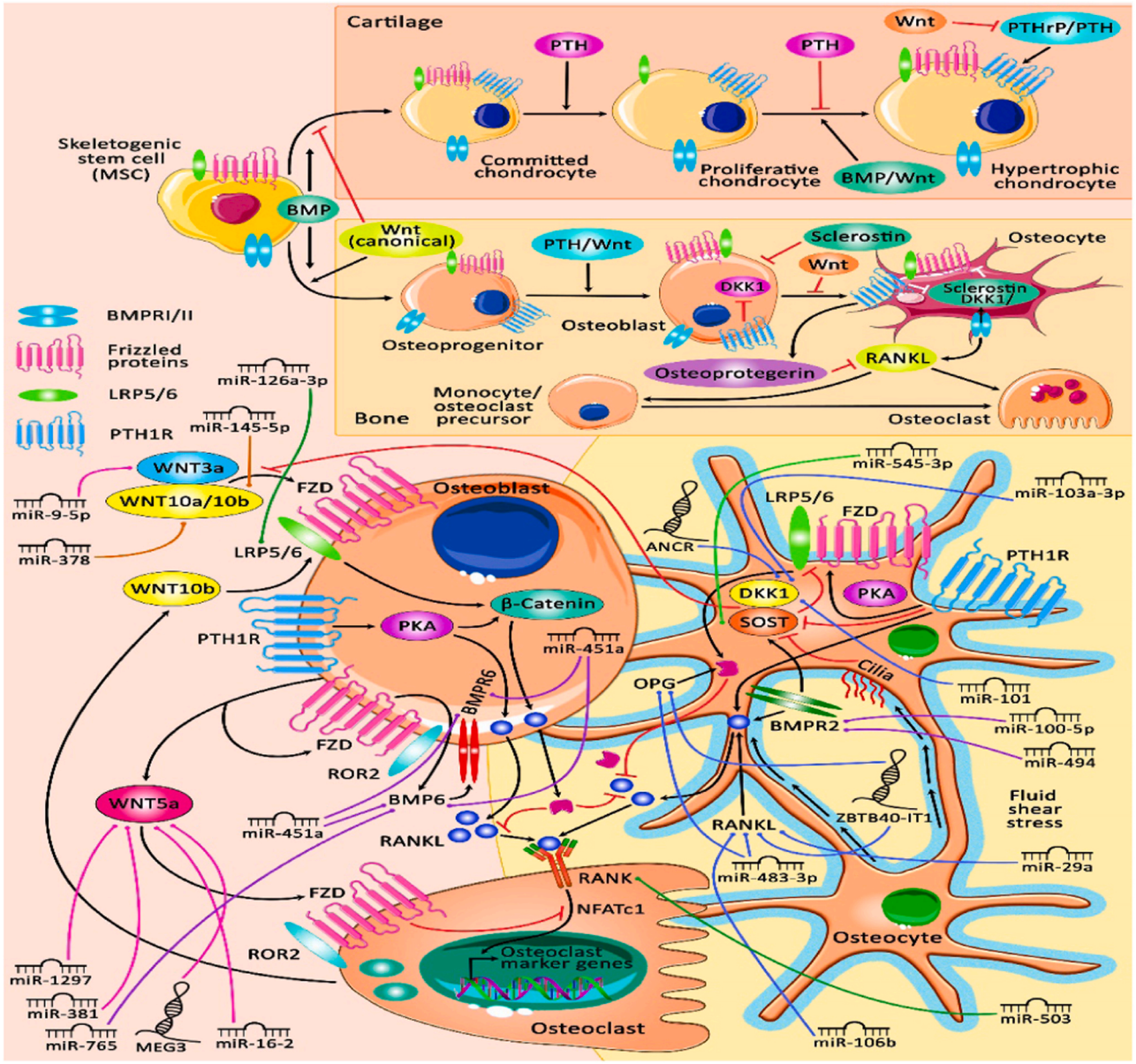

Fig. 2. A schematic illustration of the crosstalk between WNT, PTH and BMP signaling cascades in cartilage and bone cell lineages and their negative regulation through various non-coding RNAs. Wnt ligands could modulate canonical pathway via β-catenin and BMP signaling that could be modulated through SMAD1, SMAD3 and SMAD5. Osteocytes could regulate bone formation via the secretion of DKK1 and the WNT antagonist sclerostin (SOST), the expression of which is modulated through mechanosignals and signaling of BMP and PTH. PTH could play an effective role in inhibiting the expression of these antagonists whilst BMPR1A-mediated BMP pathway could trigger their expression. In addition, WNT cascade in osteocytes could regulate the generation of OPG that is the decoy receptor for the key osteoclast differentiation factor RANKL. Furthermore, osteoblast-expressed WNT5a could promote the differentiation of osteoclast precursors through binding to the FZD–ROR2 receptor complex. Osteoclasts could enhance the local differentiation of osteoblasts at the end of the resorption stage via producing WNT ligands as a result of the feedback loop for bone remodeling. Besides, the activation of PTH1R-mediated cascade in osteocytes and osteoblasts results in β-catenin stabilization, and thereby triggering the activation of WNT pathway [5,7]. Ectopic expression of miRNAs and lncRNAs could negatively modulate the BMP, PTH and Wnt effects on osteoclast differentiation which could in turn have an important role in dysregulation the expression of various factors involved in the osteogenesis, and thereby causing serious bone diseases.

mineralization of matrix, and increasing expressions of the osteogenic proteins RUNX2, BMP-2, and COLIA1, while suppression of miR-128 has inhibited differentiation of osteoblast. Functionally, miR-128 targets DKK2, an antagonist for Wnt signaling pathway. Through this pathway, miR-128 enhances activity of Wnt/β-catenin [9]. miR-130a-3p is another miRNA that can increase the osteogenic differentiation of ADSCs through reducing expression of SIRT7 and subsequent enhancement of Wnt signaling-related proteins [10].

On the other hand, miR-139-5p has been found to repress osteogenic differentiation of BMSCs through targeting Wnt/β-Catenin cascade. This result has been verified through monitoring ALP levels of activity, and expression levels of osteogenic proteins such as Runx2, Col-1, and OCN. miR-139-5p has been shown to directly target CTNNB1 and FZD4, to important molecules in Wnt/β-catenin cascade [11]. In addition, miR-378 has been shown suppress osteogenesis of human MSCs through targeting Wnt6 and Wnt10a. This miRNA inactivates Wnt/β-catenin signaling [12]. Moreover, expression of miR-145 has been demonstrated to be diminished during osteogenesis of h-JBMMSCs. Suppression of miR-145 expression has led to induction of osteogenic differentiation of these cells, as documented by activation of ALP, enhancement of

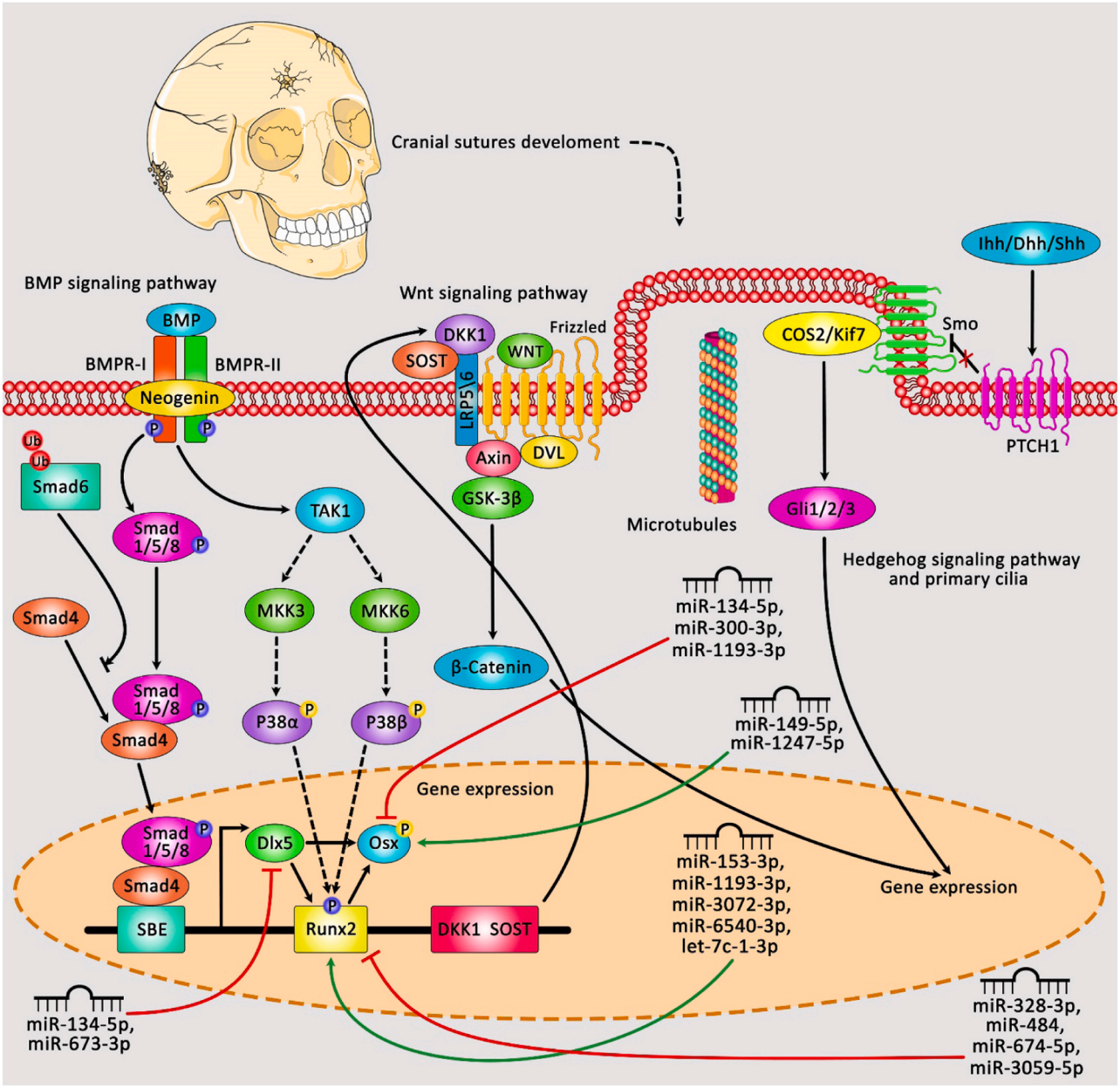

Fig. 3. A schematic summary of regulation of TGF/BMP, Wnt, Hedgehog pathways by various miRNAs in the development of skull vault. Several miRNAs have been detected as crucial regulators of organogenesis contributing in a range of developmental processes. In the skull vault, multiple miRNAs were recognized to target Runx2, Dlx5, and Osterix in neural crest derived frontal bone and mesoderm derived parietal bone. Green arrows indicate up-regulated miRNAs and red arrows show down-regulated ones. These miRNAs play an important role in enhancing or regulating cell capacities for osteogenesis [8]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mineralization, and induction of expression RUNX2, OSX, ALP and COL1A1. The effects of this miRNA in suppression of osteogenesis is mediated through inhibition of SEMA3A [13]. miR-126a-3p also affects osteogenesis through inhibition of LRP6 expression and subsequent blocking of Wnt activity [14]. Table 1 shows the impact of miRNAs in regulation of osteogenesis.

3. Contribution of miRNAs in the pathogenesis of osteoporosis

Dysregulation of miRNAs expression has also been involved in the pathogenesis of osteoporosis. For instance, experiments in bone tissues obtained from patients with osteoporosis have shown that miR-16-2* levels are inversely correlated with expression of genes involved in the bone formation. Further experiments have demonstrated reduction in expression of this miRNA during differentiation of osteoblasts. Moreover, over-expression of miR-16-2* in hBMSCs has interfered with their osteogenic differentiation through blocking the WNT signaling, since miR-16-2* directly targets WNT5A [49]. Another experiment has shown the presence of miR-186 in hBMSCs-derived exosomes and their impact on enhancement of osteogenesis in ovariectomized rats, suggesting possible role of this miRNA in attenuation of post-menopausal osteoporosis [50]. Another experiment in ovariectomized mice model has shown increase in bone volume in miR-185 knock out mice compared to wild-type mice. Dual-luciferase reporter assay has shown direct targeting of biglycan (Bgn) by miR-185. Notably, Bgn enhances osteogenesis through the BMP/Smad pathway. Therefore, miR-185 silencing enhances bone formation in the course of osteoporosis, possibly via modulation of Bgn expression and BMP/Smad signaling [51].

Table 1
miRNAs in the osteogenesis.

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
miR-128	Rat	rBMSCs	DKK2, RUNX2, BMP-2, COLIA1, Lef-1, Tcf-4, Cyclin-D1, Axin2	WNT/β-catenin	miR-128 by targeting DKK2 and activating downstream molecules of WNT signaling pathways could promote osteogenic differentiation of rBMSCs.	[9]
miR-139-5p	Human	hBMSCs	CTNNB1, FZD4, RUNX2, Alp, OCN, Col I	WNT/β-catenin	miR-139-5p via targeting WNT/β-catenin signaling pathway could represses BMSC osteogenesis.	[11]
miR-378	TG Mouse, Human	BMSCs	WNT10a, WNT6	WNT/β-catenin	miR-378 via inactivating WNT/β-catenin signaling could suppress osteogenesis and bone formation.	[12]
miR-145	orthognathic surgery patients (n = 3)	293T, hFOB1.19, h-JBMMSCs	SEMA3A, Runx2, Osx, NRP1	WNT/β-catenin	miR-145 by targeting SEMA3A could suppress osteogenic differentiation of h-JBMMSCs.	[13]
miR-130a-3p	human	ADSCs	ALP, RUNX2, Osterix, Axin2, WNT1, SIRT7	WNT/β-catenin	Exosomal miR-130a-3p by mediating SIRT7/WNT/β-catenin axis could promote osteogenic differentiation of ADSCs.	[10]
miR-126a-3p	Human	hAMSCs	RUNX2, ALP, IBSP, OPN, LRP6, CTNNB1	WNT	miR-126a-3p by suppressing the WNT/LRP6 pathway could suppress osteogenesis.	[14]
miR-27a	Labrador dogs	Canine BMSCs	SFRP1, DKK2, Runx2, BMP-2, OCN, COLIA1, VEGF, Ang1	WNT	miR-27a by targeting DKK2 and SFRP1 could promote osteogenesis–angiogenesis in BMSCs.	[15]
miR-145-5p	Rats	ADSCs	Sema3a, RUNX2, ALP, COL I, WNT3a, Axin2, WNT10b	WNT/β-catenin	miR-145-5p by targeting sema3a, could suppress osteogenic differentiation of ADSCs partly through WNT signaling pathway.	[16]
miR-21	Labrador dogs	BMSCs	HIF-1α, VEGF, BMP-2, OPN, OCN, Runx2, PTEN	PI3K/AKT	miR-21 via the PTEN/PI3K/Akt/HIF-1α pathway could promote osteogenesis and enhance bone regeneration in critical size defects.	[17]
miR-181a/b-1	Human osteoarthritic (OA) articular cartilage tissue, human cancellous bone	Human primary de-differentiated chondrocytes (DDCs)	OSX, RUNX2, OCN, PTEN	PI3K/AKT	miR-181a/b-1 by modulating PTEN/PI3K/AKT signaling could enhance osteogenic differentiation of DDCs and mitochondrial metabolism.	[18]
miR-19b-3p	SD rat, SCI (spinal cord injury, n = 12), control group (n = 12)	BMSCs	Osterix, osteocalcin, LC3II/I, p62, Beclin-1, PTEN	Akt/mTOR	miR-19b-3p via regulating the PTEN/Akt/mTOR signaling could suppress osteogenesis after SCI.	[19]
miR-29b	Human	hAMSCs	Runx2, BSP, OPN, ALP, osteocalcin, PTEN, GSK-3β	AKT/β-catenin	miR-29b via the PTEN/AKT/β-catenin signaling pathway could promote the osteogenic differentiation of hADSCs.	[20]
miR-877-3p	Mouse	MC3T3-E1	Smad2/3/7, RUNX2, COL1A1, OSX, TGF-β1	–	miR-877-3p via silencing Smad7 could promote osteoblastic differentiation of MC3T3-E1 cells induced by TGF-β1.	[21]
miR-200b	Rat, Human	rBMSCs, HUVECs	Alp, Runx2, Ocn, Col 1, Cx43, Cxcl9, Cxcl12, VEGF-A, ZEB2, ETS1, KDR, GATA2, CXCR3	TGF-β, ERK1/2	Inhibition of miR-200b in BMSCs could increase osteogenic differentiation through downregulation of VEGF-A.	[22]
miR-765	–	hBMSCs	BMP6, RUNX2, OCN, Smad1/5/9	–	miR-765 by targeting BMP6 via regulation of the BMP6/Smad1/5/9 signaling pathway could inhibit osteogenic differentiation of hMSCs.	[23]
miR-137	Human	hAMSCs	RUNX2, ALP, OCN, LSD1, BMP2, SMAD4	–	miR-137 knockdown via the LSD1/BMP2/SMAD4 signaling network could promote the osteogenic differentiation of hASCs.	[24]
miR-494	Mouse	C2C12, 293T	ALP, OC, OSX, RUNX2, BMP2, BMPR2, MYOD, MYOGENIN, PPARγ	–	miR-494 by regulating BMP signaling could inhibit osteoblast differentiation.	[25]
miR-206	Human	hDPSCs	RUNX2, OCN, ALP, CX43	circAKT3	circAKT3 by arresting the inhibitive effect of miR-206 on CX43 expression could positively regulate osteogenic differentiation of hDPCSs.	[26]
miR-137	BALB/c-nu/nu nude mice	hAMSCs	NOTCH1, HES1, RUNX2, LSD1, BMP2, SMAD4		miR-137 by targeting NOTCH1/LSD1/BMP2 co-regulatory network could regulate osteoblastic differentiation of hASCs.	[27]
miR-24	Rat, Human	hAMSCs	Runx2, Osterix, OPN, BSP, C/EBPα, PPARγ	HOXB7/β-catenin	miR-24 via HOXB7/β-catenin complex could repress osteogenesis of AMSCs.	[28]
miR-22e3p	–	MC3T3-E1	Bmp7, RUNX2, Alp	Mm9_circ_009056	Mm9_circ_009056 by targeting BMP7 via calcitonin gene-related peptide (CGRP)-mediated miR-22e3p could enhance osteogenesis.	[29]
miR-193a-3p	Human	hBMSCs	MAP3k3, RUNX2, OCN, ERK5, ERK1	JNK	miR-193a-3p by targeting MAP3k3 could regulate substrate Topography-Induced osteogenesis of hBMSCs.	[30]
miR-21	–	hBMSCs	RUNX2, OSX, OPN, OCN	–	Adrenaline via repressing miR-21 could inhibit osteogenesis.	[31]
miR-101-3p	Human	HGF, hBMSCs	BMP2, OC, ETV1, SOX11, FOXP1, GATA6	–	miR-101-3p by regulating humoral factors from HGFs could suppress osteogenesis in MSCs.	[32]
miR-146a	Rat, Human	BMSCs, HUVECs	VEGF, ANG1, BMP-2, Runx2, NF2, Smad4	–	Sr-CS-Exo by stimulating BMSCs via miR-146a could regulate angiogenesis and osteogenesis.	[33]

