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REVIEW

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The role of LncRNAs and CircRNAs in osteoporosis: a focus on osteogenesis and osteoclastogenesis signaling pathways

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Abstract

Background Osteoporosis is a crucial health concern interconnected with physical disabilities as well as financial burdens. It arises from an imbalance between osteoblasts and osteoclasts, provoking the reduction of bone mass and the disturbances in bone structure with high fracture risk. Considerable efforts were done to prevent and mitigate this public health issue. Nonetheless, further understanding of the etiopathology of osteoporosis and the underlying genetic and epigenetic pathways is required.

Main body Emerging evidence indicates that noncoding RNAs, including long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs), play crucial roles as epigenetic regulators in various pathological processes, including osteoporosis. LncRNAs are RNA transcripts with higher structural complexity that are developed owing to their secondary and tertiary structures, which allow them to create different binding sites for other biomolecules, such as DNA, RNA, and proteins. Another class of noncoding RNAs is circRNAs, which have a covalently closed loop structure without the 5′ cap and 3′ polyA tail and are formed by back-splicing of pre-mRNAs. Because of their closed structure, circRNAs are largely stable, resistant to RNA-degrading nucleases, and possess substantially longer circulatory half-lives than linear RNAs. Interestingly, both lncRNAs and circRNAs serve as competing endogenous RNAs by sponging multiple miRNA binding sites as well as interact with RNA-binding proteins (RBPs), thereby controlling the expression of their target genes. Several studies indicated that altered expression of these regulators could influence many biological processes in bone cells.

Conclusion The current review provides current opinions on the role and the underlying mechanisms by which lncRNAs and circRNAs affect osteoblastic and osteoclastic activities. The deep understanding of these noncoding RNAs in osteoporosis offers distinctive avenues for innovative treatment strategies.

Keywords LncRNAs, CircRNAs, Osteoporosis, Osteogenesis, Osteoclastogenesis

Background

Osteoporosis is a devasting metabolic bone disease with declined bone mass, loss of microarchitecture, fragility, and high susceptibility to fractures. Globally, it is one of the crucial reasons for the long-term physical impairments prevailing in an aging population. Therefore, osteoporosis represents a serious universal health issue that imposes a heavy load on society and healthcare systems [1].

Bone homeostasis is a constant state of formation and resorption through osteoblast and osteoclast activities,

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respectively. Osteoporosis occurs due to elevated osteoclastic activity without osteoblastic compensation [2]. Diverse molecules such as estrogen, parathyroid hormone, calcitonin, and vitamin D are implicated in the development and progression of the disease [3]. Earlier studies have also linked the development of osteoporosis to a battery of risk factors, such as modifiable and non-modifiable ones. Modifiable risk factors include weight, smoking, alcohol consumption, inactivity, calcium/vitamin D status, and the administration of corticosteroids. On the other hand, non-modifiable risk factors comprise advancing age, sex, race, and genetic characteristics [4]. Interestingly, the majority of these variables influence osteoporosis by modulating the activity of osteoblasts and osteoclasts. Nevertheless, genetic factors are regarded as one of the most significant predictors of osteoporosis [5].

Osteoporosis can be classified as either a primary or secondary disease. Primary osteoporosis includes juvenile, postmenopausal (type-I), and senile osteoporosis (type-II) [6]. Juvenile osteoporosis occurs in childhood and adolescence as a result of genetic mutations that could predispose to quantitative or qualitative disturbances in the connective tissue component of bone. Type-I osteoporosis, also named hormonal osteoporosis, is triggered by estrogen decrement during menopause; meanwhile, type-2 or senile osteoporosis, as the name implies, affects both genders and reaches peak incidence in the mid-seventies. Secondary osteoporosis occurs as a result of underlying medical conditions, such as renal disorders, malignancies, endocrine diseases, or therapeutic interventions [7].

Currently, dual-energy X-ray absorptiometry (DEXA) is the gold standard technique for diagnosing osteoporosis and predicting skeletal fracture risk. Despite its value, DEXA can only detect changes in bone structure that have already occurred, which can take a considerable time to become detectable, and it provides limited insights into disease progression and treatment effectiveness [8]. As well, since osteoporosis is recognized as a 'silent disease', it is frequently undiagnosed until a symptomatic fracture occurs [9]. Therefore, there has been a growing interest in exploring alternative approaches, such as epigenetic studies, for the early detection of osteoporosis before the occurrence of fractures.

The epigenetic landscape exhibits a fundamental role in osteoporosis pathogenesis. Intriguingly, epigenetics arises from the overlapping between genes, a non-modifiable risk factor, and the environment, as a modifiable risk factor for osteoporosis. Previous reports documented that epigenetics control a variety of biological processes, such as chromosome inactivation and cell differentiation [10]. Moreover, epigenetic regulations could manipulate the etiopathogenesis of osteoporosis via controlling osteoblasts and osteoclast cells [11], as shown in Fig. 1.

LncRNAs are noncoding RNA transcripts > 200 nt that are not translated into proteins. LncRNAs are implicated in physiological and pathological cascades, so they are nominated as important regulators and possible biomarkers for a variety of human disorders, including osteoporosis [12]. lncRNAs exert their role in several human diseases via functioning as miRNA reservoirs, binding to messenger RNAs (mRNAs) or pre-mRNAs, and controlling post-transcriptional expression [13]. In osteoporosis, lncRNAs participate in bone proliferation, apoptosis, and the inflammatory response, resulting in the regulation of osteogenic and osteoclastogenic processes.

Circular RNA is a distinct form of endogenous ncRNA, with transcripts ranging in length from hundreds to thousands of nucleotides. The reverse splicing that occurs between the splice acceptor at the 5′ end and the splice donor at the 3′ end of the pre-mRNA creates a covalently closed loop structure for circRNAs. The unique structure of circRNAs confers significant stability, rendering them resistant to RNA-degrading nucleases and resulting in significantly longer half-lives in the circulatory system compared to linear RNAs [14]. Recent findings indicate circRNAs have significant involvement in key cellular processes relevant to the progression of various diseases, such as cell differentiation and proliferation, thus serving as innovative biomarkers for diagnosis and prognosis. CircRNAs act as epigenetic regulators through controlling gene splicing or transcription, translating proteins, interacting with RNA-binding proteins (RBPs), and sponging miRNA [15]. Many circRNAs are differentially expressed in osteoporosis to influence the expression of certain genes that are implicated in osteoblastic and osteoclastic activities.

Based on that, the current review endeavors to combine these data and show the expression profiles of lncRNAs and circRNAs in osteoporosis. It also focuses on their regulatory roles as well as their clinical utility as promising therapeutic targets from the perspective of osteogenesis and osteoclastogenesis.

Main text

Osteogenic signaling pathways

Osteogenesis is the differentiation of committed mesenchymal stem cells (MSCs) into mature, active osteoblasts through several stages of precursors. Osteogenesis is achieved through interrelated cascades including hippo, Wnt, notch, and bone morphogenetic protein (BMP). These axes modulate diverse transcription factors, such as runt-related transcription factor 2 (RUNX2). RUNX2 participates in triggering the dedication of MSCs to the

