BIO Integration

The Roles of Long Non-coding RNAs in Osteogenic Differentiation and Bone Diseases

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Abstract

Bone marrow mesenchymal stem cells play an important role in osteogenic differentiation, and they complete this important biological process through the coordination of various transcription factors and signal pathways. In recent years, studies have clearly confirmed that long non-coding RNAs (lncRNAs) are involved in osteogenic differentiation, which plays an important biological role in the occurrence and development of osteogenesis-related bone disease. This article reviews the roles and related mechanisms of lncRNAs in osteogenic differentiation, as well as their potential effects on a variety of bone diseases. This understanding may help researchers identify potential therapeutic targets and biological markers in the future.

Keywords

Long non-coding RNA, osteogenesis differentiation, osteosarcoma, osteoarthritis, osteoporosis.

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Introduction

Bone marrow mesenchymal stem cells (BMSCs) have a variety of differentiation routes, including adipogenic differentiation, myogenic differentiation, and osteogenic differentiation [1]. Osteoblasts are produced primarily by BMSCs, which have a crucial biological function in maintaining the balance between bone production and resorption. In recent years, abundant evidence has indicated that a variety of molecules can regulate osteogenic differentiation and serve as markers of osteogenic differentiation, including short stature-related transcription factors (RUNX2), alkaline phosphatase (ALP), and osteopontin (OPN) [2]. Although several studies have revealed the factors and pathways regulating the osteogenic differentiation of BMSCs, the specific molecular mechanisms remain unknown.

Long non-coding RNAs (lncRNAs) are usually defined as a type of transcript with a length of more than 200 nucleotides, which have almost no protein coding ability. These lncRNAs are derived mainly from overlapping protein coding regions and intergenic protein coding regions of genes, and transcribed by polymerase II [3]. LncRNAs are named according to their neighboring protein-coding genes. They can be divided into five types according to the correspondence of their spatial position with related protein coding genes: long intergenic, intron, bidirectional, antisense, and sense [4]. LncRNAs have long been considered to be a by-product of RNA polymerase II transcription and to have no biological functions. However, through shearing, lncRNAs obtain the characteristic structure of a 5′ cap and 3′ polyadenylic acid, which activate the transcription process. We briefly summarize several transcription patterns of lncRNAs in **Figure 1**.

Although the exact roles of most lncRNAs are still being studied, current studies have confirmed that lncRNAs play important roles in the biological processes of cell proliferation, differentiation, and migration [5]. LncRNAs have the ability to mediate alternative splicing, chromatin modification, RNA metabolism, and gene expression at the epigenetic, transcriptional, and post-transcriptional levels, thereby regulating these biological processes [6]. Therefore, lncRNAs are involved in the occurrence and development of many diseases, including bone diseases.

To the best of our knowledge, no literature review has summarized and discussed the osteogenic differentiation