(*continued on next page*)

Table 1 (*continued*)

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
miR-31	–	hMSCs	SATB2, Ocn, BSP, Runx2, OSX	–	miR-31 by targeting SATB2 could regulate the osteogenesis of hMSCs.	[34]
miR-199b-5p	Human	hBMSCs	GSK-3b, β-catenin, ALP, RUNX2	–	miR-199b-5p via suppressing GSK-3b/β-catenin signaling pathway could regulate osteoblast differentiation of BMSCs during osteogenesis.	[35]
miR-130b	–	MC3T3-E1, C2C12	PTEN, ALP, Col I, OPN, OCN, RUNX2, SMAD1, BMP-2	–	Ortho-silicic acid by targeting PTEN via miR-130b could enhance osteogenesis of osteoblasts.	[36]
miR-145a	C57BL/6 mice	mBMSCs	p21, RUNX2, BMP9, Alp, p53	–	p53-induced miR-145a could promote cellular senescence and inhibit the osteogenic differentiation of MSCs.	[37]
miR-1323	atrophic non-union fracture specimens (n = 5), standard healing fracture specimens (n = 5)	hMSc	BMP4, SMAD4, ALP, Col I, RUNX2	–	miR-1323 by targeting BMP4 and SMAD4 via modulating the nuclear translocation of the transcriptional co-activator TAZ could down-regulate osteogenic differentiation of hMSc.	[38]
miR-144-3p	Aplastic anemia patients (n = 23), healthy subjects (n = 18)	hBMSCs	TET2	–	miR-144-3p via repressing TET2 could impair the osteogenic capacity of BMSCs from patients with aplastic anemia.	[39]
miR-199a-5p	Human	hMSCs	RUNX2, OCN, MSX2, BMP2, SP7, SPP1, HIF-1α, Twist	–	miR-199a-5p by inhibiting HIF1a-Twist1 pathway could enhance osteogenesis maturation of hMSCs.	[40]
miR-30e	$ApoE^{-/-}$ mice/ wild-type mice, Human	Mouse smooth muscle cells (SMCs), mBMSCs	CNN1, SM22a, VCL, Igf2, Runx2	–	miR-30e by targeting IGF2 could repress the osteogenic program in MSCs and SMCs and drive their differentiation into adipogenic or smooth muscle lineage, respectively.	[41]
miR-34a	Rat	rBMSCs	Runx2, Alp, Col I, Ocn, NOTCH1	–	miR-34a by suppressing NOTCH1 could improve the osteogenic differentiation of irradiated BMSCs.	[42]
miR-143	C57BL/6 mice, human; tibiae and femurs, serum from patients with fractures (n = 42)	MC3T3-E1, BMSCs, $CD31^{hi}EMCN^{hi}$ endothelial cells	HDAC7, BGLAP, ALP	–	miR-143 by targeting HDAC7 could promote angiogenesis and osteoblast differentiation.	[43]
miR-148b-3p	Human	hBMSCs	ALP	–	miR-148b-3p overexpression could stimulate osteogenesis of BM-MSCs.	[44]
miR-130a, miR-27b	Human	mBMSCs BMSCs	RUNX2, Osterix, COL1A1, PPARγ, C/EBPβ	–	miR-130a and miR-27b by targeting the PPARγ could enhance osteogenesis in human MSCs.	[45]
miR-195	Mouse, Human	hBMSCs, MC3T3	ALP, RUNX2, OSX, OPN, VEGF, HOX10A, SMAD5	–	miR-195 could regulate proliferation and osteogenesis of human primary MSC and paracrine effect on angiogenesis.	[46]
miR-128-3p	Rats	MSCs	Smad5, Runx2, ALP, Collagen I	–	miR-128-3p by targeting Smad5 could regulate osteogenesis and bone fracture healing.	[47]
miR-185-5p	–	LS8 a, MC3T3-E1	Dlx2, Amel, Enam, Klk4, Mmp20, Ocn, ALP	–	miR-185-5p, induced by mutant Runx2, through suppression of the Dlx2 could negatively regulate amelogenesis and osteogenesis.	[48]

Assessment of expression of miRNAs between tissues obtained from patients with osteoporosis and normal tissues has shown differential expression of 170 miRNAs between two groups. Notably, miR-1249-5p has been the most significantly under-expressed miRNA in the osteoporotic patients. Mechanistically, miR-1249-5p has been found to increase osteogenic differentiation and levels of p-PI3K and p-Akt proteins. Luciferase assay has shown that miR-1249-5p targets PDX1 [52]. Table 2 shows the role of miRNAs in the osteoporosis.

4. Contribution of miRNAs in osteopenia

Expression of miR-3648 has been shown to be activated by PRMT3, an enzyme that facilitates formation of ω-mono- or asymmetric dimethyl arginine. Up-regulation of miR-3648 has amended osteogenesis defects in PRMT3-deficient cells. Notably, administration of *Prmt3* short hairpin RNA or a chemical inhibitor of PRMT3 has led to an osteopenia phenotype in animal models. Therefore, miR-3648 might be involved in the pathogenesis of osteopenia [170].

miR-136-3p has been found to be significantly downregulated in the mice model of alcohol-associated osteopenia. Alcohol-induced down-regulation miR-136-3p has inhibited vascularization and osteogenic differentiation of HUVECs and BMSCs, respectively. This miRNA can target PTEN in these cells, therefore significantly influencing the ability of vessel construction and osteogenic differentiation. Over-expression of miR-136-3p has amended alcohol-associated osteopenia in the animal models and restored both bone mass and construction of type-H vessels [171]. Table 3 shows the role of miRNAs in the pathogenesis of osteopenia.

5. Contribution of miRNAs in periodontal disease

Several ncRNAs contribute in the development of teeth and bones around the teeth. Fig. 4 demonstrates the role of some miRNAs as well as lncRNAs in regulating BMP and Wnt signaling cascades and their involvement in the development of teeth.

miR-4262 has been shown to be involved in the pathogenesis of periodontitis. Suppression of miR-4262 expression has led to induction of expression of SOCS4, protecting against periodontitis through reduction of inflammatory responses and induction of osteogenesis and differentiation of periodontal stem cells [173]. Another experiment in patients with periodontitis has shown high levels of miR-23a in their PDLSCs and gingival crevicular fluid. Notably, expression of this miRNA has been reduced after treatment of periodontitis. Up-regulation of miR-23a has suppressed osteogenesis of PDLSCs and decreased Smad1/5/9 phosphorylation. miR-23a has been predicted to target BMPR1B [174]. Expression of miR-132 has been decreased during osteogenic differentiation of PDLSCs, parallel with up-regulation of ALP, BMP2, Runx2 and OCN. Up-regulation of miR-132 has decreased

Table 2
miRNA in osteoporosis.

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
miR-16-2	Human	hBMSCs	WNT5A, RUNX2, Alp, OSX, OPN, OCN, COL1A1	WNT	miR-16-2 by Interfering WNT5A could regulate osteogenesis of hBMSCs.	[49]
miR-186	SD Rat	hBMSCs, mBMSCs	Alixs, CD81, CD63, BMP2, YAP, Mob1	Hippo signaling pathway	miR-186 exosomes derived from hBMSCs through hippo signaling pathway could promote osteogenesis in mBMSCs.	[50]
miR-1249-5p	Human	ADSCs	PDX1, ALP, OSX	PI3K/Akt	miR-1249-5p by targeting PDX1 could enhance the osteogenesis of ADSCs through PI3K/Akt signaling pathway.	[52]
miR-185	Mice	C2C12, 293T, MC3T3-E1, MSCs	Bgn, Osx, OC, Col1a1, Dix2, Alp, Bmp2, Smad1/5/8	BMP/Smad	miR-185 depletion by targeting Bgn could promote osteogenic differentiation and suppress bone loss in osteoporosis through the BMP/Smad pathway.	[51]
miR-216a	Human	hAMSCs	c-Cbl, RUNX2, ALP, OPN, IBSP, COL1A1, Smad7, p85	PI3K/AKT	miR-216a by regulating c-Cbl-mediated PI3K/AKT pathway could rescue dexamethasone suppression of osteogenesis, promote osteoblast differentiation and enhance bone formation.	[53]
miR-483-3p	Human	hFOB1.19	DKK2, caspase-3, WNT1, β-catenin, cyclin D1, RANKL, OPG, ALP, RUNX2, OCN, OPN	WNT	miR-483-3p by targeting DKK2 could promote the osteogenesis of hFOB1.19 via the WNT signaling pathway.	[54]
miR-330-5p	Mouse	mBMSCs	Bgn, BMP2, Smad1/5/8	BMP/Smad	Silencing of miR-330-5p by activating Bgn-mediated BMP/Smad pathway could stimulate osteogenesis in mBMSCs and inhibit bone loss in OS.	[55]
miR-29a	C57BL/6J Mice, Human	BMSC, HUVECs	VASH1, syntenin 1, TSG101	–	BMSC-derived exosomal miR-29a could promote angiogenesis and osteogenesis in mice.	[56]
miR-16-5p	Peripheral Blood Samples; Healthy Volunteers (N = 10), Postmenopausal Osteoporosis Patients (N = 10)	hMSCs	VEGFA, TP53, RPS27A, ALP, OCN, RUNX2	–	miR-16-5p by directly targeting VEGFA could regulate postmenopausal osteoporosis.	[57]
miR-149-3p	C57BL/6J Mice	mBMSCs	CEBPA, CEBPB, CEBPD, FABP4, PPARG, ALP, BGLAP, COL1A1, BMP4, SPP1, FTO	–	miR-149-3p by targeting FTO could regulate the switch between adipogenic and osteogenic differentiation of mBMSCs.	[58]
miR-545-3p	Human	MC3T3-E1, 293T	LRP5, OC, ALP, Runx2, SOST, SP1	WNT/β-catenin	SP1-stimulated miR-545-3p via targeting LRP5-activated WNT/beta-catenin signaling could inhibit osteogenesis.	[59]
miR-451a	Mouse	Primary osteoblasts, MSCs	Osx, Col1a1, Osteocalcin, Dlx2, Bmp6, BmpR, SMAD1/5/8	–	Suppression of miR-451a could accelerate osteogenic differentiation and inhibit bone loss via Bmp6 signaling during osteoporosis.	[60]
miR-146a	C57Bl6 Mice	mBMSCs	Runx2, Smad4	BMP	miR-146a by down-regulating Smad4 could decrease osteogenic differentiation of BMSCs under inflammation.	[61]
miR-135-5p	–	MC3T3-E1	HIF1AN, Runx2, OPN, OCN, OSX	–	MiR-135-5p by targeting HIF1AN could promote osteoblast differentiation of MC3T3-E1 cells.	[62]
miR-30b	SD Rat	rBMSCs	ALP, RUNX2, OCN, OPN, BMP2	JAK/STAT, PI3K/AKT	miR-30b suppressing by estrogen could promote osteogenesis in rBMSCs.	[63]
miR-106b	Mouse, Human	PMSCs	BMP2, ALP, RUNX2, OSX, COL1A1, OCN, SMAD1/5, PINP, CTx-1	–	miR-106b by targeting BMP2 could inhibit osteoblastic differentiation of MSCs and bone formation.	[64]
miR-26b	Rat	rBMSCs	Runx2, GSK-3β	WNT/β-catenin	miR-26b by directly targeting GSK-3β and activating canonical WNT signal pathway could promote BMSC osteogenesis.	[65]
miR-384-5p	Rat	rBMSCs	Gli2, OCN, ALP, OSX, p21, p16	–	miR-384-5p by targeting Gli2 could negatively regulate osteogenic differentiation of BMSCs and accelerate cell senescence.	[18]
miR-100-5p	Mouse	mBMSCs	FGF21	–	miR-100-5p by regulating FGF21 could inhibit osteoclastogenesis and bone resorption.	[66]
miR-103a-3p	Human	hBMSCs	DKK1	WNT	LINC00707 regulated DKK1 expression by targeting miR-103a-3p to regulate osteogenic differentiation.	[67]

(*continued on next page*)

Table 2 (*continued*)

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
miR-10b	Human	hADSCs	SMAD2	TGF-β	miR-10b could stimulate osteogenesis and inhibit adipogenesis partly through the TGF-β/SMAD2 signaling pathway.	[68]
miR-128	Human	C2C12	SIRT6	–	miR-128 by down-regulating SIRT6 expression could inhibit osteoblast differentiation in OP.	[69]
miR-1297	Human	hBMSCs	WNT5A	WNT	miR-1297 could regulate the osteogenesis of BMSCs by combining with WNT5A so as to accelerate the progression of osteoporosis.	[70]
miR-130a	Mouse, Human	hBMSCs, mBMSCs	PPAR gamma	Smurf2	miR-130a by negatively regulating Smurf2 expression could promote osteoblastic differentiation of BMSCs; and by targeting the PPAR gamma could suppress adipogenic differentiation of BMSCs.	[70]
miR-135a-5p	Human	hBMSCs	FOXO1	miR-135a-5p/FOXO1	GAS5 by regulating the miR-135a-5p/FOXO1 pathway could promote osteogenic differentiation of hBMSCs.	[25]
miR-137	Human	U-2, MC3T3	LGR4	–	miR-137 dysregulation via suppression of LGR4 expression could predispose to osteoporotic fracture by impeding ALP activity.	[71]
miR-138-5p	Mice/Human	Osteoblast	MACF1	–	miR-138-5p by targeting MACF1 could regulate mechanosensitivity and bone anabolic action.	[72]
miR-139-5p	Rat	rBMSCs	NOTCH1	WNT/Beta-Catenin	Inhibition of miR-139-5p via targeting WNT/beta-catenin signaling pathway could promote osteogenic differentiation of BMSCs.	[73]
miR-142	–	MC3T3-E1	beta-catenin	–	miR-142 by targeting beta-catenin could protect MC3T3-E1 cells against high glucose-induced apoptosis.	[72]
miR-142-5p	Rat	rBMSCs	VCAM-1	–	miR-142-5p could promote OP in BMMSCs involving targeting VCAM-1 and inhibiting cell migration.	[74]
miR-144	Human	hBMSCs	SFRP1	–	miR-144 by down-regulating the expression of SFRP1 could promote the proliferation and differentiation of hBMSCs.	[75]
miR-148a	Rat	Osteoblasts	PI3K	PI3K/AKT	miR-148a inhibition through PI3K/AKT signaling by estrogen receptor α could protect cells against ovariectomy-induced osteoporosis.	[76]
miR-16a-5p	Human	hBMSCs	VEGFA	–	miR-16-5p by inhibiting VEGFA expression could suppress osteogenesis.	[77]
miR-17-3p	Human	MC3T3-E1	Sox6	–	MiR-17-3p by down-regulating Sox6 expression could inhibit osteoblast differentiation.	[78]
miR-182	Mouse	mBMSCs	PKR	miR-182-PKR-IFN-beta	miR-182 by mediating PKR-IFN-beta axis could regulate osteoclastogenesis.	[79]
miR-182-5p	Rat	rBMSCs	ADCY6	Rap1/MAPK	Decreased miR-182-5p via the Rap1/MAPK pathway could promote osteoblast proliferation and differentiation in osteoporosis.	[80]
miR-185	Mouse	primary osteoblasts, mBMSCs	Bgn	BMP/Smad	Mmu-miR-185 depletion through the Bgn-mediated BMP/Smad pathway could promote osteogenic differentiation and suppress bone loss in osteoporosis.	[81]
miR-188–3p	Human	hDPSCs	Beclin-1, RUNX1	–	hsa_circ_0026827 through the Beclin1 and RUNX1 signaling pathways by sponging miR-188-3p could promotes osteoblast differentiation of hDPSCs.	[82]
miR-196a	Mouse	mBMSCs	GNAS	–	overexpression of miR-196a by activating the Hedgehog signaling pathway could repress GNAS expression, thus promote osteogenic differentiation in mice with OP.	[83]
miR-19a-3p	Mouse, Human	mBMSCs, hBMSCs	Hoxa5	Xist	Xist by sponging miR-19a-3p could regulate osteoblast differentiation in aging-induced osteoporosis.	[84]
miR-19a-3p	Human	hMSCs	HDAC4	–	MiR-19a-3p by inhibiting HDAC4 expression could promote the osteogenic differentiation of hMSCs.	[85]

(*continued on next page*)

Table 2 (*continued*)