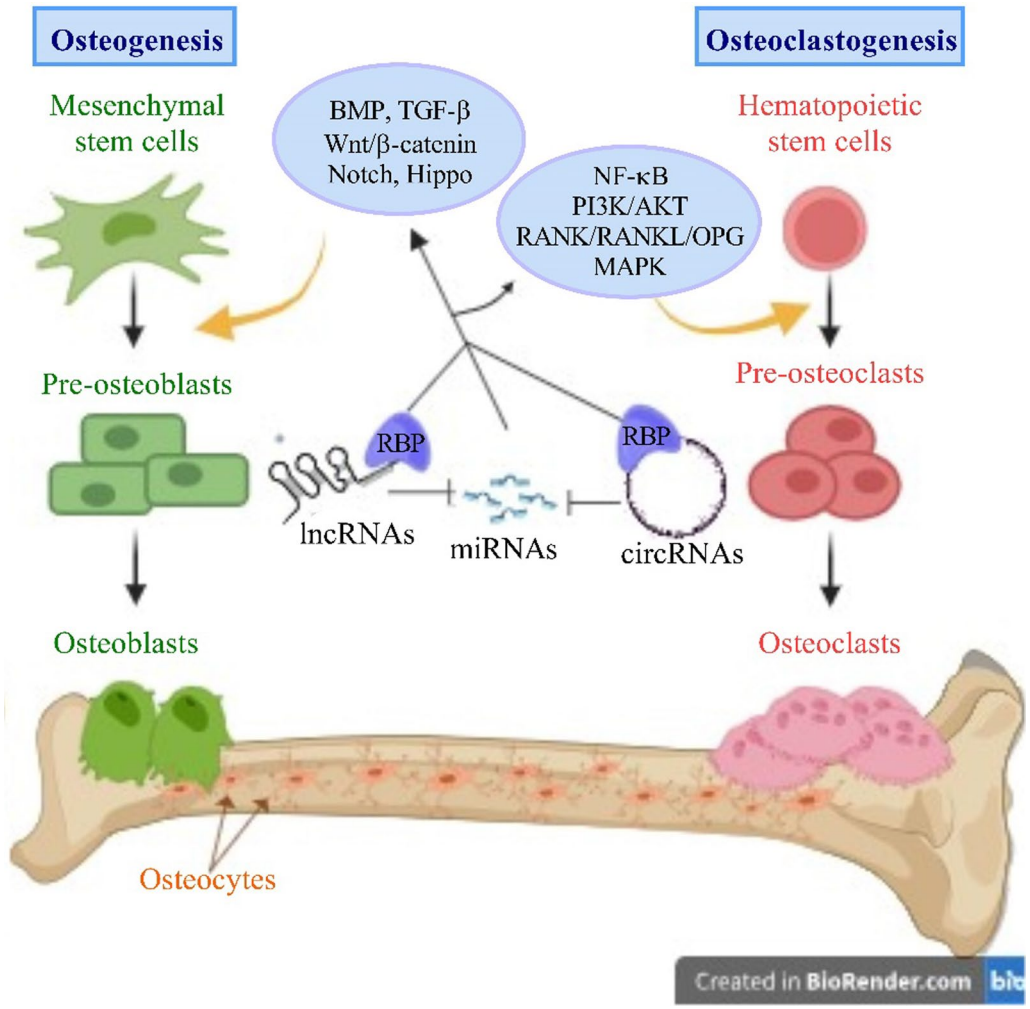

Fig. 1 ncRNAs regulate osteogenesis and osteoclastogenesis signaling pathways involved in the development of osteoporosis

osteogenic lineage and functions upstream from the other transcription factors specific to osteoblasts, such as osterix (Osx) and distal-less homeobox 5 (Dlx5) [16]. The Wnt/β-catenin pathway plays a potential role in the stabilization of β-catenin that sequentially migrates to the nucleus and controls the expression of genes related to osteoblastogenesis [17]. Dickkopf-1 (DKK1) is mainly expressed by osteoblasts and bone marrow stromal cells (BMSCs) and antagonizes the Wnt pathway.

Another signaling pathway is BMP, which is one of the members of the transforming growth factor (TGF)-β superfamily and plays a crucial role in regenerating osteogenic differentiation in osteoblasts. Briefly, BMP receptors bind with BMP ligands, resulting in phosphorylation of Smad1/5/8, which then attaches to the co-Smad (Smad4) to form a complex. The resultant complex moves to the nucleus, where it regulates the genes that affect osteoblast development in conjunction with co-activators and corepressors [18].

The Hippo signaling cascade modulates osteoblastic activity and thereby participates in bone development and maintenance. Sometimes, the Hippo pathway is turned off by inactivating (dephosphorylating) mammalian STE20-like protein kinases 1 and 2 (MST1/2) and large tumor suppressors 1 and 2 (LATS1/2). This results in the activation of the yes-associated protein (YAP) and the transcriptional coactivator with the PDZ-binding motif (TAZ), allowing them to translocate into the nucleus. Subsequently, YAP and TAZ act as transcriptional co-activators, interacting with transcription factors to regulate the expression of target genes related to osteoblast cell proliferation, differentiation, and survival [19].

Notch signaling, a highly preserved intercellular pathway, governs cell differentiation and proliferation as

well as determines cell fate via the activation of cell surface receptors (Notch 1-4) and their delta-like ligands (DLL) 1, 3, 4, and Jagged 1, 2. This pathway promotes the expression of downstream target genes involved in osteogenesis regulation [20].

LncRNAs involved in osteogenesis regulation

LncRNAs that promote osteogenesis

BMSCs have a high osteogenic capability, which is considered an effective practical strategy for hindering bone loss. Previous reports elucidated the involvement of the lncRNAs in BMSC proliferation and differentiation. Herein, we review the expression of potential lncRNAs in osteoporosis and their significant roles in either promoting or inhibiting osteogenic differentiation, as shown in Table 1 and Fig. 2, respectively.

LncRNA homeobox D gene cluster antisense growth-associated long noncoding RNA (HAGLR) exhibited a significant decrease in the peripheral blood of patients with postmenopausal osteoporosis (PMOP) compared to healthy controls. Conversely, its expression increased during BMSC osteogenic differentiation. In OVX mice, the overexpression of HAGLR alleviated PMOP by upregulating homeobox protein A10 (Hoxa10) expression through inhibition of miR-182-5p [21]. Indeed, Hoxa10, a crucial transcription factor in the osteogenic process, plays a pivotal role in regulating the production of osteoblasts [22]. In parallel, the **lncRNA RAD51-Antisense RNA 1 (RAD51-AS1)** was remarkably downregulated in human bone marrow stem cells (hBMSCs) obtained from osteoporotic patients compared to those from controls. It was observed that RAD51-AS1 knockdown inhibited the proliferation and differentiation of hBMSCs and boosted their apoptosis. Mechanistically, RAD51-AS1 was determined to stimulate the osteogenic differentiation of hBMSCs by interacting with Y-Box Binding Protein 1 (YBX1) to generate mRNA-protein complexes with SMAD7 and Smad ubiquitin regulatory factor 2 (SMURF2), thus hampering their translation. Additionally, it could transcriptionally upregulate proliferating cell nuclear antigen (PCNA) and SIVA1 by binding to their promoter regions, resulting in activation of the TGF-β signaling pathway [23]. **LncRNA KCNQ1OT1** also showed a significant decrease in PMOP patients compared to control group. Its overexpression enhanced the osteogenic differentiation of MC3T3-E1 cells and alleviated osteoporosis in OVX mice through upregulation of mTOR via sponging miR-421-3p [24].

Besides, GATA-binding protein 4 (GATA4) is crucial in modulating osteoblastic differentiation, bone remodeling, and mineralization [25]. Huang et al. linked GATA4 with **lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)** in BMSCs during osteogenesis [26]. The study found that GATA4 overexpression promoted BMSC osteoblastic differentiation through upregulating lncRNA MALAT1. Notably, the expression of both GATA4 and lncRNA MALAT1 was reduced in the bone tissues of both PMOP patients and ovariectomized (OVX) mice. It was confirmed that GATA4 activated the transcription of MALAT1, which in turn formed an RBP complex with K-homology splicing

Table 1 The expression of lncRNAs-related osteogenesis in osteoporosis

LncRNAs that promote osteogenesis			
LncRNA	**Expression in osteoporosis**	**Samples**	**References**
LncRNA HAGLR	Downregulated	Peripheral blood of PMOP patients and OVX mice	[21]
LncRNA RAD51-AS1	Downregulated	hBMSCs of osteoporotic patients	[23]
LncRNA KCNQ1OT1	Downregulated	Bone tissue samples of PMOP and OVX mice	[24]
GATA4-mediated lncRNA MALAT1	Downregulated	Bone tissues of PMOP patients and OVX mice	[26]
Quercetin-mediated lncRNA MALAT1	Downregulated	OVX mice	[29]
Prrx-2-mediated lncRNA MIR22HG	Downregulated	OVX mice	[30]
LncRNA TERC	Downregulated	DEX-induced osteoporosis in BMSCs	[31]
LncRNA SNHG14	Downregulated	OVX mice	[34]
LncRNAs that inhibit osteogenesis			
LINC00205	Upregulated	Bone tissue samples of osteoporotic patients	[35]
LINC01234	Upregulated	Plasma of osteoporotic patients	[37]
LncRNA PCBP1-AS1	Upregulated	Bone tissue samples of osteoporotic patients	[38]
LncRNA KCNMA1-AS1	Upregulated	Bone tissue samples of osteoporotic patients	[40]
LncRNA SNHG1	Upregulated	Serum of osteoporotic patients	[41]
IRF-1-mediated lncRNA XIST	Upregulated	OVX mice	[42]