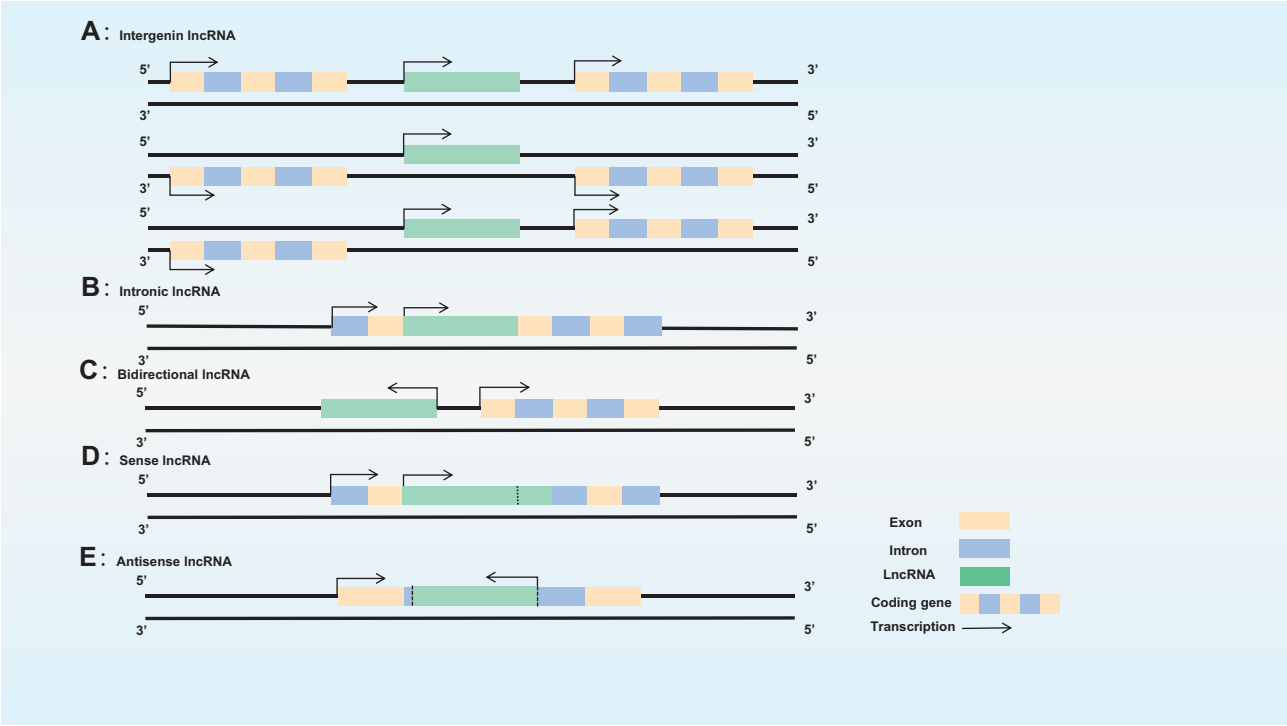

Figure 1 Transcriptional pattern of lncRNAs. (A) Intergenic lncRNAs transcribed from both strands intergenically. (B) Intronic lncRNAs transcribed exclusively from the introns of protein-coding genes. (C) Bidirectional lncRNAs appear near the transcription start site of the coding gene but run in the opposite direction. (D) Sense lncRNAs, transcribed from the sense strand of protein-coding genes, contain exons from protein-coding genes, either overlapping with parts of protein-coding genes or covering the whole sequence of a protein-coding gene via an intron. (E) Antisense lncRNAs are transcribed in the opposite direction from their completely or partially overlapping mRNA. The black arrows represent transcription.

roles of lncRNAs and their specific roles in bone diseases. In this paper, we conducted a systematic search of the relevant literature, and review the modes of action and mechanisms of lncRNAs in osteogenic differentiation and bone diseases.

Modes of action and mechanisms of lncRNAs

LncRNAs perform their biological functions in different ways, and we describe their modes of action (**Figure 2**) as follows: signal, decoy, guide, and support [7]. LncRNAs play biological roles through one or more of four prototypical mechanistic networks. They perform their functions by participating in each stage of regulating gene expression, including epigenetic modification of chromatin, regulation of transcription, and post-transcriptional regulation.

LncRNAs can be used as scaffolds providing sites for regulation at the level of epigenetic modification of chromatin. They participate in the regulation of related target gene expression by recruiting chromatin remodeling complexes to specific regions or recruiting modifiers to chromatin regulatory regions. *HOTAIR* shows high affinity for target genes and certain proteins. It is capable of attracting polycomb inhibitory complex 2 (PRC2) and histone demethylase 1A (LSD1) [8]. Subsequently, targeting of histone H3K4 demethylation and H3K27 trimethylation affect chromosomal condensation and, ultimately, gene silencing [8].

The regulation of transcription levels is relatively complex and involves multiple mechanisms. First, lncRNAs control the expression of target genes by acting directly on transcription factors. *NRON* inhibits downstream target gene expression by blocking nucleocytoplasmic trafficking of the transcription factor NFAT [9]. Second, lncRNAs compete with transcription factors or function as bait to prevent transcription factors from binding to homologous DNA sites, thereby controlling target gene expression. Glucocorticoid is a negative regulator of bone formation. Its receptor gene binding domain is bound by *Gas5*, which acts as a bait, or is competitively bound, thus resulting in a decline in receptor function and finally encouraging osteogenic differentiation [10]. Furthermore, certain promoter-related lncRNAs can act on RNA-binding proteins and regulate genes by influencing the promoter. Cyclin D1 (CCND1) is transcribed in the 5′ upstream region, and the promoter-related non-coding RNA-D (pncRNA-D) specifically binds to the RNA-binding protein TLS, thus inhibiting its activity and exerting a transcriptional inhibitory effect [11]. Finally, lncRNAs recruit transcription factors and act as transcription regulators that exert gene regulation. *Evf2* recruits the transcription factor Dlx2, forms a complex, and then induces the expression of related genes [12].