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
miR-19b	Human	hMSCs, MC3T3-E1	PTEN, Runx2	AKT	Circulating miR-19b through regulation of the PTEN/pAKT/Runx2 pathway could enhance osteoblastogenesis.	[86]
miR-19b-3p	–	BMSCs	–	lncRNA H19	miR-19b-3p by interacting with lncRNA H19 could promote cell proliferation and osteogenic differentiation of BMSCs.	[87]
miR-204	Mouse	MC3T3-E1	TRPM3	–	Puerarin by inhibiting TRPM3/miR-204 could promote MC3T3-E1 cells proliferation, differentiation and mineralization.	[88]
miR-205	Mouse, Human	mBMSCs, hBMSCs	Runx2	–	miR-205 through targeted inhibition of Runx2 could regulate bone turnover in elderly female patients with type 2 diabetes mellitus.	[89]
miR-20a	Human	THP-1	PPAR gamma	–	miR-20a by down-regulating PPAR gamma could negatively regulate the proliferation and osteoclastogenesis of THP-1 cells during its osteoclast differentiation progress.	[90]
miR-21	–	BMSCs	SMAD7	–	miR-21 by targeting SMAD7 could inhibit osteogenic differentiation induced by exosomes from osteoporosis-derived MSCs.	[91]
miR-21	Human	hBMSCs	SMAD7	–	miR-21-containing exosomes of patients with osteoporosis could inhibit osteogenesis through targeting SMAD7.	[92]
miR-214-5p	–	BMSCs	Smad2	TGF-β	miR-214-5p through regulation of the TGF-beta/Smad2/COL4A1 signaling pathway could promote the adipogenic differentiation of BMSCs.	[93]
miR-217	Human	hBMSCs	RUNX2	–	Circ-VANGL1 could promote the development of OP via binding to miRNA-217 to downregulate RUNX2 expression.	[94]
miR-218	Human	hAMSCs	APC, GSK3-β	WNT/β-catenin	miR-218 by regulating β-catenin inhibitors could induct osteogenic differentiation of hAMSCs.	[95]
miR-223-5p	–	MC3T3-E1	HDAC2	–	miR-223 by targeting HDAC2 could promote osteoblast differentiation of MC3T3-E1 cells.	[96]
miR-22-3p	Mouse	mBMSCs	FTO, MYC	PI3K/AKT	Extracellular vesicle-encapsulated miR-22-3p from BMSC via FTO repression could promote osteogenic differentiation.	[97]
miR-23	Human	hBMSCs	MEF2C	MEF2C/MAPK	miR-23 through the MEF2C/MAPK signaling pathway could decrease the osteogenic differentiation of hBMSCs.	[98]
miR-23b	Human	hBMSCs	runx2	TNF	miR-23b was involved in TNF-mediated reduction of BMSC osteogenesis by targeting runx2.	[99]
miR-25-3p	–	RAW 264.7	NFIX	–	miR-25-3p through NFIX could regulate osteoclasts.	[100]
miR-27a	–	Osteoclasts	PPAR gamma/APC	–	miR-27a by targeting PPARγ and APC played a significant role in the process of estrogen-inhibited osteoclast differentiation and function.	[99]
miR-27a	Rat	BM025SS13	PPAR	–	miR-27a could regulate arthritis via PPARγ.	[101]
miR-27a-3p	–	MC3T3-E1	osterix (Osx)	–	miR-27a-3p by targeting osterix could negatively regulate osteogenic differentiation of MC3T3-E1 preosteoblasts.	[102]
miR-29a	Mouse	BMMs	SOCS2	–	miR-29a could counteract Glucocorticoid Induction of Bone Loss through repressing TNFSF13b modulation of osteoclastogenesis.	[103]
miR-29a	Mouse	macrophage precursor cells, mBMSCs	RANKL, CXCL12, OCN		MiR-29a by regulating PCAF-mediated RANKL and CXCL12 could repress osteoclast formation and protect against osteoporosis.	[104]
miR-29b	Rat	rBMSCs	Smad	PI3K/AKT, TGF-β	miR-29b through the PI3K/AKT and TGF-β/Smad signaling pathways could enhance the proliferation and migration of BMSCs in rats with castration-induced osteoporosis.	[105]

(*continued on next page*)

Table 2 (*continued*)

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
miR-320a	Human	MC3T3E1	MAP9	PI3K/AKT	miR-320a by reducing MAP9 and inhibiting PI3K/AKT signaling pathway could negatively regulate MC3T3E1 cells in postmenopausal osteoporosis.	[106]
miR-330-5p	Mouse	mBMSCs	Bgn	BMP/Smad	Knockdown of miR-330-5p through the Bgn-induced BMP/Smad pathway could facilitate osteogenesis in BMSCs.	[105]
miR-338-3p	–	RAW264.7	MafB	–	miR-338-3p via targeting transcription factor MafB could regulate osteoclastic differentiation.	[107]
miR-342-3p	–	–	ATF3	–	miR-342-3p via targeting ATF3 could promote osteogenic differentiation.	[108]
miR-342-5p	Human	MC3T3-E1, hMSCs	Bmp7	MEK/ERK	miR-342-5p inhibition could promote proliferation, migration and differentiation of osteoblasts via regulating Bmp7, along with activation of the MEK/ERK pathway.	[66]
miR-363-3p	Rat	rBMSCs	TRAF3	–	miR-363-3p by targeting TRAF3 could suppress senescence and regulates the balance between osteoblastic and adipocytic differentiation of rat BMSCs.	[109]
miR-365a-3p	Human	hBMSCs	RUNX2	–	MiR-365a-3p via targeting RUNX2 could promote the progression of osteoporosis by inhibiting osteogenic differentiation of hBMSCs.	[110]
miR-373	Rat, Human	rBMSCs hBMSCs	TRPS1	PI3K/AKT	MiR-373 by targeting TRPS1 could promote the osteogenic differentiation of BMSCs from the estrogen deficiency induced osteoporosis.	[111]
miR-375	Human	hMSCs	RUNX2	–	Teriparatide via miR-375/RUNX2 axis could alleviate osteoporosis by promoting osteogenic differentiation of hMSCs.	[112]
miR-376c	–	–	WNT-3, ARF-GEF-1	WNT/β-catenin	MiR-376c could inhibit osteoblastogenesis by targeting Wnt3 and ARF-GEF-1-facilitated augmentation of beta-catenin transactivation.	[113]
miR-378	Human	hBMSCs	BMP-2	–	circRNA_0007059 by promoting the miR-378/BMP-2 axis could regulate postmenopausal osteoporosis.	[114]
miR-378a-3p	Rat	rBMSCs	Grb2	–	Low-magnitude vibration(LMV) through miR-378a-3p/Grb2 pathway could induce osteogenic differentiation of BMSCs.	[115]
miR-384-5p	Rat	rBMSCs	Gli2	–	miR-384-5p by targeting Gli2 could negatively regulate age-related osteogenic differentiation of rBMSCs.	[116]
miR-409-5p	Mouse	Osteoblasts	Lrp-8	WNT/β-catenin	miR-409-5p by targeting Lrp-8 could negatively regulate Wnt/Beta catenin signaling pathway to increase bone density.	[117]
miR-410	Mouse, Human	peripheral blood mononuclear cells (PBMCs)	BMP2	–	MiR-410 by downregulating BMP2 could participate in the pathological process of postmenopausal osteoporosis.	[118]
miR-429	Human	hAMSCs	SCD-1	–	miR-429 could suppress the osteogenic differentiation of hADMSCs under oxidative stress via downregulating SCD-1.	[119]
miR-449b-5p	–	hBMSCs	Satb2	–	miR-449b-5p through targeting Satb2 could aggravate osteoporosis by inhibiting osteogenic differentiation of BMSCs.	[118]
miR-450b	Human	hAMSCs	BMP3	–	miR-450b by targeting BMP3 could promote osteogenic differentiation in vitro and enhance bone formation in vivo.	[120]
miR-485-5p	Rat	rBMSCs	Osterix	–	miR-485-5p via targeting Osterix could promote osteoporosis.	[121]
miR-488	Human	hBMSCs	RUNX2	–	miR-488 by targeting Runx2 could negatively regulate osteogenic differentiation of hBMSCs induced by psoralen.	[122]
miR-532-5p	–	C2C12	FOXO1	–	miR-532-5p by regulating the expression of FOXO1 could regulate osteoblast differentiation and osteoporosis.	[123]
miR-539	Rat		AXIN1	WNT		[124]

(*continued on next page*)

Table 2 (*continued*)

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
		Osteoblast, osteoclast			miR-539 through the AXNA-dependent Wnt signaling pathway could promote osteoblast proliferation and differentiation and osteoclast apoptosis in osteoporotic rats.	
miR-548x-3p	–	Osteoblast-like cells	STAT1 and MAFB	–	miR-548-3p overexpression by targeting STAT1 and MAFB could inhibit proliferation, migration and invasion in osteoblast-like cells.	[125]
miR-579-3P	Human	hBMSCs	Sirt1	–	miR-579-3P by regulating Sirt1 could inhibit osteogenic differentiation of hMSCs.	[126]
miR-655-3p	Mouse	MC3T3-E1	LSD1	LSD1/BMP-2/Smad	miR-655-3p by targeting LSD1 and activating BMP-2/Smad signaling pathway could inhibit the progression of osteoporosis.	[84]
miR-664a-5p	Human	hBMSCs	HMGA2	–	miR-664a-5p by directly downregulating HMGA2 could promote osteogenic differentiation of hBMSCs.	[127]
miR-705	Mouse	Mandibular bone marrow MSCs	HOXA10 and FoxO1	–	miR-705 by targeting HOXA10 and FoxO1 could regulate the differentiation of mouse mandibular bone marrow MSCs.	[128]
miR-874	Rat	Osteoblast	SUFU	Hedgehog	miR-874 by targeting SUFU could involve in osteoblast proliferation and differentiation in osteoporosis rats through the Hedgehog signaling pathway.	[129]
miR-9-5p	Human	MSCs	WNT3a	–	miR-9-5p via targeting Wnt3a could promote osteoporosis development through inhibiting osteogenesis and promoting adipogenesis.	[130]
miR-101	–	BMSCs	SNHG1 and DKK1	WNT/β-catenin	lncRNA SNHG1 could attenuate BMSC osteogenic differentiation via the miR-101/DKK1 axis as a competitive endogenous RNA.	[131]
miR-106b	–	MC3T3-E1	RANKL	–	Puerarin via microRNA-106b by targeting receptor activator of nuclear factor-κB ligand could promote the proliferation and differentiation of MC3T3-E1 cells.	[132]
miR-126-5p	Human	H9c2	IL-17A	PI3K/AKT	miR-126-5p by targeting IL-17A could regulate H9c2 cell proliferation and apoptosis under hypoxic conditions.	[133]
miR-139-3p	Mouse	MC3T3-E1	ELK1	ODSM/miR-139-3p/ELK1	MiR-139-3p by targeting ELK1 and interacting with long noncoding RNA ODSM could regulate osteoblast differentiation and apoptosis.	[134]
miR-140-5p	Mouse	mBMSCs	BMP2	MSC-AS1/microRNA-140-5p/BMP2	LncRNA MSC-AS1 could promote osteogenic differentiation and alleviate osteoporosis through sponging microRNA-140-5p to upregulate BMP2.	[91]
miR-141	Rat	rBMSCs	Runx2 and Osterix	WNT/beta-catenin	Overexpression of miR-141 by activating the WNT/beta-catenin pathway could inhibit the osteoporosis of jawbones in ovariectomized rats.	[135]
miR-142	Mouse	MC3T3-E1	BMP2	BMP/Smad	MiR-142 by targeting BMP2 could regulate osteoblast differentiation and apoptosis of mouse pre-osteoblast cells.	[136]
miR-146a	–	MC3T3-E1	Rtn4-Exos	MTT	Exosomes derived from circRNA Rtn4-modified BMSCs by sponging miR-146a could attenuate TNF-α-induced cytotoxicity and apoptosis in murine MC3T3-E1 cells.	[137]
miR-152	Rat	MC3T-E1	RICTOR	–	MiR-152 by targeting RICTOR could influence osteoporosis through regulation of osteoblast differentiation.	[138]
miR-153	Mouse	MC3T3-E1	Runx2	miR-153/Runx2	Icariin by targeting Runx2 could regulate the osteoblast differentiation and cell proliferation of MC3T3-E1 cells through microRNA-153.	[139]
miR-155	Mouse	vascular smooth muscle cells	VSMCs	Akt-FOXO3a	MiR-155 by regulating Akt-FOXO3a signaling could modulate vascular	[140]

(*continued on next page*)

Table 2 (*continued*)

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
					calcification and apoptosis in vascular smooth muscle cells.	
miR-186	Rat	rBMSCs	Sirtuin6 (SIRT6)	miR-186/SIRT6	MiR-186 by targeting SIRT6 could modulate osteogenic differentiation of rBMSCs.	[141]
miR-187-3p	Human	human osteoblastic precursor cells	CNR2	miR-187-3p/CNR2	miR-187-3p by suppressing CNR2 could inhibit osteogenic differentiation of osteoblast precursor cells.	[142]
miR-187-5p	Mouse	mBMSCs	ICAM1	–	miR-187-5p by targeting ICAM1 could regulate osteoblastic differentiation of mBMSCs.	[143]
miR-196a-5p	Mouse	Myo-EVs	Raw264.7	–	MiR-196a-5p in extracellular vesicles secreted from myoblasts could suppress osteoclast-like cell formation in mouse cells.	[144]
miR-199a	–	BMSCs	ALP, BMP2, COL1A1, and Runx2	receptor 1/extracellular-signal-regulated kinase & Janus kinase 1/signal transducer & activator of transcription 1 pathways	miR-199a through regulation of Klotho expression could counteract glucocorticoid inhibition of BMSCs osteogenic differentiation.	[145]
miR-200a-3p	Human	hBMSCs	GLS	microRNA-200a-3p/GLS	MiR-200a-3p via targeting GLS could suppress osteogenic differentiation of MSCs, thereafter accelerate the progression of OP.	[146]
miR-200b-3p	–	MC3T3-E1	Chrdl1 3′-UTR	–	Lycium barbarum polysaccharide (LBP) by regulating miR-200b-3p/Chrdl1/PPARγ could inhibit palmitic acid (PA)-induced MC3T3-E1 cell apoptosis.	[147]
miR-204	–	MC3T3-E1	LC3B	–	Puerarin by enhancing LC3B-mediated autophagy through downregulation of miR-204 could promote the viability and differentiation of MC3T3-E1 cells.	[148]
miR-21	Rat	rBMSCs	CMCS	CMCS/n (miR-21)	MiR-21 nanocapsules by targeting CMCS could promote osteogenic differentiation of BMSCs derived from the osteoporosis rat model.	[149]
miR-21	–	–	PDCD4	–	MiR-21 suppression by upregulation of PDCD4 and downregulation of cathepsin K could inhibit osteoclastogenesis.	[150]
miR-211	–	MC3T3-E1	PI3K/Akt	TGF-beta/PI3K/Akt	miR-211 by involving the TGF-beta/PI3K signaling pathway could function in post-fracture bone cell apoptosis.	[151]
miR-218-5p	Mouse	mBMSCs	COL1A1	–	MiR-218-5p could relieve postmenopausal osteoporosis through promoting the osteoblast differentiation of BMMSCs.	[152]
miR-221	–	MC3T3-E1	ZFPM2	WNT/Notch, and Smad	miR-221 overexpression by regulation of ZFPM2 and deactivating the WNT/Notch and Smad signaling pathways could promote osteoblast proliferation, migration, and differentiation.	[153]
miR-30a-5p	Human	hBMSCs	RUNX2	–	LncRNA XIXT by targeting miRNA-30a-5p could promote osteogenic differentiation of BMSCs and alleviate osteoporosis progression.	[154]
miR-31	Mouse	mBMSCs	RUNX2	RUNX2-miR31	miR-31 inhibition could partially ameliorate the deficiency of BMSCs from cleidocranial dysplasia.	[155]
miR-31a-5p	Rat	rBMSCs	SATB2	–	MiR-31a-5p from aging BMSCs could link bone formation and resorption in the aged bone marrow microenvironment.	[156]
miR-338-3p	Rat	rBMSCs	PCSK5	–	miR-338-3p could suppress age-associated osteoporosis by regulating PCSK5.	[157]
miR-34c	Mouse	mBMSCs	SATB2	SATB2	BMSCs-derived exosomal MALAT1 by mediating the miR-34c/SATB2 axis could enhance osteoblast activity in osteoporotic mice.	[158]
miR-3619-5p	Human	hBMSCs	BMP2	BMP2	lncRNA LINC01535 by upregulating BMP2 expression levels could promote osteogenic differentiation via sponging miR-3619-5p.	[159]
miR-451	Human	hBMSCs	YWHAZ	YWHAZ-mediated RUNX2	MiR-451 blockade by promoting YWHAZ-mediated RUNX2 protein stabilization could promote osteoblastic	[160]

(*continued on next page*)

Table 2 (*continued*)

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
					differentiation and skeletal anabolic effects.	
miR-497-5p	–	MC3T3-E1	HMGA2	JNK	miR-497-5p via targeting HMGA2 could inhibit the development of OP by promoting osteogenesis.	[161]
miR-498	Human	hMSCs	RUNX2	–	LncRNA GAS5 overexpression could alleviate the development of osteoporosis through promoting osteogenic differentiation of MSCs via targeting microRNA-498 to regulate RUNX2.	[162]
miR-503	Human	RAW264.7	RANK	ER alpha/miR-503/RANK	Oleanolic acid via ER alpha/miR-503/RANK signaling pathway could inhibit RANKL-induced osteoclastogenesis in RAW264.7 cells.	[163]
miR-505	–	MC3T3-E1	RUNX2	–	MiR-505 partially by targeting RUNX2 is involved in the regulation of osteogenic differentiation of MC3T3-E1 cells.	[119]
miR-582-5p	Human	hBMSCs	SNHG5	–	SNHG5/miR-582-5p/RUNX3 feedback loop could regulate osteogenic differentiation and apoptosis of BMSCs.	[164]
miR-590-5p	–	MC3T3-E1	Smad7	–	miR-590-5p by suppressing Smad7 in MC3T3-E1 cells could antagonize the inhibitory effect of high glucose on osteoblast differentiation.	[165]
miR-7	Mice	–	Neat1	–	lncRNA Neat1 via sponging miR-7 could stimulate osteoclastogenesis.	[166]
miR-7-5p	–	–	CRY2	CLOCK/BMAL1/P300	Inhibition of CRY2 by STAT3/miRNA-7-5p could promote osteoblast differentiation through upregulation of CLOCK/BMAL1/P300 expression.	[167]
miR-7b-5p	Human	hMSCs	IRS2	–	MiR-7b-5p via regulating IRS2 could attenuate the progression of osteoporosis by inhibiting adipose differentiation of hMSCs.	[168]
miR-92b-5p	–	BMSCs	ICAM-1	–	MiR-92b-5p by targeting ICAM-1 could modulate melatonin-mediated osteogenic differentiation of BMSCs.	[42]
miR-96	Mouse, Human	mBMSCs, hBMSCs	Osterix	–	MiR-96 by targeting osterix could regulate bone metabolism.	[169]

Table 3
miRNAs in osteopenia.

miRNA	Sample	Cell line	Target	Function	Ref.
miR-3648	Human	hMSCs	PRMT3, RUNX2, H4R3me2a	PRMT3 via miR-3648 could regulate osteoblastic differentiation of MSCs.	[170]
miR-136-3p	Human	HUVECs, hBMSCs	PTEN	miR-136-3p by targeting PTEN could regulate vascularization and bone formation in HUVECs and BMSCs, respectively.	[171]

expression of osteogenic markers as well as activity of osteoblasts and NF-κB cascade. These effects are mediated through suppression of GDF5 [175]. Table 4 shows the role of miRNAs in periodontal diseases.