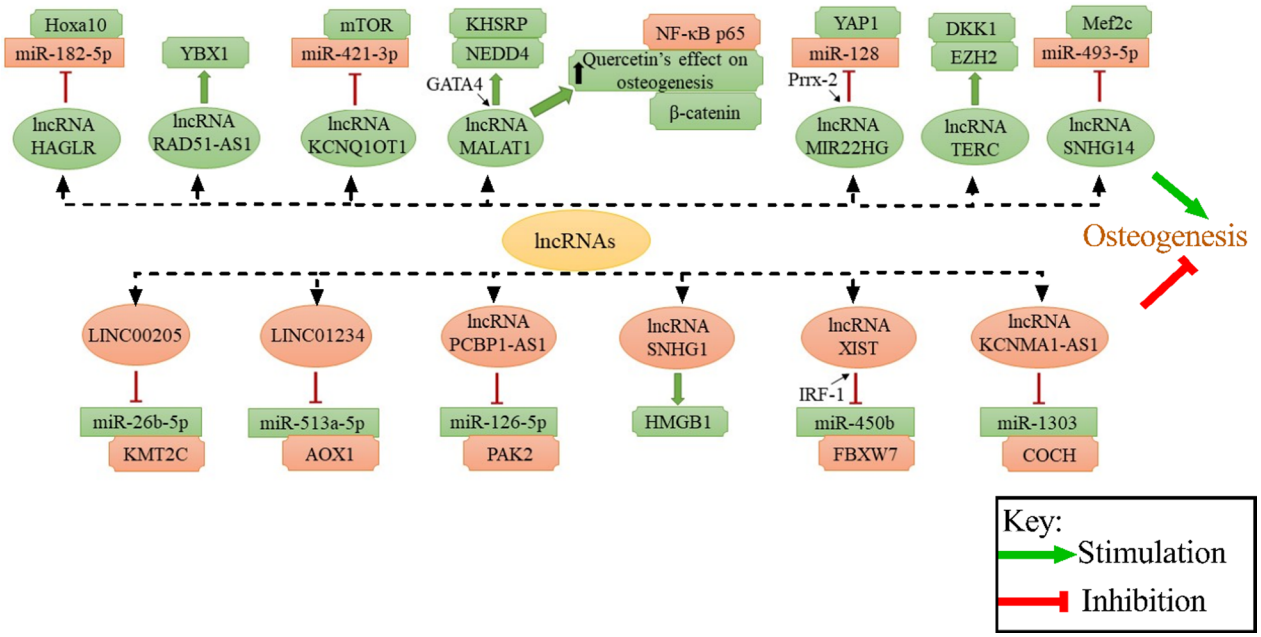

Fig. 2 Role and mechanistic insights of lncRNAs in osteogenesis. All shapes shaded in green denote biomarkers increased during osteogenesis. All shapes shaded in red denote biomarkers decreased during osteogenesis

regulatory protein (KHSRP) to decay the stability of neuronal precursor cell-expressed developmentally downregulated 4 (NEDD4) mRNA, the one that is responsible for the promotion of RUNX1 degradation by ubiquitination [27]. In sum, GATA4-mediated lncRNA MALAT1 stimulated osteogenic differentiation of BMSCs via inhibiting RUNX1 degradation through modulation of the KHSRP/NEDD4 axis, ultimately driving bone formation in PMOP. Furthermore, another study has also investigated the role and molecular mechanism of MALAT1 in osteoporosis. Interestingly, several phytochemicals have been found to be effective therapeutics for osteoporosis. Among them is quercetin, which has a promoting effect on BMSC osteogenesis [28]. Feng et al. documented that quercetin treatment could attenuate tumor necrosis factor alpha (TNFα)-impaired BMSCs osteogenesis via upregulating MALAT1 expression [29]. In OVX mice, serum MALAT1 level was markedly decreased, while quercetin treatment restored its level to some extent. Additionally, MALAT1 was involved in the modulating effect of quercetin on TNFα-impaired BMSC osteogenesis. Its knockdown abolished the rescuing effect of quercetin; stimulation of β-catenin expression and mitigation of NF-κB p65 translocation. This, in turn, compromised quercetin's osteogenic ability and facilitated the progression of osteoporosis. In the same context, Paired-Related Homeobox Protein 2 (Prrx2) is a transcription factor that belongs to the paired-related homeobox protein family and has been found to be involved in the regulation of lncRNA expression. Li et al. reported that myoblast-derived exosomal Prrx2 directly attached to the **MIR22HG** promoter and enhanced its expression [30]. Relevantly, high levels of MIR22HG alleviated OVX-induced bone loss by accelerating BMSC osteogenic differentiation through inhibition of miR-128, which in turn stimulated YAP1 expression and thus activated the Hippo pathway.

Other factors have been implicated in the regulation of lncRNAs during osteogenesis, impacting the development of osteoporosis. Dexamethasone (DEX) is a synthetic glucocorticoid that has been reported to regulate MSC osteogenic lineages. **LncRNA TERC** is among the lncRNAs identified to alleviate DEX-induced osteoporosis. It was observed that TERC overexpression mitigated the inhibitory effect of DEX on BMSC osteogenic differentiation by increasing the level of the enhancer of zeste homolog 2 (EZH2) protein. This elevation, in turn, facilitated the histone modification of DKK1, thereby activating the Wnt signaling pathway. Thus, TERC overexpression by lessening DEX-induced osteoporosis could provide an additional therapeutic strategy for glucocorticoid-induced osteoporosis [31]. Also, Autophagy is a mechanism beneficial for cell survival and growth [32], known to maintain bone remodeling by removing reactive oxygen species (ROS) [33]. Xue et al. have found that **lncRNA Small nucleolar RNA host gene 14 (SNHG14)** overexpression activated autophagy in BMSCs as well as raised bone mineral density (BMD) and bone trabecular

number in OVX mice [34]. Mechanically, an elevated level of SNHG14 stimulated myocyte enhancer factor 2C (Mef2c)-mediated autophagy activation through inhibition of miR-493-5p, predisposing to enhancement of the osteogenic ability of BMSCs. Thus, SNHG14 could alleviate osteoporosis progression via activation of autophagy by regulating the miR-493-5p/Mef2c axis.

LncRNAs that inhibit osteoblastogenesis

Certain lncRNAs have been identified as inhibitors of osteogenesis, which impede the process of bone formation and trigger osteoporosis development. For example, **LINC00205** was upregulated in bone tissue samples of osteoporotic patients with or without a spinal fracture, while it was downregulated during the osteogenic differentiation of human mesenchymal stem cells (hMSCs). Precisely, LINC00205 inhibited osteogenic differentiation by targeting miR-26b-5p and enhancing lysine (K)-specific methyltransferase 2C (KMT2C) expression. This latter contributed to a decrease in the expression of osteogenic-related genes such as RUNX2, alkaline phosphatase (ALP), and osteocalcin (OCN), resulting in the progression of osteoporosis [35]. Likewise, **LINC01234** was highly expressed in the plasma of patients with osteoporosis while exhibiting a gradual decrease during osteogenic differentiation of hMSCs. In this study, it was observed that LINC01234 impeded hMSC osteogenic differentiation by augmenting aldehyde oxidase 1 (AOX1) via regression of miR-513a-5p. Notably, the AOX1 gene encodes the cytosolic enzyme that catalyzes the formation of superoxide [36]. Thus, targeting LINC01234 could promote osteogenesis and hinder osteoporosis development [37].