When stable complementary sequences exist between lncRNAs and miRNAs, the two combine to form a double-stranded complex that stabilizes the miRNA structure.

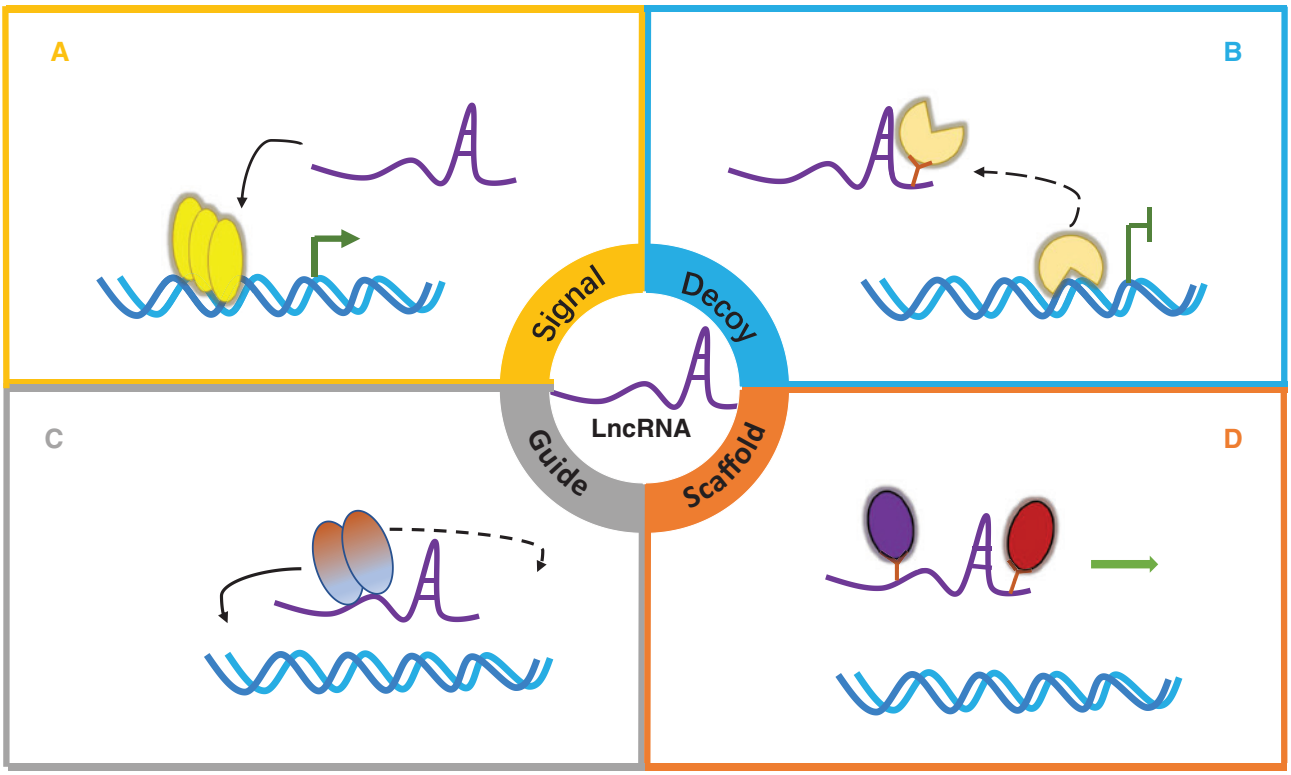

Figure 2 Models of lncRNA roles. (A) Signal: As a signal transduction molecule, lncRNA is specifically transcribed and participates in the transmission of specific signal pathways. After some lncRNA molecules are transcribed, they function by regulating the transcription of downstream genes. (B) Decay: After a lncRNA is transcribed, it binds to transcription factors or certain protein molecules, thus preventing their binding to chromatin, and blocking the roles of molecules and the transmission of signals. (C) Guide: LncRNA functions similarly to a "lighthouse" in guiding chromatin-modifying enzymes to bind to target genes. This effect can be either *cis*- (on adjacent genes) or *trans*-acting (on distant genes). (D) Scaffold: As a platform, lncRNAs have binding sites and bind to multiple related transcription factors. When multiple signal pathways are activated at the same time, downstream effectors can bind the same lncRNA molecule to achieve information exchange and integration between different signal pathways.