6. Contribution of miRNAs in osteonecrosis

miRNAs have also been demonstrated to be involved in the pathogenesis steroid-associated osteonecrosis of the femoral head (ONFH). Wu et al. have collected bone marrow samples from the proximal femurs of patients with this disorder and patients with new femoral neck fracture. Subsequently, they isolated MSCs from these samples. They reported down-regulation of miR-155-5p in MSCs of patients with ONFH compared with controls. Functional studies have shown that miR-155-5p inhibits GSK3B, thus promoting nuclear translocation of β-catenin and increasing levels of osteogenesis-associated genes. Through this route, miR-155-5p facilitates proliferation and differentiation of these stem cells. Therefore, down-regulation of miR-155-5p in steroid-associated ONFH decreases osteogenic differentiation [171].

miR-137-3p is another miRNA which is involved in the osteonecrosis. miR-137-3p silencing has facilitated osteogenic differentiation of BMSCs and enhanced angiogenesis by HUVECs in the presence or absence of glucocorticoids. miR-137-3p suppresses Runx2 and CXCL12, though suppression of these genes, it regulates osteogenesis and angiogenesis, respectively. Notably, transplantation of miR-137-3p-knocked down BMSCs has remarkably enhanced bone regeneration and ameliorated steroid induced ONFH [176]. Table 5 shows the role of miRNAs in osteonecrosis.

7. Contribution of miRNAs in atrophic nonunion

Contribution of miRNAs in the pathogenesis of atrophic nonunion has been studied in two papers (Table 6). First, miR-140-5p silencing has enhanced osteogenesis of ACSs through modulating expressions of TLR4 and BMP2. Notably, combination of adipose scaffolds and miR-140-5p silencing in ASCs has enhanced fracture-healing and bone construction in rat models of atrophic nonunion [180]. Moreover, miR-381 via suppressing WNT signaling pathway could modulate BMSCs osteogenesis during atrophic nonunion development [181].

8. Contribution of lncRNAs in osteogenesis and related disorders

Several lncRNAs have been shown to regulate osteogenesis, thus

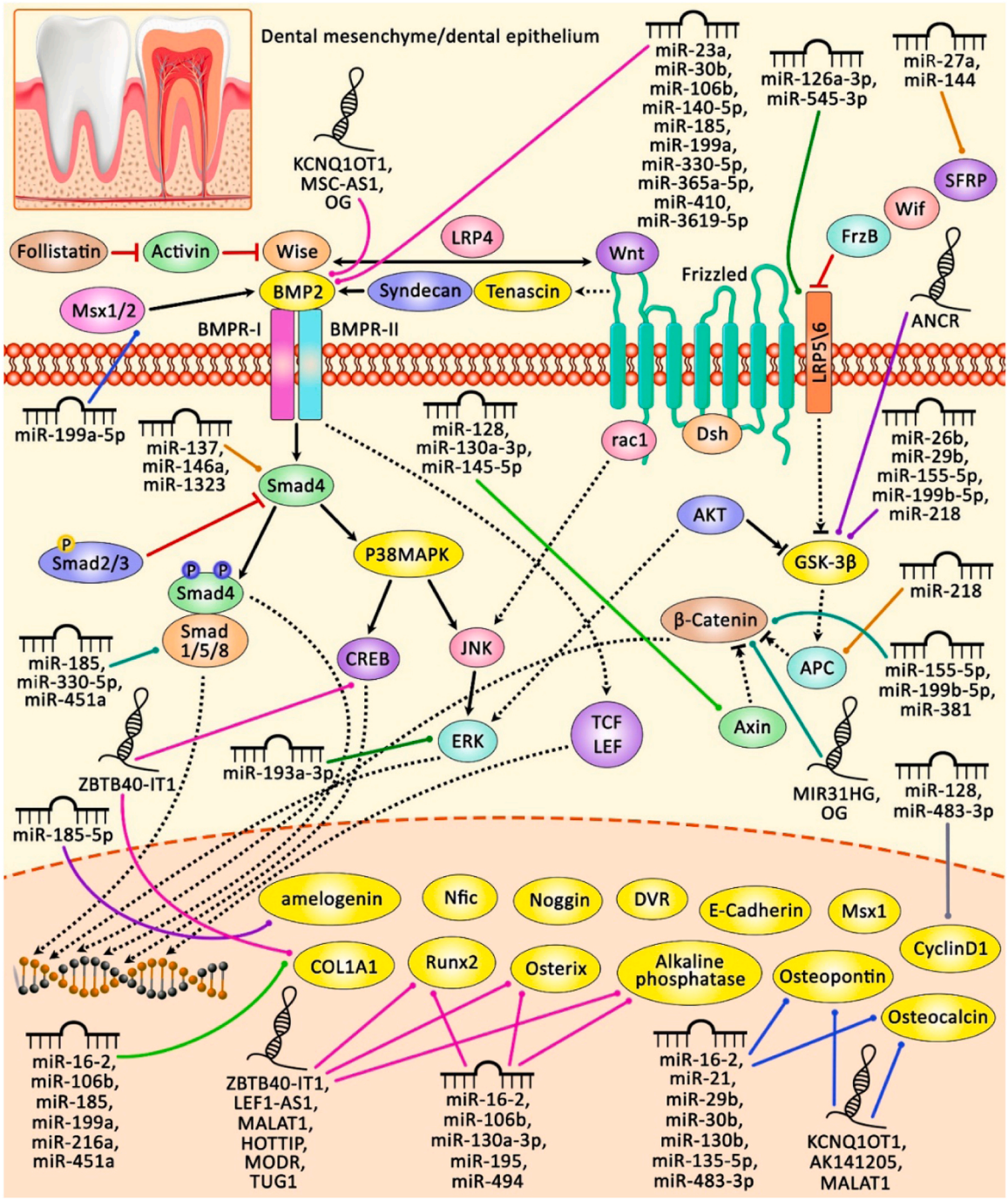

Fig. 4. The schematic diagram of the WNT and BMP signaling crosstalk in modulating dental stem cell growth and differentiation. Wnt signaling cascade could modulate cell growth, migration, differentiation, apoptosis, and epithelial-mesenchymal interactions, thus contributing in the dental and periodontal tissue morphogenesis [172]. Ectopic expression of some miRNAs as well as lncRNAs, namely miR-16-2, miR-451a, miR-195, MALAT1, ZBTB40-IT1, and AK141205 via targeting BMP2, COL1A1, amelogenin, Runx2, osteocalcin, osteopontin, and osterix could have an effective part in dysregulating these cascades in teeth, bone, or cartilage.

being involved in the pathogenesis of bone disorders. HOTAIRM1, MEG3 and MALAT1 are among the mostly assessed lncRNAs in this regard (Tables 7–9). For instance, HOTAIRM1 has been found to be upregulated in human DFSCs compared with hPDLSCs. This lncRNA has a role in regulation of proximal and distant HOXA genes through modulation of methylation marks in histones and DNA. HOTAIRM1 has suppressed total DNMT1 levels and DNMT1 recruitment on promoter of HOXA2. Functionally, HOTAIRM1 increases osteogenesis of hDFSCs through regulation of HOXA2 [182]. Moreover, HOTAIRM1 can promote osteogenesis through controlling JNK/AP-1 signaling-mediated RUNX2 expression [183].

In the course of osteogenic differentiation, expression of MEG3 has been found to be lower in MSCs from patients with multiple myeloma compared with normal persons. MEG3 silencing has remarkably decreased levels of osteogenic markers Runx2, osterix, and osteocalcin. Moreover, MEG3 silencing has reduced expression of BMP4. Functionally, MEG3 has a critical role in SOX2-mediated suppression of BMP4 [184] (Table 8).

Moreover, MALAT1 has been reported to influence osteogenic differentiation through modulating miR-30/Runx2 [183] as well as

Table 4
miRNAs in periodontal diseases.

miRNA	Sample	Cell line	Target	Function	Ref.
miR-4262	–	hPDLSCs	SOCS4, RUNX2, OPN, Col I	miR-4262 via elevating the expression of SOCS4 could regulate differentiation and osteogenesis of hPDLSCs.	[173]
miR-23a	Gingival crevicular fluid samples; control subjects (n = 21), patients with chronic periodontitis (n = 29)	hPDLSCs	BMPR1B, BMP2, BMP7, BMP10, Smad1/5/9, Col I, ALP, Runx2, osteoglycin	miR-23a by targeting BMP signaling could inhibit osteogenesis of PDLSCs.	[174]
miR-132	Human	hPDLLSCs	ALP, BMP2, Runx2, OCN, GDF5, IκBα, P65, NF-κB	miR-132 via targeting GDF5 and activating NF-κB axis could inhibit osteogenic differentiation of PDLLSCs.	[175]

miR-214/ATF4 axes [186] (Table 9).

A number of other lncRNAs including ANCR, AK016739, AK141205, MIR31HG, OG, ZBTB40-IT1, LEF1-AS1, Bmcob, Dnm3os, MCF2L-AS1, MSC-AS1 and HOTTIP regulate osteogenesis (Table 10). For instance, down-regulation of ANCR has enhanced proliferation of PDLSCs and osteogenic differentiation of these cells through increasing expression of osteogenic differentiation markers. Notably, the canonical WNT signaling pathway has been induced by ANCR silencing in the course of proliferation and osteogenic induction [187]. Down-regulation of ANCR can also affect expressions of EZH2 and Runx2, thus promoting

Table 7
Contribution of HOTAIRM1 in osteogenesis and related disorders.

Samples	Cell line	Target	Pathway	Function	Ref.
human	hDFSCs, hPDLLSCs	HOXA2, DNMT1, RUNX2, ALP, OCN	–	HOTAIRM1 by epigenetically regulating HOXA2 via DNMT1 could promote osteogenesis of hDFSCs in vitro.	[182]
Human	MenSCs, UCMSCs	Runx2, SP7, SSP1	JNK/AP-1	HOTAIRM1 by controlling JNK/AP-1 signaling-mediated RUNX2 expression could promote osteogenesis.	[183]

Table 5
miRNAs in osteonecrosis.

Diseases	miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
Osteonecrosis	miR-155-5p	Patients with new femoral neck fracture (n = 10), patients with steroid-associated osteonecrosis of the femoral head (ONFH) (n = 10)	hBMSCs	GSK-3β, β-catenin	–	miR-155-5p via targeting GSK3B could regulate hbMSCs proliferation and osteogenesis in ONFH.	[171]
Steroid-induced osteonecrosis of the femoral head (SONFH)	miR-137-3p	Rat	rBMSCs, EPCs, 293T, HUVEC	RUNX2, ALP, CXCL12, COL I, C/EBPα, VEGF, SDF-1α	–	miR-137-3p silencing by up-regulating Runx2 and CXCL12 could facilitate osteogenic differentiation and increase the number of circulating EPCs.	[176]
Non-traumatic osteonecrosis of the femoral head (NONFH)	miR-100-5p	NONFH (stage III and IV) patients (n = 40), femoral neck fracture (FNF) patients (n = 40), femoral head samples	hBMSCs, UVECs	BMPR2, PPARγ, OPN, RUNX2, Col I, ALP, FGF2, VEGFA, CD63, CD9, Alix, Calnexin, TSG101, SMAD1/5/9	–	Exosomal miR-100-5p by suppressing BMPR2/Smad1/5/9 signaling pathway could inhibit osteogenesis of BMSCs and angiogenesis of VECs.	[177]
Glucocorticoid (GC)-induced osteonecrosis of the femoral head (GIONFH)	miR-26a	Rat, Human	hBMSCs, HUVECs	CD9, CD63, CD81, Alix, ALP, RUNX2, COL I	–	miR-26a-CD34+-exosomes could prevent GIONFH by promoting angiogenesis and osteogenesis.	[178]
GIONFH	miR-365a-5p	Rat, Human	BMSCs, HUC-MSCs	Runx2, BMP2, Sp7, SAV1, LATS, YAP	Hippo signaling pathway	Exosomal miR-365a-5p derived from HUC-MSCs could promote osteogenesis of BMSCs and prevent the development of GIONFH in rats via activation of the Hippo signaling pathway.	[179]

Table 6
miRNA in atrophic nonunion.

miRNA	Sample	Cell line	Target	Pathway	Function	Ref.
miR-140-5p	Rat, Human	hAMSCs	TLR4, BMP2, RUNX2, OCN	BMP, TLR	Knockdown of miR-140-5p through influencing TLR4 and BMP2 could promote osteogenesis of AMSCs and fracture healing in the atrophic nonunion rat model.	[180]
miR-381	atrophic nonunion patients (n = 10), standard healing patients (n = 10)	hBMSCs	WNT5A, FZD3, PPARγ, Runx2, ALP, Col I, β-catenin, Histone H3	WNT	miR-381 via suppressing WNT signaling pathway could modulate BMSCs osteogenesis during atrophic nonunion development.	[181]

Table 8
Contribution of MEG3 in osteogenesis and related disorders.

Samples	Cell line	Target	Pathway	Function	Ref.
Multiple myeloma (MM) patients	bone-derived MSCs	RUNX2, Osx, Osteocalcin, SOX2, BMP4	–	Overexpression of MEG3 by targeting BMP4 transcription could promote osteogenic differentiation of MSCs from MM patients.	[184]
–	human dental follicle stem cells (hDFSCs)	EZH2, OCN, Runx2, ALP, WNT5a, WNT1, H3K27me3	WNT/β-catenin	Lower expression of MEG3 by epigenetically regulating the WNT pathway could promote osteogenic differentiation of hDFSCs.	[185]

Table 9
Contribution of MALAT1 in osteogenesis and related disorders.

Samples	Cell line	Target	Function	Ref.
–	ADSCs, 293T	miR-30, Runx2, OCN, OPN, OSX, ALP	MALAT1 via the miR-30/Runx2 could promote osteoblast differentiation of ADSCs.	[183]
Human	hBMSCs	miR-214, Runx2, ALP, OCN, ATF4	MALAT1 via regulating ATF4 by sponging miR-214 could promote osteogenic differentiation.	[186]

osteoblast differentiation [188]. In addition, MIR31HG/NF-κB axis has been found to improve the osteogenic capacity of human adipose-derived stem cells under an inflammatory microenvironment [189]. HOTTIP is another lncRNA which interacts with WDR5 and activates the WNT/β-catenin pathway, thus enhancing osteogenic differentiation of BMSCs [190]. Contribution of other lncRNAs in the osteogenesis is demonstrated in Table 10.