LncRNA PCBP1-AS1 was highly expressed in osteoporotic tissues and decreased during the development of hBMSCs into osteoblasts. The knockdown of PCBP1-AS1 promoted the osteogenic differentiation capacity of hMSCs, while its overexpression exhibited an opposite effect. Mechanistically, PCBP1-AS1 targeted Pak family member p21-activated kinase 2 (PAK2) by inhibiting miR-126-5p [38]. Remarkably, PAK2 is required for various cellular activities, such as cytoskeletal remodeling and chromatin modulation [39]. Additionally, **lncRNA KCNMA1-AS1** was elevated in the osteoporotic subjects. Its suppression upregulated miR-1303, which resulted in the downregulation of cochlin (COCH), a known suppressor of embryonic stem cell differentiation. This led to the promotion of osteogenic differentiation in hMSCs and the mitigation of the progression of osteoporosis [40].

The intricate interplay between lncRNAs and apoptosis reveals a novel aspect of the pathogenesis of osteoporosis. Pan et al. reported that **lncRNA SNHG1** could regulate osteogenic differentiation by influencing pyroptosis, an inflammatory type of apoptosis triggered by inflammasomes and caspase-1 [41]. SNHG1 was observed to be elevated in the serum of osteoporotic patients. Its overexpression could suppress BMSC osteogenic differentiation through interaction with HMGB1, enhancing its expression. This, in turn, activated pyroptosis-associated factors (caspase-1 p20 and gasdermin D-N (GSDMD)-N) and the production of inflammatory interleukins (IL-1β and IL-18), leading to the development of osteoporosis. In tandem, interferon regulatory factor-1 (IRF-1) also participated in controlling cellular apoptosis during osteogenic differentiation through the regulation of **lncRNA X-inactive-specific transcript (XIST)**. Elevated levels of lncRNA XIST were observed in OVX mice, and its knockdown not only alleviated osteoporosis symptoms but also promoted osteogenic differentiation in hBMSCs. Simultaneously, IRF-1 accelerated osteogenic differentiation by repressing the transcription of XIST, which in turn upregulated miR-450b and subsequently decreased F-box and WD repeat domain-containing 7 (FBXW7) expression [42]. FBXW7 is regarded as an efficient tumor suppressor due to its role in cellular apoptosis and has also been observed to be involved in the osteogenic differentiation of BMSCs [43, 44].

CircRNAs involved in osteogenesis regulation

CircRNAs that promote osteogenesis

Several studies, conducted in BMSC-induced osteogenic differentiation, focused on RUNX2 regulation through various circRNA/miRNA axes. For instance, **circ-3626**, an exonic circRNA that arises from the STAG1 gene, was significantly increased during osteogenic differentiation of BMSCs, whereas it was decreased in bone tissues derived from osteoporotic patients and BMSCs of aged mice. Moreover, its overexpression dramatically accelerated the osteogenic capability of BMSCs. Circ-3626 increased RUNX2 regulation by inhibiting miR-338-3p and thereby upregulating many osteogenic-related genes [45]. Similarly, **circ-RBM23** acted as a suppressor of miR-338-3p, enhancing RUNX2 and regulating the switch between osteogenesis and adipogenesis in MSCs. The authors reported that circ-RBM23 was elevated in osteogenesis, whereas it was depressed during adipogenesis in MSCs, providing a crucial goal for diagnosing and alleviating osteoporosis [46]. Furthermore, **circ_0011269, circ-VANGL1, and circ_0076690** were notably decreased in the clinical samples of osteoporotic patients. In hMSCs, circ_0011269, circ-VANGL1, and circ_0076690 upregulated RUNX2 expression via sponging miR-122, miR-217, and miR-152, respectively. These findings pointed out that the overexpression of

these circRNAs promoted osteogenic differentiation and could be implicated in the pathogenesis of osteoporosis [47–49].

Previous reports have revealed the functions of various circRNAs in influencing SMAD5 expression, making them potential targets for therapeutic interventions related to skeletal disorders. **Circ_0001825** is newly recognized to be significantly downregulated in osteoporotic patients. The suppression of circ_0001825 reduced hMSC viability and osteogenic differentiation. Circ_0001825 promoted osteogenesis via sponging miR-1270, resulting in SMAD5 overexpression, which signifies the potential contribution of circ_0001825 to osteoporosis [50]. Another circRNA that has been detected to regulate SMAD5 in osteoporosis is **CircGLIS2.** The expression of circGLIS2 was obviously decreased in osteoporotic patients, while increased in hBMSCs upon osteogenic differentiation. Regression of circGLIS2 notably inhibited osteogenesis-related genes, such as osteopontin (OPN), OCN, and ALP activity. The study reported that circGLIS2 sponged miR-214-3p and upregulated Smad5, which stimulated osteogenic differentiation of the hBMSCs [51]. **Circ_0062582** was also observed to lessen the development of osteoporosis by affecting SMAD5 expression. It was reported that circ_0062582 was remarkably decreased in osteoporosis. Meanwhile, circ_0062582 was increased in osteoblast medium-induced hBMSCs, where it sequestered miR-197-3p and resulted in an elevation of SMAD5, thereby reflecting hBMSC proliferation and osteogenic differentiation [52].

In vitro studies using MSCs revealed that circRNAs play a regulatory role on several genes related to the BMP pathway. Both **circRNA_0048211** and **circ_0016624** were suppressed in PMOP patients compared to healthy controls. During hMSC osteogenic differentiation, the upregulated circRNA_0048211 and circ_0016624 increased BMP2 regulation through targeting miRNA-93-5p and miR-98, respectively, so attenuated development of PMOP [53, 54].

Regarding the Notch pathway, **circRNA_0001795** and **circ-ITCH** promoted osteogenic differentiation of hBMSCs by targeting YAP1 through sponging their respective miRNAs, miR-339-5p and miR-214 [55, 56]. Notably, the expression levels of both circRNAs were notably reduced in osteoporosis, and their depletion correlated with a decrease in the expression of osteogenic-related genes. Additionally, in vivo experiments demonstrated that the upregulation of circ-ITCH enhanced osteogenesis in ovariectomized (OVX) mice.

It has been found that **hsa_circ_0114581** is negatively correlated with osteoporosis pathogenesis. The upregulated hsa_circ_0114581 enhanced the expression of heterogeneous nuclear ribonucleoprotein A3 (HNRNPA3) to encourage osteogenic differentiation by suppressing hsa-miR-155-5p. This study also proved that HNRNPA3 was directly associated with osteogenic-related proteins in BMSCs and femur samples of either human bone tissue or OVX mice, suggesting its relationship with osteogenesis and bone formation [57]. Moreover, low levels of **circ_0019693** were recognized in osteoporotic patients. Its expression was further enhanced during the stages of osteogenic differentiation in BMSC. Intriguingly, it was indicated that circ_0019693 could promote osteogenesis through inhibiting miR-942-5p and increasing purkinje cell protein 4 (PCP4) [58]. When PCP4 is bound to CaM-dependent protein kinase, the rate of Ca^{+2} dissociation from calmodulin (CaM) increases, promoting calcium deposition during mineral nodule formation, which is a valid predictor of bone-forming ability [59]. **Hsa_circ_0006215** is another circRNA coupled between osteogenesis and angiogenesis and involved in the pathogenesis of senile osteoporosis. It was significantly downregulated in the BMSCs of osteoporotic patients, while its overexpression promoted the osteogenic differentiation of BMSCs. In vivo, its overexpression induced the repair of the single cortical bone defect model, suggesting that it could promote bone defect repair. Furthermore, it has been demonstrated that hsa_circ_0006215 influences RUNX2 and VEGF expression in BMSCs through sponging miRNA-942-5p [60]. In GIOP patients, the **hsa_circ_0006393** level was downregulated compared to control ones. Furthermore, overexpression of hsa_circ_0006393 boosted the expression of osteogenic genes in bone tissue samples obtained from male GIOP patients as well as a GIOP mouse model. It was suggested to have osteogenic influence through inhibiting miR-145-5p and increasing FOXO1 expression [61].

Numerous studies have been conducted on human adipose stem cells (ASCs). It was found that **CircFOXP1** was significantly downregulated in the bone tissues of osteoporotic patients. Indeed, the pro-osteogenic activity of circFOXP1 was evaluated in vivo and in vitro, where circFOXP1 was found to enhance hASC osteogenesis by sponging miR-33a-5p and targeting FOXP1 expression [62]. Thus, circFOXP1 could be regarded as a candidate target for hASC-based therapy of osteoporosis.