According to the competitive endogenous RNA (ceRNA) theory, RNA sequences with the same miRNA response element (MRE) might compete for miRNA, serving as an RNA sponge that prevents miRNA from binding to its target [13]. *HOTAIR* affects the expression of its target gene *Smad7* by competitively binding *miR-17-5p*, thereby participating in the regulation of osteogenic differentiation [14].

Roles of lncRNAs in osteogenic differentiation

In the process of osteogenic differentiation, lncRNAs expressed to different degrees may have varying influence on the normal proliferation, differentiation, and apoptosis of BMSCs. The regulation of osteogenic differentiation by lncRNAs can take the following three forms: as a precursor of miRNA, lncRNAs participate in the regulation of osteogenic differentiation, in the regulation of osteogenic differentiation by regulating various signal pathways, and in the regulation of osteogenic differentiation as ceRNAs or "miRNA sponges." In the following and in **Figure 3**, we briefly summarize some lncRNAs and their specific forms of regulation.

LncRNAs that promote osteogenic differentiation

H19

H19 is generated from the transcription product of the *H19*/insulin growth factor 2 (IGF2) gene cluster on human chromosome 11p5.5 [15]. It may be utilized as a precursor of *miR-675*, which can then be sheared to create two stable miRNAs, *miR-675-5p* and *miR-675-3p*, and influence the downstream Wnt signaling pathway to govern stem cell osteogenic development [16, 17]. Second, *H19* controls osteogenesis via the Notch molecules' cellular signaling pathway [18]. The Notch signaling system is crucial in controlling osteogenic differentiation. *H19* expression suppression and constitutive expression both result in upregulation of the expression of miRNAs that influence Notch ligands and receptors, encouraging the osteogenic differentiation of MSCs [18]. Similarly to the Notch signaling pathway, the Wnt signaling pathway, as a downstream target of *H19*, plays an important role in the regulation of osteogenic differentiation. *H19*'s involvement in inducing osteogenic differentiation via this route has also been well established [19]. Finally, *H19* acts as a ceRNA regulating osteogenic differentiation. A binding site exists between *H19* and *miR-138*, which can be utilized as the miRNA's ceRNA. Both work together to suppress *miR-138* and