9. NcRNAs as biomarkers and potential therapeutics for osteogenesis and related disorders

Recent advances in high throughput sequencing techniques have enabled researchers to find distinctive expression profiles of miRNAs,

Table 10
Contribution of other lncRNAs in osteogenesis and related disorders.

lncRNA	Samples	Cell line	Target	Pathway	Function	Ref.
ANCR	Human	PDLLSCs	DKK1, GSK-3β, ALP, DSPP, OCN, BSP, Runx2	WNT/β-catenin	Lower expression of ANCR could promote osteogenic differentiation PDLSCs.	[187]
	–	hFOB1.19	EZH2, Runx2, ALP	–	Lower expression of ANCR by targeting EZH2 and regulating Runx2 could promote osteoblast differentiation.	[188]
AK016739	C57BL/6 mice	MC3T3-E1, mBMSCs	Alp, Col Iα1, Runx2, Tcf7, Lef1, Osterix	–	AK016739 could inhibit bone formation and osteoblast differentiation.	[191]
AK141205	Rat	rBMSCs	CXCL13, OPN, OCN, Runx2	–	AK141205/CXCL13 axis had been considered as a regulator of osteogenic growth peptide (OGP)-induced osteogenic differentiation of SMCs.	[192]
MIR31HG	–	human adipose-derived stem cells	NF-κB, TNF-α, IL-17, p65, ALP, RUNX2, OCN, β-catenin	–	MIR31HG/NF-κB axis could improve the osteogenic capacity of human adipose-derived stem cells under an inflammatory microenvironment.	[189]
OG	Human	hBMSCs	hnRNPK, ALP, RUNX2, OCN, β-catenin, OSX, Smad1, BMP2/4/6/7/9	ERK1/2,	LncRNA-OG under the regulation of hnRNPK could promote the osteogenic differentiation of BM-MSCs.	[193]
ZBTB40-IT1	–	U-2OS, 293T, hFOB1.19, Saos-2	WNT4, RUNX2, OSX, ALP, COL1A1, OPG RANKL, CREB1	–	ZBTB40-IT1 could be modulated by osteoporosis GWAS risk SNPs suppresses osteogenesis.	[194]
LEF1-AS1	Human	hDPSCs	miR-24-3p, TGFBR1, Runx2, OSX, ALP	–	LEF1-AS1 via sponging miR-24-3p could promote osteogenic differentiation of DPSCs.	[195]
Bmcob	Mouse	mBMSCs	Sepp1, ALP, Runx2, SBP2	–	Bmcob could regulate osteoblastic differentiation of BMSCs.	[196]
Dnm3os	Mouse	MSCs	–	–	Dnm3os could regulate osteogenesis.	[197]
MCF2L-AS1	Rat	MSCs	miR-33a, ALP, OCN, Runx2	–	MCF2L-AS1 by regulating miR-33a could control osteogenic differentiation.	[198]
MSC-AS1	–	BMSCs	miR-140-5p, BMP2, Runx2	–	MSC-AS via sponging miR-140-5p to upregulate BMP2 could promote osteogenic differentiation.	[199]
HOTTIP	Human	hBMSCs	Runx2, ALP, OSX, WDR5	WNT/β-catenin	HOTTIP via interacting with WDR5 and activating the WNT/β-catenin pathway could enhance human osteogenic BMSCs differentiation.	[190]
NKILA	Human	MenSCs, UCMSCs	RXFP1, NF-κB, RUNX2, SP7, SPP1	AKT	NKILA via integrating the RXFP1/AKT and NF-κB signaling could regulate osteogenesis of MSCs.	[200]
TUG1	Human	hBMSCs	Smad5, Osterix, Runx2, ALP, OCN, OGN		TUG1 via Smad5 could inhibit osteogenesis of BMMSCs after irradiation.	[142]
H19	Mouse	iMEFs, iMADs, 293pTP	ALP, miR-449b, Runx2	Notch	H19 through Notch signaling could mediate BMP9-induced osteogenic differentiation of MSCs.	[201]
ENST00000502125.2	Human	hBMSCs	ALP	–	ENST00000502125.2 could be involved in the osteogenic differentiation of hBMMSCs.	[202]
LncRNA-TWIST1	Human	PPDLSCs	Runx2, ALP, OCN, TWIST1		LncRNA-TWIST1 by inhibiting TWIST1 expression could promote osteogenic differentiation in periodontal mesenchymal stem cells.	[203]
KCNQ1OT1	Human	BMSCs	miR-214, ALP, BMP2, Runx2, OPN, OCN	–	KCNQ1OT1 by sponging miR-214 could promote BMP2 expression to regulate osteogenic differentiation.	[96]
MODR	–	MSMSCs	miR-454, ALP, RUNX2, OSX	–	lncMODR by sponges miR-454 to promote osteogenic differentiation in MSMSCs.	[204]
HOXA-AS2	Human	UCMSCs	NF-kB, SP7, SPP1, Runx2	–	HOXA-AS2 via inactivating NF-κB signaling could regulate osteogenesis of MSCs.	[205]
ODIR1	Human	UCMSCs	FBXO25, OPN, H2BK120ub, H3K4me3, OSX,	–	ODIR1 via the FBXO25/H2BK120ub/H3K4me3/OSX axis could inhibit osteogenic differentiation of hUC-MSCs.	[205]

lncRNAs and circRNAs during different stages of osteogenesis. The impact of these transcripts on expression of osteogenic markers has also been validated. The presence of these transcripts in cell-derived exosomes and the observed association between exosomes cargo and different osteogenesis-related disorders further support the importance of ncRNAs as biomarkers for these conditions. miR-130a-3p, miR-146a, miR-186, miR-29a and miR-21 are among miRNAs whose expression levels in the exosomes could reflect the presence of an osteogenesis-related disorder. Exosomes can also been used as vehicles for transfer of miRNAs or lncRNAs with therapeutic effects in these types of disorders. Yet, this application of exosomes has not been thoroughly examined in bone disorders.

10. Discussion

Bone formation is a complex process involving several transcription factors and proteins. Moreover, a number of signaling cascades, particularly Wnt/β-catenin and TGFβ/BMP pathways regulate this process. Hippo and NF-κB signaling cascades are other cascades that are involved in this process. NcRNAs have essential roles in the regulation of these transcription factors and signaling cascades. Experiments in different types of mesenchymal stem cells have verified the importance of miRNAs in the regulation of osteogenic process in these cells. Moreover, exosomes containing certain miRNAs can affect this process. These observations have practical significance in the regenerative medicine particularly in the treatment of bone disorders.

While the effects of miRNAs on Wnt/β-catenin signaling have been vastly explored, their effects of TGFβ/BMP pathway are less understood. miR-877-3p, miR-200b, miR-10b, miR29b, miR-214-5p and miR-211 are among miRNAs that contribute in the regulation of osteogenesis through modulation of TGFβ/BMP. On the other hand, expressions of Wnt proteins as well as FZD and LRP proteins have been shown to be modulated by several miRNAs. RUNX2, the master transcription factor for osteogenic differentiation [206], is also regulated by a number of miRNAs, namely miR-133a-5p, miR-205, miR-217, miR-23b, miR-365a-3p, miR-375, miR-488, miR-137-3p and miR-30. Moreover, some lncRNAs including MALAT1, GAS5 and HOTAIRM1 regulate expression of this transcription factor mainly through sponging miRNAs that interact with this transcription factor.

miRNAs have also been found to mediate effects of a number of chemical and herbal substances on bone density. For instance, the anticancer agent curcumin has been reported to suppress osteogenesis through enhancing expression of miR-126a-3p [14].

11. Conclusion

miRNAs which are involved in the pathogenesis of osteoporosis mainly regulate activity of Wnt, Hippo, PI3K/Akt, BMP/Smad and JAk/STAT pathways. These miRNAs also influence pathogenesis of osteopenia, osteonecrosis and periodontitis through possibly similar mechanisms. LncRNAs can directly affect expression of these pathways or osteogenic transcription factors. Moreover, they can serve as a molecular sponge for miRNAs. MALAT1/miR-30, MALAt1/miR-214, LEF1-AS1/miR-24-3p, MCF2L-AS1/miR-33a, MSC-AS1/miR-140-5p and KCNQ1OT1/miR-214 are examples of such kind of interaction between lncRNAs and miRNAs in the context of osteogenesis.

In brief, several miRNAs and lncRNAs have been found to alter expression of osteogenic transcription factors and related signaling pathways, thus being involved in both normal bone formation and pathogenesis of bone disorders. Exosomal transfer of these transcripts represents a novel strategy for treatment of bone disorders.

Author contributions

SGF and MT wrote the draft and revised it. AA depicted the figures and revised it. STA, SR, HS and MS collected the data and designed the tables. All the authors are read and approved submitted version.

Conflict of interest statement

The authors declare they have no conflict of interest.

Acknowledgements

This study was financially supported by Shahid Beheshti University of Medical Sciences.

References

[1] S. Gilbert, Osteogenesis: the development of bones, Dev. Biol. 6 (2000).
[2] B.K. Hall, The embryonic development of bone, Am. Sci. 76 (2) (1988) 174–181.
[3] J.H. Kim, X. Liu, J. Wang, X. Chen, H. Zhang, S.H. Kim, J. Cui, R. Li, W. Zhang, Y. Kong, J. Zhang, W. Shui, J. Lamplot, M.R. Rogers, C. Zhao, N. Wang, P. Rajan, J. Tomal, J. Statz, N. Wu, H.H. Luu, R.C. Haydon, T.-C. He, Wnt signaling in bone formation and its therapeutic potential for bone diseases, Ther. Adv. Musculoskelet. Dis. 5 (1) (2013) 13–31.
[4] T.P. Rao, M. Kühl, An updated overview on Wnt signaling pathways: a prelude for more, Circ. Res. 106 (12) (2010) 1798–1806.
[5] R. Baron, M. Kneissel, WNT signaling in bone homeostasis and disease: from human mutations to treatments, Nat. Med. 19 (2) (2013) 179–192.
[6] B.C. Silva, J.P. Bilezikian, Parathyroid hormone: anabolic and catabolic actions on the skeleton, Curr. Opin. Pharmacol. 22 (2015) 41–50.
[7] T.A. Einhorn, L.C. Gerstenfeld, Fracture healing: mechanisms and interventions, Nat. Rev. Rheumatol. 11 (1) (2015) 45–54.
[8] G. Chen, Y. Yao, G. Xu, X. Zhang, Regional difference in microRNA regulation in the skull vault, Dev. Dyn. 248 (10) (2019) 1009–1019.
[9] C. Wang, X. Qiao, Z. Zhang, C. Li, MiR-128 promotes osteogenic differentiation of bone marrow mesenchymal stem cells in rat by targeting DKK2, Biosci. Rep. 40 (2) (2020). BSR20182121.
[10] S. Yang, S. Guo, S. Tong, X. Sun, Exosomal miR-130a-3p regulates osteogenic differentiation of human adipose-derived stem cells through mediating SIRT7/Wnt/β-catenin axis, Cell Prolif. 53 (10) (2020) 12890.
[11] H. Long, B. Sun, L. Cheng, S. Zhao, Y. Zhu, R. Zhao, J. Zhu, miR-139-5p represses BMSC osteogenesis via targeting Wnt/β-catenin signaling pathway, DNA Cell Biol. 36 (8) (2017) 715–724.
[12] L. Feng, J.-f. Zhang, L. Shi, Z.-m. Yang, T.-y. Wu, H.-x. Wang, W.-p. Lin, Y.-f. Lu, J. H.T. Lo, D.-h. Zhu, MicroRNA-378 suppressed osteogenesis of mscs and impaired bone formation via inactivating wnt/β-catenin signaling, Mol. Ther. Nucleic Acids 21 (2020) 1017–1028.
[13] Y. Jin, F. Hong, Q. Bao, Q. Xu, R. Duan, Z. Zhu, W. Zhang, C. Ma, MicroRNA-145 suppresses osteogenic differentiation of human jaw bone marrow mesenchymal stem cells partially via targeting semaphorin 3A, Connect. Tissue Res. 61 (6) (2020) 577–585.
[14] H. Li, L. Yue, H. Xu, N. Li, J. Li, Z. Zhang, R.C. Zhao, Curcumin suppresses osteogenesis by inducing miR-126a-3p and subsequently suppressing the WNT/LRP6 pathway, Aging 11 (17) (2019) 6983–6998.
[15] A. Xu, Y. Yang, Y. Shao, M. Wu, Y. Sun, Inhibiting effect of microRNA-187-3p on osteogenic differentiation of osteoblast precursor cells by suppressing cannabinoid receptor type 2, Differ. Res. Biol. Divers. 109 (2019) 9–15.
[16] X. Liu, W. Zhu, L. Wang, J. Wu, F. Ding, Y. Song, miR-145-5p suppresses osteogenic differentiation of adipose-derived stem cells by targeting semaphorin 3A, Vitr. Cell. Dev. Biol. Anim. 55 (3) (2019) 189–202.
[17] C. Yang, X. Liu, K. Zhao, Y. Zhu, B. Hu, Y. Zhou, M. Wang, Y. Wu, C. Zhang, J. Xu, Y. Ning, D. Zou, miRNA-21 promotes osteogenesis via the PTEN/PI3K/Akt/HIF-1α pathway and enhances bone regeneration in critical size defects, Stem Cell Res. Ther. 10 (1) (2019) 65.
[18] H. Zheng, J. Liu, E. Tycksen, R. Nunley, A. McAlinden, MicroRNA-181a/b-1 overexpression enhances osteogenesis by modulating PTEN/PI3K/AKT signaling and mitochondrial metabolism, Bone 123 (2019) 92–102.
[19] D. Liu, B. Wang, M. Qiu, Y. Huang, MiR-19b-3p accelerates bone loss after spinal cord injury by suppressing osteogenesis via regulating PTEN/Akt/mTOR signalling, J. Cell. Mol. Med. (2020).
[20] T. Xia, S. Dong, J. Tian, miR-29b promotes the osteogenic differentiation of mesenchymal stem cells derived from human adipose tissue via the PTEN/AKT/β-catenin signaling pathway, Int. J. Mol. Med. 46 (2) (2020) 709–717.
[21] G. He, J. Chen, D. Huang, miR-877–3p promotes TGF-β1–induced osteoblast differentiation of MC3T3–E1 cells by targeting Smad7, Exp. Ther. Med. 18 (1) (2019) 312–319.
[22] X. Fan, Y. Teng, Z. Ye, Y. Zhou, W.-S. Tan, The effect of gap junction-mediated transfer of miR-200b on osteogenesis and angiogenesis in a co-culture of MSCs and HUVECs, J. Cell Sci. 131 (13) (2018).
[23] T. Wang, C. Zhang, C. Wu, J. Liu, H. Yu, X. Zhou, J. Zhang, X. Wang, S. He, X. Xu, B. Ma, X. Che, W. Li, miR-765 inhibits the osteogenic differentiation of human bone marrow mesenchymal stem cells by targeting BMP6 via regulating the BMP6/Smad1/5/9 signaling pathway, Stem Cell Res. Ther. 11 (1) (2020) 62.
[24] X. Ma, C. Fan, Y. Wang, Y. Du, Y. Zhu, H. Liu, L. Lv, Y. Liu, Y. Zhou, MiR-137 knockdown promotes the osteogenic differentiation of human adipose-derived