Accumulating data indicates that circRNAs have the ability to interact with RBPs and alter their functions [63]. **CircStag1** was remarkably suppressed in the BMSCs of osteoporotic rats and bone tissue samples isolated from osteoporotic patients. Briefly, circStag1 interacted with human antigen R (HuR) and promoted its translocation into the cytoplasm. Sequentially, cytoplasmic HuR led to the stimulation of the Wnt cascade by stabilizing low-density lipoprotein receptor-related protein 5/6 (Lrp5/6), co-receptors for Wnt ligands, and enhancing

β-catenin expression. It was also observed that the induction of circStag1 fostered osteogenesis in OVX mice [64]. According to Yao et al., **circ-Plod2** is an exon-type circRNA found in the cytoplasm, where it destabilized the Mpo-dependent osteogenic differentiation of BMSCs while having no effect on adipogenic differentiation or chondrogenic differentiation of these cells [65]. The study also found that the expression of circ-Plod2 was remarkably downregulated in OVX rats BMSCs, and its overexpression effectively lessened osteoporosis among them. Circ-Plod2 mediated its effect by interacting with IGF2BP2 to form an RNA–protein complex, which in turn inhibited the expression of Mpo mRNA in BMSCs. Another circRNA that plays a role in osteoporosis by interacting with RBP is **circPVT1**. CircPVT1 stimulates osteogenesis by inhibiting miR-30d-5p to increase integrin beta-3 (ITGB3) expression [66]. ITGB3, a member of the integrin family, functions as a downstream gene of Homeobox D3, which triggers the Wnt/β-catenin signaling pathway through the involvement of β3 integrin.

CircRNAs that inhibit osteogenesis

Other circRNAs exert a pivotal regulatory role in impeding osteogenesis through modulation of essential pathways and gene expression networks, thereby influencing the overall process of bone formation. A recent study has highlighted the mechanistic insight of **hsa_circ_0006859** in vitro. It was recognized that the expression of hsa_circ_0006859 was augmented in OVX mouse-derived BMSCs but remained modest expressed during osteogenic differentiation. Hsa_circ_0006859 overexpression hindered osteogenesis of BMSCs in the human fetal osteoblast cell line by targeting both miR-642b-5p/ephrin A2 (EFNA2) and miR-483-3p/dedicator of cytokinesis 3 (DOCK3) axes, resulting in the inactivation of the Wnt-signaling pathway [67]. Additionally, it has been reported that **hsa_circ_0008842**, identified as **circZNF367**, was substantially upregulated in the bone tissue of osteoporotic patients and dramatically downregulated in hBMSCs during osteogenic differentiation. The overexpression of circZNF367 suppressed migration and osteogenic differentiation of hBMSCs, both in vitro and in vivo, while its knockdown exhibited opposite effects. CircZNF367 could reduce osteogenic differentiation of hBMSCs through interaction with HuR, which reduced LRP5 mRNA stability [68].

Circ_0006873 was upregulated in the sera of osteoporotic patients and decreased during osteoblastic differentiation. Circ_0006873 could suppress osteoblastic differentiation and favor osteoporosis by sponging miR-142-5p, which in turn enhances PTEN expression and regulates the Akt signaling pathway [69]. Another study has also reported that circ_0006873 was significantly elevated in both serum samples and bone tissue samples of osteoporotic patients. Its overexpression was associated with a significant reduction in osteogenic differentiation of hMSCs through the sequestration of miR-20a and targeting SMURF2 [70].

Lipopolysaccharide (LPS) is a potent inducer of bone loss, resulting in inflammation that exacerbates osteoporosis by disrupting regular bone homeostasis. **CircAtp9b** is LPS-inducible, and its knockdown alleviates the inflammation triggered by LPS [71]. Interestingly, circAtp9b was significantly upregulated in plasma samples and osteoblasts derived from osteoporotic patients. LPS-treated osteoblasts increased circAtp9b expression in a dose-dependent manner, confirming that the circAtp9b overexpression is likely triggered by LPS. Also, it was shown that circAtp9b upregulation increased LPS-induced osteoblast apoptosis in osteoporosis by sponging premature miR-17-92a and suppressing its maturation, which in turn accelerated osteoporosis progression [72].

There is little known about the role of circRNAs in melatonin (MEL)-induced BMSC osteogenic differentiation and osteoporosis progression. MEL has been detected as a booster of osteoblast proliferation and differentiation, fostering bone formation and reducing bone destruction in osteoporotic mice [73]. In this regard, Wang et al. found that melatonin improved osteogenic differentiation and repressed osteoporosis development by hampering **circ_0003865** expression [74]. This circRNA acts as a sponge for miR-3653-3p, consequently boosting the expression of growth arrest-specific gene 1 (GAS1) while suppressing the expression of bone-forming genes. Similarly, the expression of **circ_0005753** was significantly reduced during the osteogenic differentiation of BMSCs triggered by MEL. Molecularly, circ_0005753 maintained the stability of TXNIP mRNA through the recruitment of PTBP1. This study pointed out that MEL enhanced BMSC osteogenic differentiation through the regulation of the circ_0005753/PTBP1/TXNIP axis, which could shed light on a new treatment pathway to prevent osteoporosis [75].

Zhi et al. determined that exosomal **hsa_circ_0006859** was obviously upregulated in the serum of PMOP, efficiently distinguishing osteoporotic and osteopenic patients from healthy controls [76]. As well, it discriminated between osteoporotic and osteopenic patients with high specificity and sensitivity. Besides, ectopic expression of circ_0006859 provoked adipogenic differentiation and impeded osteoblastic differentiation in BMSCs via sponging miR-431-5p to induce ROCK1 expression. Thus, hsa_circ_0006859 may be a potential biomarker for the diagnosis and prognosis of osteoporosis and could modulate the harmony between adipogenesis and osteogenesis in BMSCs. According to whole transcriptome

sequencing, Zhang et al. determined the expression profile of circRNAs in the peripheral blood of male osteoporotic patients versus healthy controls, and found that a total of 398 circRNAs were differentially expressed [77]. **Hsa_circ_0042409** was among the top 10 upregulated circRNAs and was recognized to be involved in the development of osteoporosis through regulating the expression level of kinesin light chain 1 (KLC1) via sponging hsa-miR-195-5p. Additionally, another study observed a significant upregulation of **circ_0134944** in both PMOP patients and OVX mice. Its enhanced expression suppressed osteogenesis in BMSCs through targeting miR-127-5p, causing an increase in pancreatic and duodenal homeobox 1 (PDX1) and sphingosine kinase 1 (SPHK1). PDX1 is a well-established transcription factor that regulates the activity of multiple genes by binding to their promoter regions, such as SPHK1, which has an impact on the regulation of osteogenic differentiation [78]. Furthermore, **Hsa_circ_0002060** knockdown in the human fetal osteoblast cell line (hFOB1.19) reversed the effect of DEX, which decreased matrix metalloproteinases (MMP) and increased ROS. Hsa_circ_0002060 modulated the survival of hFOB 1.19 cells by targeting miR-198-5p, resulting in an elevation of Bax expression that in turn triggered the apoptosis of osteoblasts. Additionally, hsa_circ_0002060 knockdown alleviated the progression of osteoporosis in OVX mice through the Jun N-terminal kinase (JNK) signaling pathway [79].

Collectively, manipulating these interrelated molecules could be beneficial in the management of osteoporosis. Thus, we reviewed the expression and molecular mechanisms by which circRNAs mediate osteoblast differentiation (Table 2 and Fig. 3).