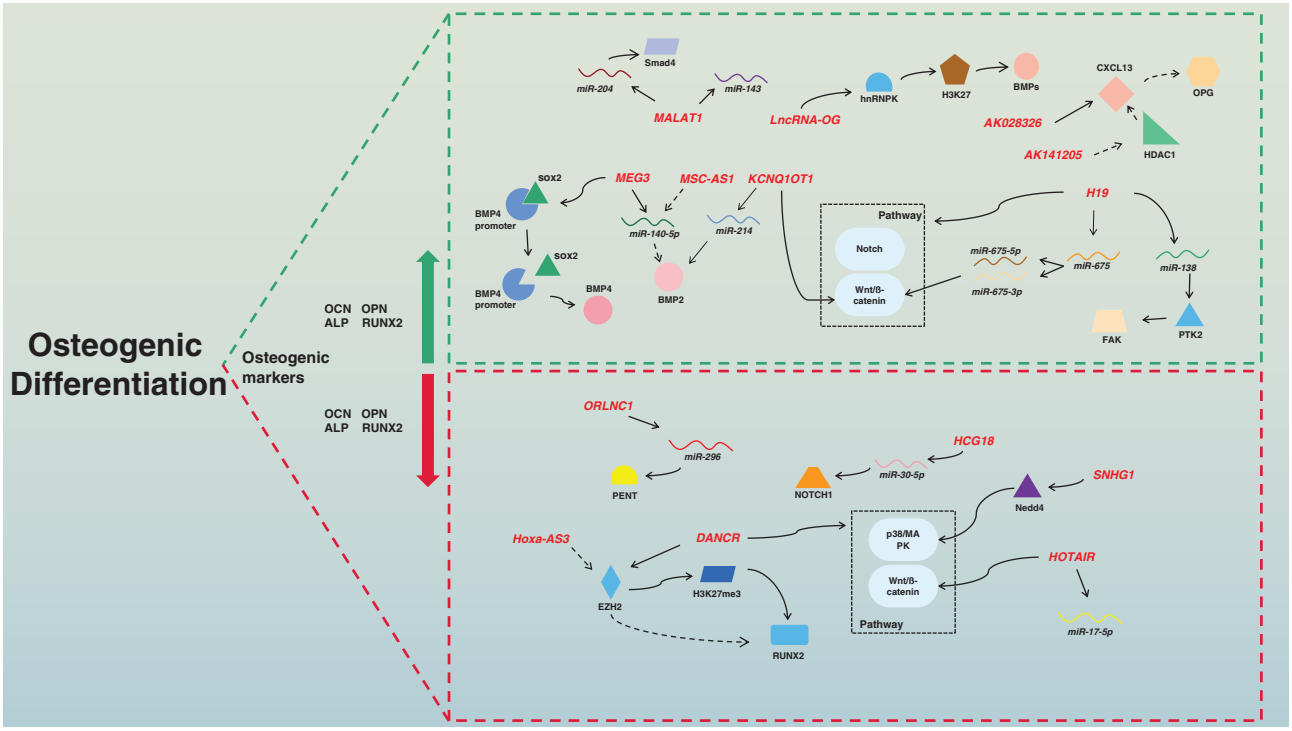

Figure 3 LncRNA mechanisms influencing osteogenic differentiation. The green arrow indicates that the osteogenic index is elevated; the red arrow indicates the opposite. The green dashed area indicates the promotion of osteogenesis; the red area indicates the opposite.

diminish the inhibitory effects of protein tyrosine kinase (*PTK2*), the gene encoding focal adhesion kinase (FAK), thus promoting FAK expression and, in turn, osteogenic differentiation [20].

MEG3

Maternally expressed gene 3 (*MEG3*), as a tumor suppressor, participates in the regulation of osteogenic differentiation of BMSCs and is closely associated with the expression of osteogenic markers. Knockout of *MEG3* gene expression decreases RUNX2, OSX, and OCN at the transcriptional level and hinders the formation of mineralized nodules, thereby inhibiting osteogenic differentiation [21]. *MEG3* can separate the negative regulator SOX2 from the promoter region of bone morphogenetic protein 4 (BMP4), thus leading to BMP4 activation [21]. In addition, in human adipose stem cells (HASCs), knockout of *MEG3* effectively promotes the differentiation of adipocytes while significantly inhibiting osteogenic differentiation [22]. This effect is mediated by *miR-140-5p*, an miRNA that inhibits osteogenic differentiation, and their expression is negatively correlated. Therefore, when *MEG3* is overexpressed, it has a significant positive regulatory effect on osteogenic differentiation.

MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) is an imprinted gene that is expressed in a range of tissues, and is linked to a number of illnesses and biological processes. In hFoB1.19 osteoblasts, although the relationship between *MALAT1* and osteogenic differentiation is not yet clear, *MALAT1* has been confirmed to regulate the expression of OPG [23]. Later, Xiao et al. [24] investigated the effect of *MALAT1* in calcified aortic valve disease and discovered that it promotes osteogenic differentiation substantially. *MALAT1* can be utilized to allow *miR-204* to control Smad4 via the ceRNA method, thus causing Smad4 to be upregulated, promoting the production of osteoblast-specific markers and eventually leading to the development of mineralized nodules and bone regeneration [24]. MALAT1 may also be utilized in *miR-143* to enhance BMSC osteogenic differentiation through the same method [25].