stem cells via the LSD1/BMP2/SMAD4 signaling network, J. Cell. Physiol. 235 (2) (2020) 909–919.
[25] W. Qin, L. Liu, Y. Wang, Z. Wang, A. Yang, T. Wang, Mir-494 inhibits osteoblast differentiation by regulating BMP signaling in simulated microgravity, Endocrine 65 (2) (2019) 426–439.
[26] B. Zhang, S. Huo, X. Cen, X. Pan, X. Huang, Z. Zhao, circAKT3 positively regulates osteogenic differentiation of human dental pulp stromal cells via miR-206/CX43 axis, Stem Cell Res. Ther. 11 (1) (2020) 1–14.
[27] C. Fan, X. Ma, Y. Wang, L. Lv, Y. Zhu, H. Liu, Y. Liu, A NOTCH1/LSD1/BMP2 Co-Regulatory Network Mediated by miR-137 Negatively Regulates Osteogenesis of Human Adipose-Derived Stem Cells, 2020.
[28] J. Shi, B. Wang, X. Cao, Y. Wang, X. Cheng, C. Jia, T. Wen, B. Luo, Z. Liu, Circular RNA_LARP4 inhibits the progression of non-small-cell lung cancer by regulating the expression of SMAD7, Eur. Rev. Med. Pharmacol. Sci. 24 (4) (2020) 1863–1869.
[29] C. Wu, Z. Zheng, W. Ren, T. Deng, Y. Li, L. Yang, J. Wu, Z. Huang, Z. Li, L. Guo, Mm9_circ_009056 enhances osteogenesis by targeting BMP7 via CGRP-mediated miR-22–3p, Biochem. Biophys. Res. Commun. 501 (1) (2018) 199–205.
[30] Y. Lv, Y. Huang, M. Xu, B.C. Heng, C. Yang, C. Cao, Z. Hu, W. Liu, X. Chi, M. Gao, The miR-193a-3p-MAP3k3 signaling axis regulates substrate topography-induced osteogenesis of bone marrow stem cells, Adv. Sci. 7 (1) (2020), 1901412 (Weinheim, Baden-Wurttemberg, Germany).
[31] D. Chen, Z. Wang, Adrenaline inhibits osteogenesis via repressing miR-21 expression, Cell Biol. Int. 41 (1) (2017) 8–15.
[32] E. Kaneda-Ikeda, T. Iwata, N. Mizuno, T. Nagahara, M. Kajiya, K. Ouhara, M. Yoshioka, S. Ishida, H. Kawaguchi, H. Kurihara, Regulation of osteogenesis via miR-101-3p in mesenchymal stem cells by human gingival fibroblasts, J. Bone Miner. Metab. 38 (2020) 442–455.
[33] L. Liu, F. Yu, L. Li, L. Zhou, T. Zhou, Y. Xu, K. Lin, B. Fang, L. Xia, Bone marrow stromal cells stimulated by strontium-substituted calcium silicate ceramics: release of exosomal miR-146a regulates osteogenesis and angiogenesis, Acta Biomater. 119 (2021) 444–457.
[34] Q. Xie, Z. Wang, X. Bi, H. Zhou, Y. Wang, P. Gu, X. Fan, Effects of miR-31 on the osteogenesis of human mesenchymal stem cells, Biochem. Biophys. Res. Commun. 446 (1) (2014) 98–104.
[35] R. Zhao, Y. Li, Z. Lin, J. Wan, C. Xu, Y. Zeng, Y. Zhu, miR-199b-5p modulates BMSC osteogenesis via suppressing GSK-3β/β-catenin signaling pathway, Biochem. Biophys. Res. Commun. 477 (4) (2016) 749–754.
[36] Y. You, W. Ma, G. Jiao, L. Zhang, H. Zhou, W. Wu, H. Wang, Y. Chen, Ortho-silicic acid enhances osteogenesis of osteoblasts through the upregulation of miR-130b which directly targets PTEN, Life Sci. 264 (2021), 118680.
[37] W. Li, Z. Chen, C. Cai, G. Li, X. Wang, Z. Shi, MicroRNA-505 is involved in the regulation of osteogenic differentiation of MC3T3-E1 cells partially by targeting RUNX2, J. Orthop. Surg. Res. 15 (1) (2020), 143-143.
[38] H. Xie, M. Liu, Y. Jin, H. Lin, Y. Zhang, S. Zheng, miR-1323 suppresses bone mesenchymal stromal cell osteogenesis and fracture healing via inhibiting BMP4/SMAD4 signaling, J. Orthop. Surg. Res. 15 (1) (2020) 1–13.
[39] N. Li, L. Liu, Y. Liu, S. Luo, Y. Song, B. Fang, miR-144-3p suppresses osteogenic differentiation of BMSCs from patients with aplastic anemia through repression of TET2, Mol. Ther. Nucleic Acids 19 (2020) 619–626.
[40] X. Chen, S. Gu, B.-F. Chen, W.-L. Shen, Z. Yin, G.-W. Xu, J.-J. Hu, T. Zhu, G. Li, C. Wan, Nanoparticle delivery of stable miR-199a-5p agomir improves the osteogenesis of human mesenchymal stem cells via the HIF1a pathway, Biomaterials 53 (2015) 239–250.
[41] W. Ding, J. Li, J. Singh, R. Alif, R.I. Vazquez-Padron, S.A. Gomes, J.M. Hare, L. A. Shehadeh, miR-30e targets IGF2-regulated osteogenesis in bone marrow-derived mesenchymal stem cells, aortic smooth muscle cells, and ApoE−/− mice, Cardiovasc. Res. 106 (1) (2015) 131–142.
[42] Y. Li, C. Feng, M. Gao, M. Jin, T. Liu, Y. Yuan, G. Yan, R. Gong, Y. Sun, M. He, Y. Fu, L. Zhang, Q. Huang, F. Ding, W. Ma, Z. Bi, C. Xu, N. Sukhareva, D. Bamba, R. Reiters, F. Yang, B. Cai, L. Yang, MicroRNA-92b-5p modulates melatonin-mediated osteogenic differentiation of bone marrow mesenchymal stem cells by targeting ICAM-1, J. Cell. Mol. Med. 23 (9) (2019) 6140–6153.
[43] R. Wang, H. Zhang, W. Ding, Z. Fan, B. Ji, C. Ding, F. Ji, H. Tang, miR-143 promotes angiogenesis and osteoblast differentiation by targeting HDAC7, Cell Death Dis. 11 (3) (2020) 1–15.
[44] S. Mollazadeh, B.S.F. Bazzaz, V. Neshati, A.A. de Vries, H. Naderi-Meshkin, M. Mojarad, M. Mirahmadi, Z. Neshati, M.A. Kerachian, Overexpression of microRNA-148b-3p stimulates osteogenesis of human bone marrow-derived mesenchymal stem cells: the role of microRNA-148b-3p in osteogenesis, BMC Med. Genet. 20 (1) (2019) 1–10.
[45] K. Seenprachawong, T. Tawornsawutruk, C. Nantasenamat, P. Nuchnoi, S. Hongeng, A. Supokawej, miR-130a and miR-27b enhance osteogenesis in human bone marrow mesenchymal stem cells via specific down-regulation of peroxisome proliferator-activated receptor γ, Front. Genet. 9 (2018) 543.
[46] M.I. Almeida, A.M. Silva, D.M. Vasconcelos, C.R. Almeida, H. Caires, M.T. Pinto, G.A. Calin, S.G. Santos, M.A. Barbosa, miR-195 in human primary mesenchymal stromal/stem cells regulates proliferation, osteogenesis and paracrine effect on angiogenesis, Oncotarget 7 (1) (2016) 7–22.
[47] T. Xu, Y. Luo, J. Wang, N. Zhang, C. Gu, L. Li, D. Qian, W. Cai, J. Fan, G. Yin, Exosomal miRNA-128-3p from mesenchymal stem cells of aged rats regulates osteogenesis and bone fracture healing by targeting Smad5, J. Nanobiotechnol. 18 (1) (2020) 1–18.
[48] H. Chang, Y. Wang, H. Liu, X. Nan, S. Wong, S. Peng, Y. Gu, H. Zhao, H. Feng, Mutant Runx2 regulates amelogenesis and osteogenesis through a miR-185-5p-Dlx2 axis, Cell Death Dis. 8 (12) (2017) 1–13.
[49] L. Duan, H. Zhao, Y. Xiong, X. Tang, Y. Yang, Z. Hu, C. Li, S. Chen, X. Yu, miR-16-2* interferes with WNT5A to regulate osteogenesis of mesenchymal stem cells, Cell. Physiol. Biochem. 51 (3) (2018) 1087–1102.
[50] L. Li, X. Zhou, J.-t. Zhang, A.-f. Liu, C. Zhang, J.-c. Han, X.-q. Zhang, S. Wu, X.-y. Zhang, F.-q. Lv, Exosomal miR-186 derived from BMSCs promote osteogenesis through hippo signaling pathway in postmenopausal osteoporosis, J. Orthop. Surg. Res. 16 (1) (2021) 1–10.
[51] Q. Cui, J. Xing, M. Yu, Y. Wang, J. Xu, Y. Gu, X. Nan, W. Ma, H. Liu, H. Zhao, Mmu-miR-185 depletion promotes osteogenic differentiation and suppresses bone loss in osteoporosis through the Bgn-mediated BMP/Smad pathway, Cell Death Dis. 10 (3) (2019) 1–14.
[52] X.-M. Yang, Y.-Q. Song, L. Li, D.-M. Liu, G.-D. Chen, miR-1249-5p regulates the osteogenic differentiation of ADSCs by targeting PDX1, J. Orthop. Surg. Res. 16 (1) (2021) 1–10.
[53] H. Li, T. Li, J. Fan, L. Fan, S. Wang, X. Weng, Q. Han, R. Zhao, miR-216a rescues dexamethasone suppression of osteogenesis, promotes osteoblast differentiation and enhances bone formation, by regulating c-Cbl-mediated PI3K/AKT pathway, Cell Death Differ. 22 (12) (2015) 1935–1945.
[54] B. Zhou, K. Peng, G. Wang, W. Chen, P. Liu, F. Chen, Y. Kang, miR-483–3p promotes the osteogenesis of human osteoblasts by targeting Dikkopf 2 (DKK2) and the Wnt signaling pathway, Int. J. Mol. Med. 46 (4) (2020) 1571–1581.
[55] S. Jin, Y. Bai, B. Zhao, Q. Wang, H. Zhang, Silencing of miR-330-5p stimulates osteogenesis in bone marrow mesenchymal stem cells and inhibits bone loss in osteoporosis by activating Bgn-mediated BMP/Smad pathway, Eur. Rev. Med. Pharmacol. Sci. 24 (8) (2020) 4095–4102.
[56] G.-d Lu, P. Cheng, T. Liu, Z. Wang, BMSC-derived exosomal miR-29a promotes angiogenesis and osteogenesis, Front. Cell Dev. Biol. 8 (2020), 608521.
[57] T. Yu, X. You, H. Zhou, W. He, Z. Li, B. Li, J. Xia, H. Zhu, Y. Zhao, G. Yu, MiR-16-5p regulates postmenopausal osteoporosis by directly targeting VEGFA, Aging 12 (10) (2020) 9500–9514.
[58] Y. Li, F. Yang, M. Gao, R. Gong, M. Jin, T. Liu, Y. Sun, Y. Fu, Q. Huang, W. Zhang, miR-149-3p regulates the switch between adipogenic and osteogenic differentiation of BMSCs by targeting FTO, Mol. Ther. Nucleic Acids 17 (2019) 590–600.
[59] L. Li, X. Qiu, Y. Sun, N. Zhang, L. Wang, SP1-stimulated miR-545-3p inhibits osteogenesis via targeting LRP5-activated Wnt/beta-catenin signaling, Biochem. Biophys. Res. Commun. 517 (1) (2019) 103–110.
[60] X.-D. Lu, W.-X. Han, Y.-X. Liu, Suppression of miR-451a accelerates osteogenic differentiation and inhibits bone loss via Bmp6 signaling during osteoporosis, Biomed. Pharmacother. Biomed. Pharmacother. 120 (2019), 109378.
[61] W. Kuang, L. Zheng, X. Xu, Y. Lin, J. Lin, J. Wu, J. Tan, Dysregulation of the miR-146a-Smad4 axis impairs osteogenesis of bone mesenchymal stem cells under inflammation, Bone Res. 5 (1) (2017) 1–9.
[62] N. Yin, L. Zhu, L. Ding, J. Yuan, L. Du, M. Pan, F. Xue, H. Xiao, MiR-135-5p promotes osteoblast differentiation by targeting HIF1AN in MC3T3-E1 cells, Cell. Mol. Biol. Lett. 24 (1) (2019) 1–11.
[63] G. Liu, Y. Lu, Z. Mai, R. Liu, Z. Peng, L. Chen, Z. Chen, R. Wang, H. Ai, Suppressing microRNA-30b by estrogen promotes osteogenesis in bone marrow mesenchymal stem cells, Stem Cells Int. 2019 (2019) 1–13.
[64] K. Liu, Y. Jing, W. Zhang, X. Fu, H. Zhao, X. Zhou, Y. Tao, H. Yang, Y. Zhang, K. Zen, Silencing miR-106b accelerates osteogenesis of mesenchymal stem cells and rescues against glucocorticoid-induced osteoporosis by targeting BMP2, Bone 97 (2017) 130–138.
[65] X. Li, B. Yang, H. Ren, T. Xiao, L. Zhang, L. Li, M. Li, X. Wang, H. Zhou, W. Zhang, Hsa_circ_0002483 inhibited the progression and enhanced the taxol sensitivity of non-small cell lung cancer by targeting miR-182-5p, Cell Death Dis. 10 (12) (2019) 1–12.
[66] L. Zhou, H.-Y. Song, L.-L. Gao, L.-Y. Yang, S. Mu, Q. Fu, MicroRNA-100–5p inhibits osteoclastogenesis and bone resorption by regulating fibroblast growth factor 21, Int. J. Mol. Med. 43 (2) (2019) 727–738.
[67] J. Liu, M. Wu, G. Feng, R. Li, Y. Wang, J. Jiao, Downregulation of LINC00707 promotes osteogenic differentiation of human bone marrow-derived mesenchymal stem cells by regulating DKK1 via targeting miR-103a-3p, Int. J. Mol. Med. 46 (3) (2020) 1029–1038.
[68] H. Li, J. Fan, L. Fan, T. Li, Y. Yang, H. Xu, L. Deng, J. Li, T. Li, X. Weng, S. Wang, R. Chunhua Zhao, MiRNA-10b reciprocally stimulates osteogenesis and inhibits adipogenesis partly through the TGF-β/SMAD2 signaling pathway, Aging Dis. 9 (6) (2018) 1058–1073.
[69] J. Zhao, S. Liu, W. Zhang, L. Ni, Z. Hu, Z. Sheng, B. Yin, MiR-128 inhibits the osteogenic differentiation in osteoporosis by down-regulating SIRT6 expression, Biosci. Rep. 39 (9) (2019). BSR20191405.
[70] Z. Lin, H. He, M. Wang, J. Liang, MicroRNA-130a controls bone marrow mesenchymal stem cell differentiation towards the osteoblastic and adipogenic fate, Cell Prolif. 52 (6) (2019) 12688.
[71] X. Liu, X. Xu, MicroRNA-137 dysregulation predisposes to osteoporotic fracture by impeding ALP activity and expression via suppression of leucine-rich repeat-containing G-protein-coupled receptor 4 expression, Int. J. Mol. Med. 42 (2) (2018) 1026–1033.
[72] T. Zheng, G. Ji, J. Chen, J. Lai, T. Liu, J. Mo, Q. Jin, MicroRNA-142 protects MC3T3-E1 cells against high glucose-induced apoptosis by targeting β-catenin, Exp. Ther. Med. 20 (6) (2020) 125.
[73] Y. Feng, P. Wan, L. Yin, X. Lou, The inhibition of microRNA-139-5p promoted osteoporosis of bone marrow-derived mesenchymal stem cells by targeting Wnt/beta-catenin signaling pathway by NOTCH1, J. Microbiol. Biotechnol. 30 (3) (2020) 448–458.

[74] Z. Teng, X. Xie, Y. Zhu, J. Liu, X. Hu, Q. Na, X. Zhang, G. Wei, S. Xu, Y. Liu, X. Zhang, C.J. Xian, miR-142-5p in bone marrow-derived mesenchymal stem cells promotes osteoporosis involving targeting adhesion molecule VCAM-1 and inhibiting cell migration, BioMed Res. Int. 2018 (2018), 3274641.

[75] L. Tang, W. Lu, J. Huang, X. Tang, H. Zhang, S. Liu, miR-144 promotes the proliferation and differentiation of bone mesenchymal stem cells by downregulating the expression of SFRP1, Mol. Med. Rep. 20 (1) (2019) 270–280.

[76] Y. Xiao, B. Li, J. Liu, MicroRNA-148a inhibition protects against ovariectomy-induced osteoporosis through PI3K/AKT signaling by estrogen receptor α, Mol. Med. Rep. 17 (6) (2018) 7789–7796.

[77] T. Yu, X. You, H. Zhou, W. He, Z. Li, B. Li, J. Xia, H. Zhu, Y. Zhao, G. Yu, Y. Xiong, Y. Yang, MiR-16-5p regulates postmenopausal osteoporosis by directly targeting VEGFA, Aging 12 (2020) 9500–9514.

[78] N. Chen, D. Wu, H. Li, Y. Liu, H. Yang, MiR-17-3p inhibits osteoblast differentiation by downregulating Sox6 expression, FEBS Open Bio 10 (11) (2020) 2499–2506.

[79] K. Inoue, Z. Deng, Y. Chen, E. Giannopoulou, R. Xu, S. Gong, M.B. Greenblatt, L. S. Mangala, G. Lopez-Berestein, D.G. Kirsch, A.K. Sood, L. Zhao, B. Zhao, Bone protection by inhibition of microRNA-182, Nat. Commun. 9 (1) (2018) 4108.

[80] B.L. Pan, Z.W. Tong, S.D. Li, L. Wu, J.L. Liao, Y.X. Yang, H.H. Li, Y.J. Dai, J.E. Li, L. Pan, Decreased microRNA-182-5p helps alendronate promote osteoblast proliferation and differentiation in osteoporosis via the Rap1/MAPK pathway, Biosci. Rep. 38 (6) (2018).

[81] Q. Cui, J. Xing, M. Yu, Y. Wang, J. Xu, Y. Gu, X. Nan, W. Ma, H. Liu, H. Zhao, Mmu-miR-185 depletion promotes osteogenic differentiation and suppresses bone loss in osteoporosis through the Bgn-mediated BMP/Smad pathway, Cell Death Dis. 10 (3) (2019) 172.

[82] C. Xia, T. Jiang, Y. Wang, X. Chen, Y. Hu, Y. Gao, The Role of p53-induced miR-145a in Senescence and Osteogenesis of Mesenchymal Stem Cells, 2020.

[83] L.N. Zhong, Y.Z. Zhang, H. Li, H.L. Fu, C.X. Lv, X.J. Jia, Overexpressed miR-196a accelerates osteogenic differentiation in osteoporotic mice via GNAS-dependent Hedgehog signaling pathway, J. Cell. Biochem. 120 (12) (2019) 19422–19431.

[84] S. Chen, Y. Li, S. Zhi, Z. Ding, Y. Huang, W. Wang, R. Zheng, H. Yu, J. Wang, M. Hu, J. Miao, J. Li, lncRNA xist regulates osteoblast differentiation by sponging miR-19a-3p in aging-induced osteoporosis, Aging Dis. 11 (5) (2020) 1058–1068.

[85] R. Chen, H. Qiu, Y. Tong, F. Liao, X. Hu, Y. Qiu, Y. Liao, MiRNA-19a-3p alleviates the progression of osteoporosis by targeting HDAC4 to promote the osteogenic differentiation of hMSCs, Biochem. Biophys. Res. Commun. 516 (3) (2019) 666–672.

[86] M. Sun, L. Hu, S. Wang, T. Huang, M. Zhang, M. Yang, W. Zhen, D. Yang, W. Lu, M. Guan, S. Peng, Circulating microRNA-19b identified from osteoporotic vertebral compression fracture patients increases bone formation, J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 35 (2) (2020) 306–316.

[87] G. Xiaoling, L. Shuaibin, L. Kailu, MicroRNA-19b-3p promotes cell proliferation and osteogenic differentiation of BMSCs by interacting with lncRNA H19, BMC Med. Genet. 21 (1) (2020) 11.

[88] X. Zeng, Q. Feng, F. Zhao, C. Sun, T. Zhou, J. Yang, X. Zhan, Puerarin inhibits TRPM3/miR-204 to promote MC3T3-E1 cells proliferation, differentiation and mineralization, Phytother. Res. PTR 32 (6) (2018) 996–1003.

[89] G. Zhang, H. Li, W. Zhao, M. Li, L. Tian, W. Ju, X. Li, miR-205 regulates bone turnover in elderly female patients with type 2 diabetes mellitus through targeted inhibition of Runx2, Exp. Ther. Med. 20 (2) (2020) 1557–1565.

[90] H. Wang, Y. Shen, MicroRNA-20a negatively regulates the growth and osteoclastogenesis of THP-1 cells by downregulating PPARγ, Mol. Med. Rep. 20 (5) (2019) 4271–4276.

[91] J. Chen, Y. Luo, T. Li, W. Yang, W. Zhang, Y. Wang, X. Li, L. Kong, Exosome-derived miR21/SMAD7 derived from donor osteoporosis mesenchymal stem cells inhibits osteogenic differentiation of reconstituted hosts, J. Biomater. Tissue Eng. 9 (2019) 1346–1354.

[92] L.B. Jiang, L. Tian, C.G. Zhang, Bone marrow stem cells-derived exosomes extracted from osteoporosis patients inhibit osteogenesis via microRNA-21/SMAD7, Eur. Rev. Med. Pharmacol. Sci. 22 (19) (2018) 6221–6229.