Osteoclastogenic signaling pathways

Osteoclastogenesis is the fusion of osteoclast precursors, which originate from hematopoietic cells to form multinucleated, active osteoclasts. Macrophage colony-stimulating factor (M-CSF), also known as CSF-1, and receptor activator for nuclear factor κB Ligand (RANKL) are two crucial cytokines that bind to their respective receptors, colony-stimulating factor-1 receptor (c-Fms) and RANK, to stimulate osteoclastogenesis through the regulation of delicate signaling pathways [80]. M-CSF stimulates the production and survival of osteoclast precursor cells by activating extracellular signal-regulated kinase (ERK) and serine/threonine kinase 1 (Akt). Meanwhile, RANKL facilitates the development of osteoclast precursors into osteoclasts by attracting TRAF6 to the RANK receptor, which then activates various downstream targets, including NF-κB, JNK, ERK, p38, and PI3K/Akt. This ultimately leads to the activation of the key regulator of osteoclast differentiation, nuclear factor of activated T cells 1 (NFATc1). This latter controls several osteoclast-specific genes, including TRAP, cathepsin K, and osteoclast-associated receptor (OSCAR) via interaction with other osteoclastic transcription factors, such as microphthalmia-associated transcription factor (MITF) and c-Fos [81]. Additionally, the RANK/RANKL/OPG pathway is crucial for the metabolism of bone tissue, as RANKL stimulates the production and differentiation of osteoclasts, while osteoprotegerin (OPG) inhibits its action through binding to it [82]. Here, we summarized the relevant research investigation of lncRNAs (Table 3) and circRNAs (Table 4) in order to offer novel insights for future osteoporosis studies and treatments, with a specific focus on osteoclasts, as depicted in Fig. 4.

LncRNAs that promote osteoclastogenesis

lncRNAs have been demonstrated to govern osteoclastogenesis by controlling the expression of certain mRNAs. **LncRNA AK077216** was considerably upregulated during osteoclastogenesis in the bone marrow and spleen tissues of OVX mice. LncAK077216 overexpression upregulated NFATc1 and accelerated RANKL-induced osteoclastogenesis by downregulating NIP45 [83]. Additionally, **lncRNA GAS5** was upregulated in the plasma of osteoporotic patients compared to healthy participants and effectively distinguished between them with high sensitivity and specificity. It has been found that GAS5 overexpression promoted osteoclast apoptosis by sponging miR-21, thus exhibiting a protective effect in osteoporosis [84]. A previous study demonstrated that miR-21 was involved in the pathogenesis of osteoporosis through modulation of reversion-inducing cysteine-rich proteins with Kazal motifs (RECK), which play a role in cell apoptosis, proliferation, and differentiation in TNF-α-treated MSCs [85]. **LncRNA CRNDE** was also highly expressed in osteoclasts obtained from PMOP compared with those from healthy controls. After CRNDE knockdown, the cell percentage was significantly increased in the G0/G1 phase but decreased in the S-phase, promoting osteoclast apoptosis rate. Moreover, CRNDE improved osteoclast proliferation by regulating the PI3K/AKT signaling pathway [86].

LncRNAs that inhibit osteoclastogenesis

Extracellular vesicles (EVs) released by MSC have significant immunoregulatory effects on bone healing in osteoporosis. The **lncRNA NRON** was rich inside BMSC-derived EVs that have been triggered by bioactive glass nanoparticles (BGN) in an osteoporosis model of OVX mice. NRON reduced osteoclast differentiation through interaction with the nuclear factor of activated T cell transcription factors and blocking the nuclear translocation of NFATc1 [87]. Likewise, **lncRNA FTX**

Table 2 The expression of circRNAs-related osteogenesis in osteoporosis

CircRNAs that promote osteogenesis			
circRNAs	**Expression in osteoporosis**	**Samples**	**References**
Circ-3626	Downregulated	Bone tissues of osteoporotic patients and aged mice	[45]
Circ-RBM23	Downregulated	Osteoporotic patients	[46]
Circ_0011269	Downregulated	Serum/plasma samples of osteoporotic patients	[47]
Circ-VANGL1	Downregulated	Serum samples of osteoporotic patients	[48]
Circ_0076690	Downregulated	Serum/plasma samples of osteoporotic patients	[49]
Circ_0001825	Downregulated	Bone marrow samples of PMOP	[50]
CircGLIS2	Downregulated	Osteoporotic patients	[51]
Circ_0062582	Downregulated	Osteoporotic patients	[52]
Circ_0048211	Downregulated	hBMSCs of PMOP patients	[53]
Circ_0016624	Downregulated	Serum/plasma samples of PMOP	[54]
Circ_0001795	Downregulated	Bone marrow samples of osteoporotic patients	[55]
Circ-ITCH	Downregulated	Bone marrow samples of PMOP and OVX mice	[56]
Hsa_circ_0114581	Downregulated	Femur tissues of patients undergoing hip replacement operation and OVX mice	[57]
Circ_0019693	Downregulated	Serum samples and bone tissues of osteoporotic patients	[58]
Hsa_circ_0006215	Downregulated	BMSCs of osteoporotic patients and femoral monocortical defect in Mouse	[60]
Hsa_circ_0006393	Downregulated	Bone tissue samples of GIOP patients and GIOP mouse model	[61]
CircFOXP1	Downregulated	Bone tissues of osteoporotic patients and heterotopic bone formation assay in nude mice	[62]
CircStag1	Downregulated	Bone tissues of PMOP and OVX mice	[64]
Circ-Plod2	Downregulated	OVX mice	[65]
CircPVT1	Downregulated	BMSCs of osteoporotic patients	[66]
CircRNAs that inhibit osteogenesis			
Hsa-circ-0006859	Upregulated	OVX mice	[67]
Hsa_circ_0008842 (circZNF367)	Upregulated	Osteoporotic patients	[68]
Circ_0006873	Upregulated	Serum samples of osteoporotic patients Serum samples and bone tissues of osteoporotic patients	[69] [70]
CircAtp9b	Upregulated	Osteoblasts and plasma samples of osteoporotic patients	[72]
Circ_0003865	Upregulated	OVX mice	[74]
Circ_0005753	Upregulated	OVX mice	[75]
Hsa_circ_0006859	Upregulated	Serum samples of PMOP	[76]
Hsa_circ_0042409	Upregulated	Peripheral blood of osteoporotic patients	[77]
Circ_0134944	Upregulated	Blood mononuclear cells and OVX mice	[78]
Hsa_circ_0002060	Upregulated	OVX mice	[79]

was significantly suppressed in the serum and bone tissues of osteoporotic patients compared to controls ones. FTX overexpression reduced osteoclastgenesis through upregulation of Notch1 by sponging miR-137 in CD14 + peripheral blood mononuclear cells (PBMCs) [88].

CircRNAs involved in osteoclastogenesis regulation

CircRNA that promote osteoclastogenesis

CircZNF367 was found to be upregulated in an OVX mouse model of osteoporosis. CircZNF367 promoted osteoclast differentiation by interacting with fused in sarcoma (FUS), facilitating its translocation into the cytoplasm to trigger the enhancement of CRY2 mRNA stability [89]. **CircFam190a** was significantly upregulated in vitro and in an OVX mouse osteoporosis model, where it induced significant bone loss. The study reported that circFam190a could promote osteoclast formation and function by enhancing the binding between AKT1 and HSP90β, thereby protecting AKT1 from proteasome-mediated degradation and augmenting its stability as well as its activity [90]. Unfortunately, the existing clinical