Other lncRNAs

Some additional lncRNAs are involved in the regulation of osteogenic differentiation. Downregulation of *lncRNA-OG* in vitro decreases the expression of RUNX2 and also inhibits the activity of ALP and the formation of mineralized nodules. *LncRNA-OG* interacts with heterogeneous ribonucleoprotein K (hnRNPK), thus enhancing H3K27 acetylation of the *lncRNA-OG* promoter and upregulating *lncRNA-OG* transcriptional activity, thereby controlling BMP signal activation [26]. *LncRNA AK028326* is the same as *lncRNA AK141205*, and their osteogenic effects are closely associated with CXC chemokine ligand-13 (CXCL13). High glucose levels normally prevent BMSCs from undergoing osteogenic differentiation. The high expression of *AK028326* upregulates CXCL13 and reverses the negative effect of high glucose levels on osteogenic differentiation [27].

Osteogenic growth peptide (OGP) is an osteogenic differentiation promoter that increases ALP activity and osteogenic marker expression. Overexpression of *AK141205* promotes H4 histone acetylation, and inhibits histone deacetylase 1 (HDAC1) and induces CXCL13 expression, thereby promoting OGP activity [28]. *MSC-AS1* is a newly discovered lncRNA involved in the osteogenic differentiation of BMSCs [29]. *MSC-AS1* and BMP2 are considerably upregulated during BMSC osteogenic development, but *miR-140-5p* expression is decreased. Consequently, *MSC-AS1* may be utilized as the ceRNA of *miR-140-5p* to enhance BMSCs osteogenic differentiation by increasing BMP2 expression [29]. Similarly, *KCNQ1OT1* works as a ceRNA toward *miR-214* that promotes osteogenic differentiation of BMSCs by further favorably regulating BMP2 expression [30]. Furthermore, *KCNQ1OT1* also promotes osteogenic differentiation by activating the Wnt/β-catenin signaling pathway [31].

LncRNAs that inhibit osteogenic differentiation

DANCR

DANCR is the first lncRNA found to inhibit osteogenic differentiation [32]. *DANCR* interacts with ZESTE homologous gene enhancer 2 (EZH2), thus increasing the methylation of histone H3 lysine 27 (H3K27me3) in the promoter of the *RUNX2* gene and resulting in the inhibition of *RUNX2* gene expression [32]. In addition, Zhang et al. [33] and Jia et al. [34] found that *DANCR* has obvious anti-osteogenesis effects in BMSCs and periodontal ligament stem cells, respectively. *DANCR* overexpression effectively inhibits the phosphorylation of p38, changing the information transduction of p38/MAPK signaling pathway, and inhibits osteogenic differentiation [33]. Furthermore, low *DANCR* expression stimulates the Wnt/β-catenin signaling pathway and causes RUNX2 production [34].

HOTAIR

HOX transcribed antisense RNA (*HOTAIR*), which can remodel chromatin to enhance its own inhibitory effect on *HOX* genes and other target genes, is another lncRNA that can have a negative effect on osteogenesis [16]. In BMSCs of patients with non-traumatic femoral head necrosis. *HOTAIR* expression is considerably enhanced, and knocking out *HOTAIR* decreases the DNA methylation level of the *miR-17-5p* promoter and increases *miR-17-5p* expression [14]. The upregulation of *HOTAIR* decreases Runx2 expression and ALP activity, and this effect is reversed by increasing *miR-17-5p* [14]. Furthermore, when *HOTAIR* is overexpressed, the expression of Wnt/β-catenin pathway-related specific proteins (β-catenin, cyclin D, and C-myc) considerably decreases, whereas the expression of the pathway's negative regulator, Dkk1, is significantly elevated [35]. *HOTAIR* may inhibit the osteogenic differentiation of BMSCs by inhibiting the Wnt/β-catenin signaling pathway.

Other lncRNAs

Some new lncRNAs have also been reported to have anti-osteogenesis effects, including *ORLNC1*, *SNHG1*, *Hoxa-AS3*, and *HCG18* [36–39]. In an ovariectomized animal model (OVX), the expression of *ORLNC1* is significantly elevated. It acts as a ceRNA that competitively targets *miR-296*, causing changes in the level of phosphatase and tensin homolog (PTEN), a downstream target, and ultimately inhibiting the osteogenic differentiation of BMSCs in model mice [36]. *SNHG1* effectively blocks the activation of p38 through Nedd4, an E3 ubiquitin ligase, and interferes with the important pathway of osteogenic differentiation (p38/MAPK signaling pathway), thereby inhibiting the osteogenic differentiation of BMSCs [37]. *Hoxa-AS3* regulates the balance between adipogenic differentiation and osteogenic differentiation and inhibits osteogenic differentiation by regulating EZH2. Overexpressed *Hoxa-AS3* binds EZH2, thus decreasing the binding of the latter to the promoter region of the *Runx2* gene and decreasing the expression of Runx2 [38]. *HCG18* is a newly discovered lncRNA that is abnormally expressed in a variety of malignant diseases. The research on osteoporosis (OP) clearly indicates that *HCG18*'s inhibitory effect on the downstream target gene NOTCH1 is decreased through sponging *miR-30a-5p* [39]. Furthermore, *HCG18* indirectly increases the expression of NOTCH1, and overexpression of NOTCH1 produced by the two forms inhibits BMSC osteogenic development [39].