[93] J. Qiu, G. Huang, N. Na, L. Chen, MicroRNA-214-5p/TGF-β/Smad2 signaling alters adipogenic differentiation of bone marrow stem cells in postmenopausal osteoporosis, Mol. Med. Rep. 17 (5) (2018) 6301–6310.

[94] L. Yang, Z. Zeng, N. Kang, J.C. Yang, X. Wei, Y. Hai, Circ-VANGL1 promotes the progression of osteoporosis by absorbing miRNA-217 to regulate RUNX2 expression, Eur. Rev. Med. Pharmacol. Sci. 23 (3) (2019) 949–957.

[95] Z. Karimi, E. Seyedjafari, A. Khojasteh, S.M. Hashemi, B. Kazemi, S. Mohammadi-Yeganeh, MicroRNA-218 competes with differentiation media in the induction of osteogenic differentiation of mesenchymal stem cell by regulating β-catenin inhibitors, Mol. Biol. Rep. 47 (11) (2020) 8451–8463.

[96] C.-G. Wang, Z. Liao, H. Xiao, H. Liu, Y.-H. Hu, Q.-D. Liao, D. Zhong, LncRNA KCNQ1OT1 promoted BMP2 expression to regulate osteogenic differentiation by sponging miRNA-214, Exp. Mol. Pathol. 107 (2019) 77–84.

[97] X. Zhang, Y. Wang, H. Zhao, X. Han, T. Zhao, P. Qu, G. Li, W. Wang, Extracellular vesicle-encapsulated miR-22-3p from bone marrow mesenchymal stem cell promotes osteogenic differentiation via FTO inhibition, Stem Cell Res. Ther. 11 (1) (2020) 227.

[98] K. Jiang, G.D. Teng, Y.Q. Chen, MicroRNA-23 suppresses osteogenic differentiation of human bone marrow mesenchymal stem cells by targeting the MEF2C-mediated MAPK signaling pathway, J. Gene Med. 22 (10) (2020) 3216.

[99] L. Guo, K. Chen, J. Yuan, P. Huang, X. Xu, C. Li, N. Qian, J. Qi, Z. Shao, L. Deng, C. He, J. Xu, Estrogen inhibits osteoclasts formation and bone resorption via microRNA-27a targeting PPARγ and APC, J. Cell. Physiol. 234 (1) (2018) 581–594.

[100] Y. Huang, K. Ren, T. Yao, H. Zhu, Y. Xu, H. Ye, Z. Chen, J. Lv, S. Shen, J. Ma, MicroRNA-25-3p regulates osteoclasts through nuclear factor I X, Biochem. Biophys. Res. Commun. 522 (1) (2020) 74–80.

[101] Y. Xiao, B. Li, J. Liu, miRNA-27a regulates arthritis via PPARγ in vivo and in vitro, Mol. Med. Rep. 17 (4) (2018) 5454–5462.

[102] Y. Xu, D. Li, Z. Zhu, L. Li, Y. Jin, C. Ma, W. Zhang, miR-27a-3p negatively regulates osteogenic differentiation of MC3T3–E1 preosteoblasts by targeting osterix, Mol. Med. Rep. 22 (3) (2020) 1717–1726.

[103] R.W. Wu, W.S. Lian, Y.S. Chen, C.W. Kuo, H.C. Ke, C.K. Hsieh, S.Y. Wang, J.Y. Ko, F.S. Wang, MicroRNA-29a counteracts glucocorticoid induction of bone loss through repressing TNFSF13b modulation of osteoclastogenesis, Int. J. Mol. Sci. 20 (20) (2019) 5141.

[104] W.-S. Lian, J.-Y. Ko, Y.-S. Chen, H.-J. Ke, C.-K. Hsieh, C.-W. Kuo, S.-Y. Wang, B.-W. Huang, J.-G. Tseng, F.-S. Wang, MicroRNA-29a represses osteoclast formation and protects against osteoporosis by regulating PCAF-mediated RANKL and CXCL12, Cell Death Dis. 10 (10) (2019) 705.

[105] S.L. Jin, Y.M. Bai, B.Y. Zhao, Q.H. Wang, H.S. Zhang, Silencing of miR-330-5p stimulates osteogenesis in bone marrow mesenchymal stem cells and inhibits bone loss in osteoporosis by activating Bgn-mediated BMP/Smad pathway, Eur. Rev. Med. Pharmacol. Sci. 24 (8) (2020) 4095–4102.

[106] Y. Kong, Z.K. Nie, F. Li, H.M. Guo, X.L. Yang, S.F. Ding, MiR-320a was highly expressed in postmenopausal osteoporosis and acts as a negative regulator in MC3T3E1 cells by reducing MAP9 and inhibiting PI3K/AKT signaling pathway, Exp. Mol. Pathol. 110 (2019), 104282.

[107] Q. Sun, B. Zhang, W. Zhu, W. Wei, J. Ma, F.R. Tay, A potential therapeutic target for regulating osteoporosis via suppression of osteoclast differentiation, J. Dent. 82 (2019) 91–97.

[108] Y. Han, K. Zhang, Y. Hong, J. Wang, Q. Liu, Z. Zhang, H. Xia, Y. Tang, T. Li, L. Li, Y. Xue, W. Hong, miR-342-3p promotes osteogenic differentiation via targeting ATF3, FEBS Lett. 592 (24) (2018) 4051–4065.

[109] D. Wang, G. Cai, H. Wang, J. He, TRAF3, a target of MicroRNA-363-3p, suppresses senescence and regulates the balance between osteoblastic and adipocytic differentiation of rat bone marrow-derived mesenchymal stem cells, Stem Cells Dev. 29 (11) (2020) 737–745.

[110] F. Cheng, M.M. Yang, R.H. Yang, MiRNA-365a-3p promotes the progression of osteoporosis by inhibiting osteogenic differentiation via targeting RUNX2, Eur. Rev. Med. Pharmacol. Sci. 23 (18) (2019) 7766–7774.

[111] L.Y. Li, X.L. Wang, G.S. Wang, H.Y. Zhao, MiR-373 promotes the osteogenic differentiation of BMSCs from the estrogen deficiency induced osteoporosis, Eur. Rev. Med. Pharmacol. Sci. 23 (17) (2019) 7247–7255.

[112] N.B. Lei, X. Liang, P. Wang, Q. Liu, W.G. Wang, Teriparatide alleviates osteoporosis by promoting osteogenic differentiation of hMSCs via miR-375/RUNX2 axis, Eur. Rev. Med. Pharmacol. Sci. 23 (24) (2019) 11043–11050.

[113] J. Kureel, A.A. John, R. Prakash, D. Singh, MiR 376c inhibits osteoblastogenesis by targeting Wnt3 and ARF-GEF-1-facilitated augmentation of beta-catenin transactivation, J. Cell. Biochem. 119 (4) (2018) 3293–3303.

[114] S. Liu, C. Wang, J. Bai, X. Li, J. Yuan, Z. Shi, N. Mao, Involvement of circRNA_0007059 in the regulation of postmenopausal osteoporosis by promoting the microRNA-378/BMP-2 axis, Cell Biol. Int. 45 (2) (2021) 447–455.

[115] X. Yu, Y. Zeng, M. Bao, J. Wen, G. Zhu, C. Cao, X. He, L. Li, Low-magnitude vibration induces osteogenic differentiation of bone marrow mesenchymal stem cells via miR-378a-3p/Grb2 pathway to promote bone formation in a rat model of age-related bone loss, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 34 (9) (2020) 11754–11771.

[116] X. Li, J. Wu, S. Liu, K. Zhang, X. Miao, J. Li, Z. Shi, Y. Gao, miR-384-5p targets Gli2 and negatively regulates age-related osteogenic differentiation of rat bone marrow mesenchymal stem cells, Stem Cells Dev. 28 (12) (2019) 791–798.

[117] R. Prakash, A.A. John, D. Singh, miR-409-5p negatively regulates Wnt/Beta catenin signaling pathway by targeting Lrp-8, J. Cell. Physiol. 234 (12) (2019) 23507–23517.

[118] J.Y. Li, X. Wei, Q. Sun, X.Q. Zhao, C.Y. Zheng, C.X. Bai, J. Du, Z. Zhang, L.G. Zhu, Y.S. Jia, MicroRNA-449b-5p promotes the progression of osteoporosis by inhibiting osteogenic differentiation of BMSCs via targeting Satb2, Eur. Rev. Med. Pharmacol. Sci. 23 (15) (2019) 6394–6403.

[119] C. Lan, L. Long, K. Xie, J. Liu, L. Zhou, S. Pan, J. Liang, Z. Tu, Z. Gao, Y. Tang, miRNA-429 suppresses osteogenic differentiation of human adipose-derived mesenchymal stem cells under oxidative stress via targeting SCD-1, Exp. Ther. Med. 19 (1) (2020) 696–702.

[120] L. Fan, J. Fan, Y. Liu, T. Li, H. Xu, Y. Yang, L. Deng, H. Li, R.C. Zhao, miR-450b promotes osteogenic differentiation in vitro and enhances bone formation in vivo by targeting BMP3, Stem Cells Dev. 27 (9) (2018) 600–611.

[121] S.Y. Zhang, F. Gao, C.G. Peng, C.J. Zheng, M.F. Wu, miR-485-5p promotes osteoporosis via targeting Osterix, Eur. Rev. Med. Pharmacol. Sci. 22 (15) (2018) 4792–4799.

[122] Y. Huang, Q. Hou, H. Su, D. Chen, Y. Luo, T. Jiang, miR-488 negatively regulates osteogenic differentiation of bone marrow mesenchymal stem cells induced by psoralen by targeting Runx2, Mol. Med. Rep. 20 (4) (2019) 3746–3754.

[123] X. Guo, S. Wei, F. Xu, X. Cai, H. Wang, R. Ding, MicroRNA-532-5p is implicated in the regulation of osteoporosis by forkhead box O1 and osteoblast differentiation, BMC Musculoskelet. Disord. 21 (1) (2020) 296.

[124] X.B. Zhu, W.J. Lin, C. Lv, L. Wang, Z.X. Huang, S.W. Yang, X. Chen, MicroRNA-539 promotes osteoblast proliferation and differentiation and osteoclast apoptosis through the AXNA-dependent Wnt signaling pathway in osteoporotic rats, J. Cell. Biochem. 119 (10) (2018) 8346–8358.

[125] E.G. Ramírez-Salazar, E.V. Almeraya, T.V. López-Perez, N. Patiño, J. Salmeron, R. Velázquez-Cruz, MicroRNA-548-3p overexpression inhibits proliferation,