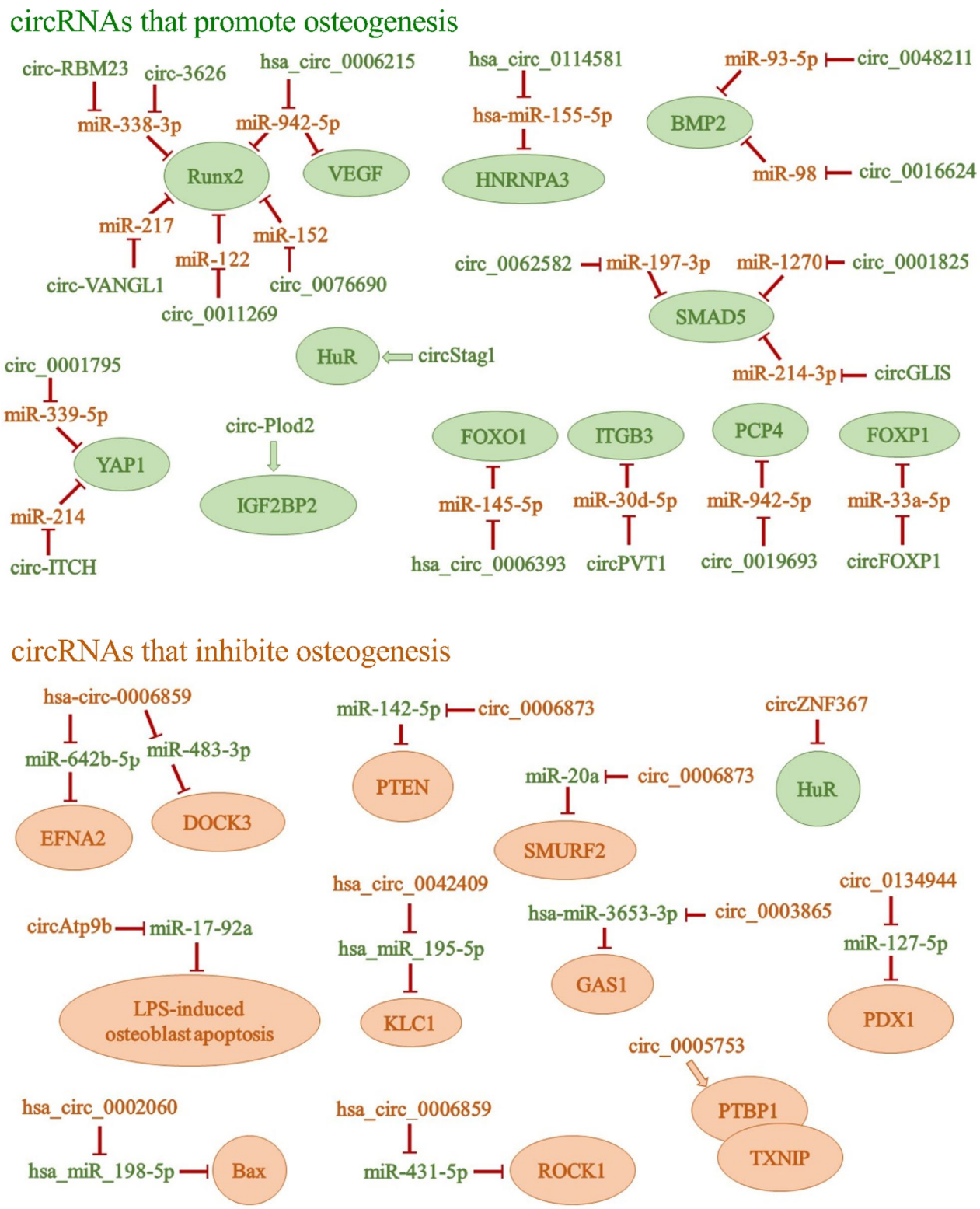

Fig. 3 Role and mechanistic insights of circRNAs in osteogenesis. All shapes shaded in green denote biomarkers increased during osteogenesis. All shapes shaded in red denote biomarkers decreased during osteogenesis

Table 3 The expression of lncRNAs-related osteoclastogenesis in osteoporosis

LncRNAs that promote osteoclastogenesis			
LncRNA	**Expression in osteoporosis**	**Samples**	**References**
LncRNA AK077216	Upregulated	Bone marrow and spleen derived monocytes/macrophages of OVX mice	[83]
LncRNA GAS5	Upregulated	Plasma samples of osteoporotic patients	[84]
LncRNA CRNDE	Upregulated	Osteoclasts of PMOP	[86]
LncRNAs that inhibit osteoclastogenesis			
BGN-mediated lncRNA NRON	Downregulated	OVX mice	[87]
LncRNA FTX	Downregulated	Bone and serum samples of osteoporotic patients	[88]

Table 4 The expression of circRNAs-related osteoclastogenesis in osteoporosis

CircRNAs that promote osteoclastogenesis			
CircRNA	**Expression in osteoporosis**	**Samples**	**References**
CircZNF367	Upregulated	OVX mice	[89]
CircFam190a	Upregulated	PBMCs of PMOP and OVX mice	[90]
CircBBS9 (hsa_circ_0134188) (mmu_circ_0001757)	Upregulated	Spine cancellous bones of osteoporotic patients and OVX mice	[91]
CircRNA_28313	Upregulated	OVX mice	[92]
CircRNAs that promote osteoclastogenesis			
Hsa_circ_0021739	Downregulated	PBMCs of POMOP	[93]
Circ_0007059	Downregulated	Bone tissue of PMOP	[94]
CircHmbox1	Downregulated	OVX mice	[95]

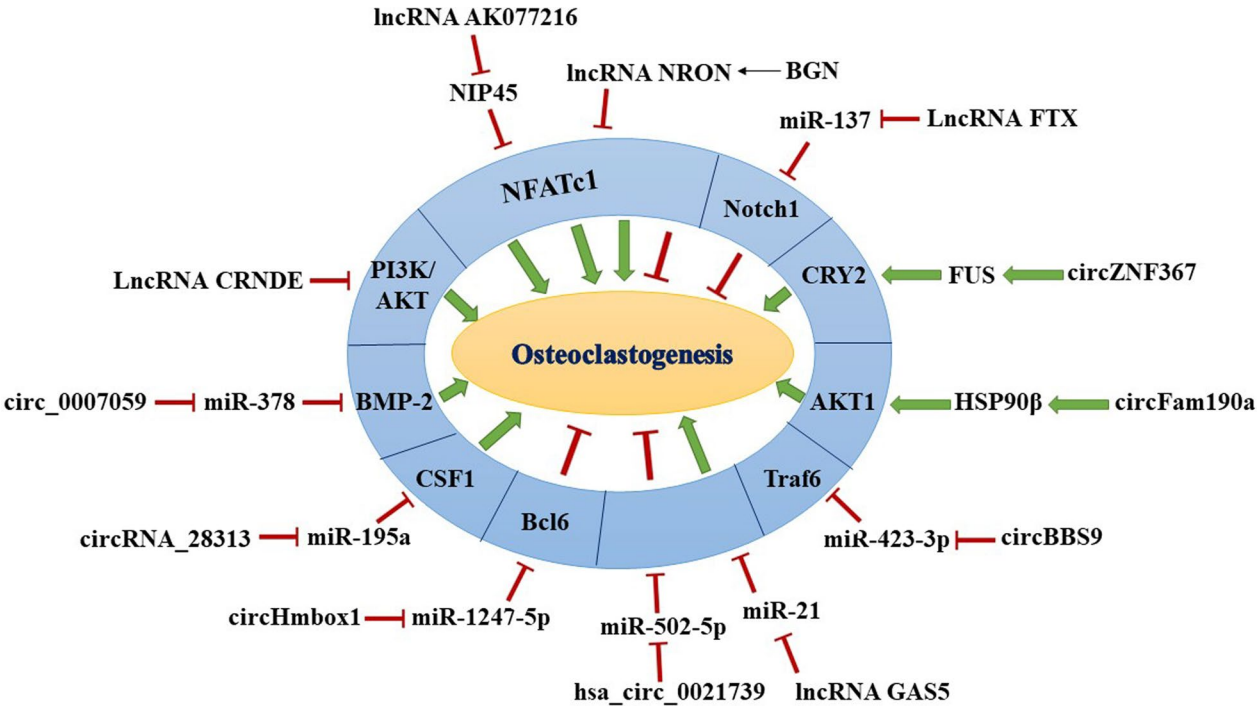

Fig. 4 Role and mechanistic insights of lncRNAs/circRNAs in osteoclastogenesis

drugs were reported to impede osteoclasts and interfere with normal bone turnover. However, targeting specific osteoclast precursors may be more effective in preserving bone homeostasis. **circBBS9 (mmu_circ_0001757),** a highly conserved circRNA, was substantially upregulated in mononucleated pre-osteoclasts versus bone marrow macrophage (BMM). Moreover, the **circBBS9** homolog in humans **(hsa_circ_0134188)** was augmented in osteoporotic human bone samples as well as in PBMC-derived osteoclasts. Knockdown of circBBS9 using siRNA-circBBS9-loaded nanoparticles inhibited BMM multinucleation in vitro. As well, these particles avoided bone loss in an OVX-induced mouse model. Molecularly, knockdown of circBBS9 in osteoclast precursors inhibited osteoclast multinucleation via the miR-423-3p/Traf6 axis, demonstrating that circBBS9 is an efficient post-transcriptional regulator [91]. C**ircRNA_28313** knockdown significantly inhibited osteoclastic differentiation within BMM cells in vitro, while suppressed OVX mice stimulated bone resorption in vivo. CircRNA_28313 acted as ceRNA by binding to miR-195a, resulting in upregulation of CSF1 and the development of osteoclast differentiation [92].

CircRNA that inhibit osteoclastogenesis

Hsa_circ_0021739 was downregulated in PMOP, and its expression was associated with the lumbar vertebra, femur, and forearm T-scores. Overexpression of hsa_circ_0021739 has also been shown to reduce hsa-miR-502-5p levels and hinder osteoclast differentiation [93]. Besides, Liu et al. screened the differential expression of circRNAs in PMOP using RNA-sequencing and found that **circ_0007059** expression was decreased in patients and during the osteoclast differentiation of hBMSCs [94]. The authors also demonstrated that circ_0007059 overexpression lessened hBMSC differentiation into the osteoclasts. Molecularly, circ_0007059 sponged miR-378 expression, which resulted in an upregulation of BMP-2 expression that was accompanied by a decrease in osteoclast-specific gene expression and TRAP staining, thus attenuating osteoporosis development. Moreover, **circHmbox1** was notably decreased during the formation of osteoclasts triggered by TNF-α in vivo and in vitro. CircHmbox1 acted by inhibiting miR-1247-5p to activate Bcl6. Interestingly, Bcl6 is a transcriptional repressor required in osteoclast development and the preservation of bone homeostasis. The study also demonstrated that exosomes with low expression of circHmbox1 produced by TNF-α-induced osteoclasts could inhibit osteoblast differentiation. Indeed, circHmbox1 overexpression remarkably alleviated the osteoporotic phenotypes in OVX mice [95].

Other CircRNAs related to osteoporosis and osteoporotic fracture

Yang et al. have observed that osteoporosis and fracture were indirectly correlated to **circ_0076906** expression while directly correlated to that of **circ_0134944** in PBMCs of postmenopausal women [96]. In vitro, inhibiting circ_0076906 expression augmented the expression of miR-548i, which in turn reduced the expression of osteoglycin (OGN). This latter is a bone anabolic factor that has been linked to the mineralization and osteogenesis processes by adjusting the expression of osteogenesis-specific genes. The study also demonstrated that the circ_0134944 upregulation suppressed miR-630 and enhanced the expression of toll-like receptor 4 (TLR4). TLR4 is highly expressed in bone marrow, immune cells, adipocytes, and osteoblasts and is involved in osteoblastogenesis and osteoclastogenesis [97, 98]. Thus, circ_0076906 and circ_0134944 were associated with a risk of osteoporotic fracture, leading to osteoporosis [96]. Besides, Wen et al. observed that the expression level of **hsa_circ_0076906** was greatly decreased in both bone tissue and serum samples of the osteoporotic group compared to the control group, besides its gradual induction during osteogenic differentiation of hMSCs [99]. Circ_0076906 was found to promote MSC differentiation and relieve osteoporosis through upregulating OGN expression by inhibiting miR-1305. Additionally, **circHIPK3** was significantly upregulated in both tissue and serum samples from osteoporotic fracture patients compared with controls. CircHIPK3 was shown to sponge miR-378a-3p and to upregulate HDAC4, which is a histone deacetylase that controls osteoblast differentiation by inhibiting Runx2 transcriptional activity [100].

Conclusions

This article provides an overview of the expression patterns of lncRNAs and circRNAs in osteoporosis. It also discusses their involvement in the differentiating of osteoblasts and osteoclasts, as well as the underlying molecular mechanisms implicated in their effects. Many lncRNAs and circRNAs act by interacting with RBP or sponging miRNAs to control the expression of targeted genes, hence impacting many pathways involved in osteogenesis and osteoclastogenesis. Despite the fact that both lncRNAs and circRNAs possess great potential in the prediction, diagnosis, and prognosis of osteoporosis, their regulatory ability in targeting proteins is still largely unknown. More future studies are also warranted on circRNAs in osteoporosis since they are scanty in comparison with those on lncRNAs. Moreover, studying the interactions of lncRNAs and circRNAs is of interest for gaining a deeper understanding of the pathogenesis of

osteoporosis and promoting the discovery of new therapeutics and drugs.

Abbreviations

AAV	Adeno-associated virus
AKT	Serine/threonine kinase 1
ALP	Alkaline phosphatase
AOX1	Aldehyde oxidase 1
AS1	Antisense RNA 1
ASCs	Adipose stem cells
BGN	Bioactive glass nanoparticles
BMM	Bone marrow macrophage
BMP	Bone morphogenetic protein
BMSCs	Bone marrow stromal cells
CaM	Calmodulin
c-Fms	Colony-stimulating factor-1 receptor
CircRNA	Circular RNAs
COCH	Cochlin
DEX	Dexamethasone
DKK1	Dickkopf-1
DLL	Delta-like ligands
Dlx5	Distal-less homeobox 5
DOCK3	Dedicator of cytokinesis 3
EFNA2	Ephrin A2
ERK	Extracellular signal-regulated kinase
EVs	Extracellular vesicles
EZH2	Enhancer of zeste homolog 2
FBXW7	F-box and WD repeat domain-containing 7
FUS	Fused in sarcoma
Fz	Frizzled
GAS1	Growth arrest-specific gene 1
GATA4	GATA-binding protein 4
GSDMD-N	Gasdermin D-N
HAGLR	Homeobox D gene cluster antisense growth-associated long noncoding RNA
HBMSCs	Human bone marrow stem cells
HFOB1.19	Human fetal osteoblast
Hh	Hedgehogg
HMGB1	High-mobility group box chromosomal protein-1
HMSCs	Human mesenchymal stem cells
HNRNPA3	Heterogeneous nuclear ribonucleoprotein A3
Hoxa10	Homeobox protein A10
HOXD3	Homeobox D3
HuR	Human antigen R
IRF-1	Interferon regulatory factor-1
ITGB3	Integrin beta-3
JNK	Jun N-terminal kinase
KHSRP	K-homology splicing regulatory protein
KLC1	Kinesin light chain 1
KMT2C	Lysine (K)-specific methyltransferase 2C
LATS1/2	Large Tumor Suppressor 1 and 2
LncRNA	Long noncoding RNA
LPS	Lipopolysaccharide
LRP5/6	Low-density lipoprotein receptor-related protein 5/6
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
M-CSF	Macrophage colony-stimulating factor
Mef2c	Myocyte enhancer factor 2C
MEL	Melatonin
MITF	Microphthalmia-associated transcription factor
MMP	Matrix metalloproteinases
mRNAs	Messenger RNAs
MST1/2	Mammalian STE20-like protein kinases 1 and 2
NEDD4	Neuronal precursor cell-expressed developmentally downregulated 4
NFATc1	Nuclear factor of activated T cells 1
NICD	Notch intracellular domain
OCN	Osteocalcin
OGN	Osteoglycin
OPG	Osteoprotegerin
OPN	Osteopontin
OSCAR	Osteoclast-associated receptor
Osx	Osterix
OVX	Ovariectomized
PAK2	P21-activated kinase 2
PBMCs	Peripheral blood mononuclear cells
PCNA	Proliferating cell nuclear antigen
PCP4	Purkinje cell protein 4
PDX1	Pancreatic and duodenal homeobox 1
PMOP	Postmenopausal osteoporosis
Prrx2	Paired-Related Homeobox Protein 2
RAD51-AS1	RAD51-Antisense RNA 1
RANKL	Receptor activator for nuclear factor κB Ligand
RBP	RNA-binding protein
RECK	Reversion-inducing Cysteine-rich proteins with Kazal motifs
ROS	Reactive oxygen species
RUNX2	Runt-related transcription factor 2
SMURF2	Smad ubiquitin regulatory factor 2
SNHG14	Small nucleolar RNA host gene 14
SPHK1	Sphingosine kinase 1
TAZ	Transcriptional coactivator with PDZ-binding motif
TGFβ	Transforming growth factor β
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor alpha
XIST	X-inactive-specific transcript
YAP	Yes-associated protein
YBX1	Y-Box Binding Protein 1

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