migration and invasion in osteoblast-like cells by targeting STAT1 and MAFB, J. Biochem. 168 (3) (2020) 203–211.
[126] B. Luo, J.F. Yang, Y.H. Wang, G.B. Qu, P.D. Hao, Z.J. Zeng, J. Yuan, R. Yang, Y. Yuan, MicroRNA-579-3p promotes the progression of osteoporosis by inhibiting osteogenic differentiation of mesenchymal stem cells through regulating Sirt1, Eur. Rev. Med. Pharmacol. Sci. 23 (16) (2019) 6791–6799.
[127] Y. Zhang, Y. Liu, M. Wu, H. Wang, L. Wu, B. Xu, W. Zhou, X. Fan, J. Shao, T. Yang, MicroRNA-664a-5p promotes osteogenic differentiation of human bone marrow-derived mesenchymal stem cells by directly downregulating HMGA2, Biochem. Biophys. Res. Commun. 521 (1) (2020) 9–14.
[128] X.H. Yang, K. Yang, Y.L. An, L.B. Wang, G. Luo, X.H. Hu, MicroRNA-705 regulates the differentiation of mouse mandible bone marrow mesenchymal stem cells, PeerJ 7 (2019) 6279, e6279-e6279.
[129] J.-C. Lin, Z.-G. Liu, B. Yu, X.-R. Zhang, MicroRNA-874 targeting SUFU involves in osteoblast proliferation and differentiation in osteoporosis rats through the Hedgehog signaling pathway, Biochem. Biophys. Res. Commun. 506 (1) (2018) 194–203.
[130] H.G. Zhang, X.B. Wang, H. Zhao, C.N. Zhou, MicroRNA-9-5p promotes osteoporosis development through inhibiting osteogenesis and promoting adipogenesis via targeting Wnt3a, Eur. Rev. Med. Pharmacol. Sci. 23 (2) (2019) 456–463.
[131] J. Xiang, H.Q. Fu, Z. Xu, W.J. Fan, F. Liu, B. Chen, lncRNA SNHG1 attenuates osteogenic differentiation via the miR-101/DKK1 axis in bone marrow mesenchymal stem cells, Mol. Med. Rep. 22 (5) (2020) 3715–3722.
[132] Z. Shan, N. Cheng, R. Huang, B. Zhao, Y. Zhou, Puerarin promotes the proliferation and differentiation of MC3T3-E1 cells via microRNA-106b by targeting receptor activator of nuclear factor-κB ligand, Exp. Ther. Med. 15 (1) (2018) 55–60.
[133] Y. Ren, R. Bao, Z. Guo, J. Kai, C.G. Cai, Z. Li, miR-126-5p regulates H9c2 cell proliferation and apoptosis under hypoxic conditions by targeting IL-17A, Exp. Ther. Med. 21 (1) (2021) 67.
[134] Y. Wang, K. Wang, Z. Hu, H. Zhou, L. Zhang, H. Wang, G. Li, S. Zhang, X. Cao, F. Shi, MicroRNA-139-3p regulates osteoblast differentiation and apoptosis by targeting ELK1 and interacting with long noncoding RNA ODSM, Cell Death Dis. 9 (11) (2018) 1107.
[135] T.J. Liu, J.L. Guo, Overexpression of microRNA-141 inhibits osteoporosis in the jawbones of ovariectomized rats by regulating the Wnt/β-catenin pathway, Arch. Oral Biol. 113 (2020), 104713.
[136] B. Luo, J. Yang, Y. Yuan, P. Hao, X. Cheng, MicroRNA-142 regulates osteoblast differentiation and apoptosis of mouse pre-osteoblast cells by targeting bone morphogenetic protein 2, FEBS Open Bio 10 (9) (2020) 1793–1801.
[137] G. Cao, X. Meng, X. Han, J. Li, Exosomes derived from circRNA Rtn4-modified BMSCs attenuate TNF-α-induced cytotoxicity and apoptosis in murine MC3T3-E1 cells by sponging miR-146a, Biosci. Rep. 40 (5) (2020).
[138] L. Feng, B. Xia, B.F. Tian, G.B. Lu, MiR-152 influences osteoporosis through regulation of osteoblast differentiation by targeting RICTOR, Pharm. Biol. 57 (1) (2019) 586–594.
[139] Z. Huang, C. Cheng, J. Wang, X. Liu, H. Wei, Y. Han, S. Yang, X. Wang, Icariin regulates the osteoblast differentiation and cell proliferation of MC3T3-E1 cells through microRNA-153 by targeting Runt-related transcription factor 2, Exp. Ther. Med. 15 (6) (2018) 5159–5166.
[140] Y. Li, W. Sun, F. Saaoud, Y. Wang, Q. Wang, J. Hodge, Y. Hui, S. Yin, S.M. Lessner, X. Kong, D. Fan, MiR155 modulates vascular calcification by regulating Akt-FOXO3a signalling and apoptosis in vascular smooth muscle cells, J. Cell. Mol. Med. 25 (1) (2021) 535–548.
[141] J. Xiao, S. Qin, W. Li, L. Yao, P. Huang, J. Liao, J. Liu, S. Li, Osteogenic differentiation of rat bone mesenchymal stem cells modulated by miR-186 via SIRT6, Life Sci. 253 (2020), 117660.
[142] W. Zhang, L. Chen, J. Wu, J. Li, X. Zhang, Y. Xiang, F. Li, C. Wu, L. Xiang, Q. Ran, Long noncoding RNA TUG1 inhibits osteogenesis of bone marrow mesenchymal stem cells via Smad5 after irradiation, Theranostics 9 (8) (2019) 2198–2208.
[143] Y. Sun, X. Wang, G. Chen, C. Song, X. Ma, Y. Fu, C. Feng, J. Yan, miRNA-187-5p regulates osteoblastic differentiation of bone marrow mesenchymal stem cells in mice by targeting ICAM1, BioMed Res. Int. 2020 (2020), 6139469.
[144] Y. Takafuji, K. Tatsumi, N. Kawao, K. Okada, M. Muratani, H. Kaji, MicroRNA-196a-5p in extracellular vesicles secreted from myoblasts suppresses osteoclast-like cell formation in mouse cells, Calcif. Tissue Int. 108 (3) (2021) 364–376.
[145] J. Tang, H. Yu, Y. Wang, G. Duan, B. Wang, W. Li, Z. Zhu, microRNA-199a counteracts glucocorticoid inhibition of bone marrow mesenchymal stem cell osteogenic differentiation through regulation of Klotho expression in vitro, Cell Biol. Int. 44 (12) (2020) 2532–2540.
[146] R. Lv, X. Pan, L. Song, Q. Sun, C. Guo, S. Zou, Q. Zhou, MicroRNA-200a-3p accelerates the progression of osteoporosis by targeting glutaminase to inhibit osteogenic differentiation of bone marrow mesenchymal stem cells, Biomed. Pharmacother. Biomed. Pharmacother. 116 (2019), 108960.
[147] L. Jing, B. Hu, Q.H. Song, Lycium barbarum polysaccharide (LBP) inhibits palmitic acid (PA)-induced MC3T3-E1 cell apoptosis by regulating miR-200b-3p/Chrdl1/PPARγ, Food Nutr. Res. 64 (2020).
[148] Q. Feng, S.Y. Cheng, R. Yang, X.W. Zeng, F.M. Zhao, X.Q. Zhan, Puerarin promotes the viability and differentiation of MC3T3-E1 cells by enhancing LC3B-mediated autophagy through downregulation of miR-204, Exp. Ther. Med. 19 (2) (2020) 883–890.
[149] X. Sun, X. Li, H. Qi, X. Hou, J. Zhao, X. Yuan, X. Ma, MiR-21 nanocapsules promote early bone repair of osteoporotic fractures by stimulating the osteogenic differentiation of bone marrow mesenchymal stem cells, J. Orthop. Transl. 24 (2020) 76–87.
[150] R. Madhyastha, H. Madhyastha, Y. Pengjam, Q.I. Nurrahmah, Y. Nakajima, M. Maruyama, The pivotal role of microRNA-21 in osteoclastogenesis inhibition by anthracycline glycoside aloin, J. Nat. Med. 73 (1) (2019) 59–66.
[151] T. Sun, D. Yang, Y. Wu, Q. Sheng, The function of microRNA-211 expression in post-fracture bone cell apoptosis involving the transforming growth factor-β/phosphoinositide 3-kinase signaling pathway, J. Int. Med. Res. 48 (7) (2020), 030006052092635, 300060520926353-300060520926353.
[152] J. Kou, X. Zheng, J. Guo, Y. Liu, X. Liu, MicroRNA-218-5p relieves postmenopausal osteoporosis through promoting the osteoblast differentiation of bone marrow mesenchymal stem cells, J. Cell. Biochem. 121 (2) (2020) 1216–1226.
[153] X. Zheng, J. Dai, H. Zhang, Z. Ge, MicroRNA-221 promotes cell proliferation, migration, and differentiation by regulation of ZFPM2 in osteoblasts, Braz. J. Med. Biol. Res. 51 (12) (2018) 7574, e7574-e7574.
[154] H.L. Zhang, X.Y. Du, Q.R. Dong, LncRNA XIXT promotes osteogenic differentiation of bone mesenchymal stem cells and alleviates osteoporosis progression by targeting miRNA-30a-5p, Eur. Rev. Med. Pharmacol. Sci. 23 (20) (2019) 8721–8729.
[155] L. Xu, Y. Fu, W. Zhu, R. Xu, J. Zhang, P. Zhang, J. Cheng, H. Jiang, microRNA-31 inhibition partially ameliorates the deficiency of bone marrow stromal cells from cleidocranial dysplasia, J. Cell. Biochem. 120 (6) (2019) 9472–9486.
[156] L. Wang, S. Liu, Y. Mao, J. Xu, S. Yang, H. Shen, W. Xu, W. Fan, J. Wang, CircRNF13 regulates the invasion and metastasis in lung adenocarcinoma by targeting miR-93-5p, Gene 671 (2018) 170–177.
[157] J. Tong, M. Zhang, X. Li, G. Ren, MicroRNA-338–3p regulates age-associated osteoporosis via targeting PCSK5, Mol. Med. Rep. 23 (2) (2021), 1-1.
[158] X. Yang, J. Yang, P. Lei, T. Wen, LncRNA MALAT1 shuttled by bone marrow-derived mesenchymal stem cells-secreted exosomes alleviates osteoporosis through mediating microRNA-34c/SATB2 axis, Aging 11 (20) (2019) 8777–8791.
[159] Y. Zhao, Y. Chen, X. Hu, N. Zhang, F. Wang, lncRNA LINC01535 upregulates BMP2 expression levels to promote osteogenic differentiation via sponging miR-3619–5p, Mol. Med. Rep. 22 (6) (2020) 5428–5435.
[160] J. Pan, C. Huang, G. Chen, Z. Cai, Z. Zhang, MicroRNA-451 blockade promotes osteoblastic differentiation and skeletal anabolic effects by promoting YWHAZ-mediated RUNX2 protein stabilization, MedChemComm 9 (8) (2018) 1359–1368.
[161] H. Zhao, Y. Yang, Y. Wang, X. Feng, A. Deng, Z. Ou, B. Chen, MicroRNA-497-5p stimulates osteoblast differentiation through HMGA2-mediated JNK signaling pathway, J. Orthop. Surg. Res. 15 (1) (2020) 515.
[162] J. Feng, J.X. Wang, C.H. Li, LncRNA GAS5 overexpression alleviates the development of osteoporosis through promoting osteogenic differentiation of MSCs via targeting microRNA-498 to regulate RUNX2, Eur. Rev. Med. Pharmacol. Sci. 23 (18) (2019) 7757–7765.
[163] B.-P. Xie, L.-Y. Shi, J.-P. Li, Y. Zeng, W. Liu, S.-Y. Tang, L.-J. Jia, J. Zhang, G.-X. Gan, Oleanolic acid inhibits RANKL-induced osteoclastogenesis via ER alpha/miR-503/RANK signaling pathway in RAW264.7 cells, Biomed. Pharmacother. Biomed. Pharmacother. 117 (2019), 109045.
[164] J. Zheng, H. Guo, Y. Qin, Z. Liu, Z. Ding, L. Zhang, W. Wang, LncRNA SNHG5 regulates cell apoptosis and inflammation by miR-132/PTEN axis in COPD, Biomed. Pharmacother. Biomed. Pharmacother. 126 (2020), 110016.
[165] Y. Chen, C. Sun, J. Lu, L. Zou, M. Hu, Z. Yang, Y. Xu, MicroRNA-590-5p antagonizes the inhibitory effect of high glucose on osteoblast differentiation by suppressing Smad7 in MC3T3-E1 cells, J. Int. Med. Res. 47 (4) (2019) 1740–1748.
[166] X. Zhang, Y. Wang, H. Zhao, X. Han, T. Zhao, P. Qu, G. Li, W. Wang, Extracellular vesicle-encapsulated miR-22-3p from bone marrow mesenchymal stem cell promotes osteogenic differentiation via FTO inhibition, Stem Cell Res. Ther. 11 (1) (2020) 227.
[167] Z. Tang, T. Xu, Y. Li, W. Fei, G. Yang, Y. Hong, Inhibition of CRY2 by STAT3/miRNA-7-5p promotes osteoblast differentiation through upregulation of CLOCK/BMAL1/P300 expression, molecular therapy, Nucleic Acids 19 (2020) 865–876.
[168] Q.Q. Li, Q. Wei, X.C. Zhai, L. Qin, H.B. Li, R. Meng, S.C. Chen, MiRNA-7b-5p attenuates the progression of osteoporosis by inhibiting adipose differentiation of hMSCs via regulating IRS2, Eur. Rev. Med. Pharmacol. Sci. 23 (21) (2019) 9207–9214.
[169] H. Liu, Q. Liu, X.P. Wu, H.B. He, L. Fu, MiR-96 regulates bone metabolism by targeting osterix, Clin. Exp. Pharmacol. Physiol. 45 (6) (2018) 602–613.
[170] Z. Min, L. Xiaomeng, L. Zheng, D. Yangge, L. Xuejiao, L. Longwei, Z. Xiao, L. Yunsong, Z. Ping, Z. Yongsheng, Asymmetrical methyltransferase PRMT3 regulates human mesenchymal stem cell osteogenesis via miR-3648, Cell Death Dis. 10 (8) (2019) 581.
[171] F. Wu, W. Huang, Y. Yang, F. Liu, J. Chen, G. Wang, Z. Sun, MicroRNA-155 contributes to plexiform neurofibroma growth downstream of MEK, Oncogene 40 (2021) 951–963.
[172] F. Zhang, J. Song, H. Zhang, E. Huang, D. Song, V. Tollemar, J. Wang, J. Wang, M. Mohammed, Q. Wei, Wnt and BMP signaling crosstalk in regulating dental stem cells: implications in dental tissue engineering, Genes Dis. 3 (4) (2016) 263–276.
[173] Z. Wei, Y. Wang, M. Du, M. Li, H. He, MiR-4262 regulates differentiation and osteogenesis of human periodontal stem cells by targeting suppressor of cytokine signaling 4, Biocell 44 (4) (2020) 631–638.
[174] Y. Zhang, S. Li, S. Yuan, H. Zhang, J. Liu, MicroRNA-23a inhibits osteogenesis of periodontal mesenchymal stem cells by targeting bone morphogenetic protein signaling, Arch. Oral Biol. 102 (2019) 93–100.
[175] Y. Xu, C. Ren, X. Zhao, W. Wang, N. Zhang, microRNA-132 inhibits osteogenic differentiation of periodontal ligament stem cells via GDF5 and the NF-κB signaling pathway, Pathol. Res. Pract. 215 (12) (2019), 152722.

[176] L. Kong, R. Zuo, M. Wang, W. Wang, J. Xu, Y. Chai, J. Guan, Q. Kang, Silencing microRNA-137-3p, which targets RUNX2 and CXCL12 prevents steroid-induced osteonecrosis of the femoral head by facilitating osteogenesis and angiogenesis, Int. J. Biol. Sci. 16 (4) (2020) 655–670.
[177] W. Yang, W. Zhu, Y. Yang, M. Guo, H. Qian, W. Jiang, Y. Chen, C. Lian, Z. Xu, H. Bai, Exosomal miR-100–5p Inhibits Osteogenesis of BMSCs and Angiogenesis of VECs by Suppressing BMPR2/Smad1/5/9 Signaling Pathway, 2021.
[178] R. Zuo, L. Kong, M. Wang, W. Wang, J. Xu, Y. Chai, J. Guan, Q. Kang, Exosomes derived from human CD34+ stem cells transfected with miR-26a prevent glucocorticoid-induced osteonecrosis of the femoral head by promoting angiogenesis and osteogenesis, Stem Cell Res. Ther. 10 (1) (2019) 1–14.
[179] M.-j. Kuang, K.-h. Zhang, J. Qiu, A.-b. Wang, W.-w. Che, X.-m. Li, D.-l. Shi, D.-C. Wang, Exosomal miR-365a-5p derived from HUC-MSCs regulates osteogenesis in GIONFH through the Hippo signaling pathway, Mol. Ther. Nucleic Acids 23 (2021) 565–576.
[180] P. Guo, L. Wu, Z. Xiao, T. Huang, X. Li, Knockdown of miR-140-5 promotes osteogenesis of adipose-derived mesenchymal stem cells by targeting TLR4 and BMP2 and promoting fracture healing in the atrophic nonunion rat model, Eur. Rev. Med. Pharmacol. Sci. 23 (5) (2019) 2112–2124.
[181] H. Long, Y. Zhu, Z. Lin, J. Wan, L. Cheng, M. Zeng, Y. Tang, R. Zhao, miR-381 modulates human bone mesenchymal stromal cells (BMSCs) osteogenesis via suppressing Wnt signaling pathway during atrophic nonunion development, Cell Death Dis. 10 (7) (2019) 1–15.
[182] Z. Chen, J. Zheng, H. Hong, D. Chen, L. Deng, X. Zhang, J. Ling, L. Wu, lncRNA HOTAIRM1 promotes osteogenesis of hDFSCs by epigenetically regulating HOXA2 via DNMT1 in vitro, J. Cell. Physiol. 235 (11) (2020) 8507–8519.
[183] L. Fu, S. Peng, W. Wu, Y. Ouyang, D. Tan, X. Fu, LncRNA HOTAIRM1 promotes osteogenesis by controlling JNK/AP-1 signalling-mediated RUNX2 expression, J. Cell. Mol. Med. 23 (11) (2019) 7517–7524.
[184] W. Zhuang, X. Ge, S. Yang, M. Huang, W. Zhuang, P. Chen, X. Zhang, J. Fu, J. Qu, B. Li, Upregulation of lncRNA MEG3 promotes osteogenic differentiation of mesenchymal stem cells from multiple myeloma patients by targeting BMP4 transcription, Stem Cells 33 (6) (2015) 1985–1997.
[185] L. Deng, H. Hong, X. Zhang, D. Chen, Z. Chen, J. Ling, L. Wu, Down-regulated lncRNA MEG3 promotes osteogenic differentiation of human dental follicle stem cells by epigenetically regulating Wnt pathway, Biochem. Biophys. Res. Commun. 503 (3) (2018) 2061–2067.
[186] X.-Z. Huang, J. Huang, W.-Z. Li, J.-J. Wang, D.-Y. Song, J.-D. Ni, LncRNA-MALAT1 promotes osteogenic differentiation through regulating ATF4 by sponging miR-214: implication of steroid-induced avascular necrosis of the femoral head, Steroids 154 (2020), 108533.
[187] Q. Jia, W. Jiang, L. Ni, Down-regulated non-coding RNA (lncRNA-ANCR) promotes osteogenic differentiation of periodontal ligament stem cells, Arch. Oral Biol. 60 (2) (2015) 234–241.
[188] L. Zhu, P.-C. Xu, Downregulated LncRNA-ANCR promotes osteoblast differentiation by targeting EZH2 and regulating Runx2 expression, Biochem. Biophys. Res. Commun. 432 (4) (2013) 612–617.
[189] C. Jin, L. Jia, Y. Huang, Y. Zheng, N. Du, Y. Liu, Y. Zhou, Inhibition of lncRNA MIR31HG promotes osteogenic differentiation of human adipose-derived stem cells, Stem Cells 34 (11) (2016) 2707–2720.
[190] R. Liu, Z. Li, E. Song, P. Hu, Q. Yang, Y. Hu, H. Liu, A. Jin, LncRNA HOTTIP enhances human osteogenic BMSCs differentiation via interaction with WDR5 and activation of Wnt/β-catenin signalling pathway, Biochem. Biophys. Res. Commun. 524 (4) (2020) 1037–1043.
[191] C. Yin, Y. Tian, Y. Yu, H. Wang, Z. Wu, Z. Huang, Y. Zhang, D. Li, C. Yang, X. Wang, A novel long noncoding RNA AK016739 inhibits osteoblast differentiation and bone formation, J. Cell. Physiol. 234 (7) (2019) 11524–11536.
[192] H. Li, Z. Zhang, Z. Chen, D. Zhang, Osteogenic growth peptide promotes osteogenic differentiation of mesenchymal stem cells mediated by LncRNA AK141205-induced upregulation of CXCL13, Biochem. Biophys. Res. Commun. 466 (1) (2015) 82–88.
[193] Sa Tang, Z. Xie, P. Wang, J. Li, S. Wang, W. Liu, M. Li, X. Wu, H. Su, S. Cen, LncRNA-OG promotes the osteogenic differentiation of bone marrow-derived mesenchymal stem cells under the regulation of hnRNPK, Stem Cells 37 (2) (2019) 270–283.
[194] B. Mei, Y. Wang, W. Ye, H. Huang, Q. Zhou, Y. Chen, Y. Niu, M. Zhang, Q. Huang, LncRNA ZBTB40-IT1 modulated by osteoporosis GWAS risk SNPs suppresses osteogenesis, Hum. Genet. 138 (2) (2019) 151–166.
[195] Y. Wu, K. Lian, C. Sun, LncRNA LEF1-AS1 promotes osteogenic differentiation of dental pulp stem cells via sponging miR-24-3p, Mol. Cell. Biochem. 475 (1) (2020) 161–169.
[196] X. Sun, Y. Yuan, Y. Xiao, Q. Lu, L. Yang, C. Chen, Q. Guo, Long non-coding RNA, Bmcob, regulates osteoblastic differentiation of bone marrow mesenchymal stem cells, Biochem. Biophys. Res. Commun. 506 (3) (2018) 536–542.
[197] C.E. Tye, J.R. Boyd, N.A. Page, M.M. Falcone, J.L. Stein, G.S. Stein, J.B. Lian, Regulation of osteogenesis by long noncoding RNAs: an epigenetic mechanism contributing to bone formation, Connect. Tissue Res. 59 (Suppl. 1) (2018) S35–S41.
[198] Q. Chen, M. Wang, S. Wu, The lncRNA MCF2L-AS1 controls osteogenic differentiation by regulating miR-33a, Cell Cycle 19 (9) (2020) 1059–1065.
[199] Y. Chi, Q. Luo, Y. Song, F. Yang, Y. Wang, M. Jin, D. Zhang, Circular RNA circPIP5K1A promotes non-small cell lung cancer proliferation and metastasis through miR-600/HIF-1α regulation, J. Cell. Biochem. 120 (11) (2019) 19019–19030.
[200] Y. Zhang, X. Cao, P. Li, Y. Fan, L. Zhang, X. Ma, R. Sun, Y. Liu, W. Li, LncRNA NKILA integrates RXFP1/AKT and NF-κB signalling to regulate osteogenesis of mesenchymal stem cells, J. Cell. Mol. Med. 24 (1) (2020) 521–529.
[201] J. Liao, X. Yu, X. Hu, J. Fan, J. Wang, Z. Zhang, C. Zhao, Z. Zeng, Y. Shu, R. Zhang, lncRNA H19 mediates BMP9-induced osteogenic differentiation of mesenchymal stem cells (MSCs) through Notch signaling, Oncotarget 8 (32) (2017) 53581–53601.
[202] X. Qiu, B. Jia, X. Sun, W. Hu, H. Chu, S. Xu, J. Zhao, The critical role of long noncoding RNA in osteogenic differentiation of human bone marrow mesenchymal stem cells, BioMed Res. Int. 2017 (2017) 1–11.
[203] Y. Xu, W. Qin, D. Guo, J. Liu, M. Zhang, Z. Jin, LncRNA-TWIST1 promoted osteogenic differentiation both in PPDLSCs and in HPDLSCs by inhibiting TWIST1 expression, BioMed Res. Int. 2019 (2019), 8735952.
[204] J. Weng, W. Peng, S. Zhu, S. Chen, Long noncoding RNA sponges miR-454 to promote osteogenic differentiation in maxillary sinus membrane stem cells, Implant Dent. 26 (2) (2017) 178–186.
[205] X. Zhu, J. Yu, J. Du, G. Zhong, L. Qiao, J. Lin, LncRNA HOXA-AS2 positively regulates osteogenesis of mesenchymal stem cells through inactivating NF-κB signalling, J. Cell. Mol. Med. 23 (2) (2019) 1325–1332.
[206] S.G. Almalki, D.K. Agrawal, Key transcription factors in the differentiation of mesenchymal stem cells, Differ. Res. Biol. Divers. 92 (1–2) (2016) 41–51.