LncRNAs and bone diseases

LncRNAs have been linked to the incidence and progression of a number of bone disorders, including osteosarcoma (OS) [40], osteoarthritis (OA) [41, 42], OP [43, 44], ankylosing spondylitis (AS) [45], and rheumatoid arthritis (RA) [46]. In the following content, we summarize the lncRNAs that are associated with bone diseases, as shown in **Table 1**.

LncRNAs in OS

OS is one of the world's most frequent primary malignant bone tumors, affecting primarily children and teenagers. Despite substantial improvement in current treatment approaches and tactics for OS, patients still have poor prognoses and high recurrence rates. Elucidating the pathogenic process of OS is critical for identifying novel treatment targets for the illness.

Some lncRNAs are highly expressed in OS tissues, thus suggesting that lncRNAs are associated with the occurrence and development of OS [40, 47–49]. *DANCR* competes with *miR-335-5p* and *miR-1972* as "ceRNA" that promotes the expression of Rho-associated coiled-coil-containing protein kinase 1 (ROCK1) in OS tissues, thereby promoting tumor cell proliferation and invasion [40]. *SNHG3* is highly expressed in OS tissues and absorbs *miR-151a-3p* through a competitive action, thus decreasing its negative regulatory effect on RAB22A in the RAS oncogene family,

Table 1 LncRNAs Associated with Bone Diseases

Bone diseases	LncRNA name	Expression	Targets	Reference
Osteosarcoma	DANCR	Upregulation	miR-335-5p/ROCK1 axis, miR-1972/ROCK1 axis	[40]
	SNHG3	Upregulation	miR-151a-3p/RAB22A axis	[48]
	LncRNA-ROR	Upregulation	miR-185-3p/YAP1 axis	[49]
	H19	Upregulation	PI3K/AKT and NF-kB pathway	[47]
	Gas5	Downregulation	miR-23a-3p/PTEN/PI3K/AKT axis	[51]
Osteoarthritis	MFI2-AS1	Upregulation	miR-130a-3p/TCF4 axis	[41]
	Gas5	Upregulation	Sponge for miR-21	[53, 60]
		Downregulation	KLF2	
	PVT1	Upregulation	Sponge for miR-488-3p	[54]
	ZFAS1	Upregulation	Wnt/β-catenin pathway	[55]
	MALAT1	Upregulation	Sponge for miR-150-5p	[42]
	MEG3	Downregulation	miR-93/TGFBR2 axis, VEGF	[57, 61]
	SNHG5	Downregulation	miR-10a-5p/H3F3B axis, miR-181a-5p/TGFBR3 axis	[56, 58]
	HOTAIR	Downregulation	miR-138/NF-kB axis	[59]
Osteoporosis	H19	Downregulation	DKK4/Wnt/β-catenin axis, DNMT1/H19/ERK-MAPK axis, miR-532-3p/SIRT1 axis, FOXC2/WNT4 axis	[63, 64] [69, 70]
	MALAT1	Downregulation	PPM1E/AMPK or PPM1E/Nrf2 axis	[73]
	ANCR	Upregulation	Binding with EZH2	[71]
	MEG3	Upregulation	Sponge for miR-133a-3p	[66]
	XIST	Upregulation	miR-758-5p/caspase 3 axis	[68]
	LOXL1-AS1	Upregulation	miR-196a-5p/Hmga2/PPARγ axis	[44]
	EPIC1	Upregulation	Myc	[72]
Rheumatoid arthritis	PICSAR	Upregulation	Sponge for miR-4701-5p	[46]
	NEAT1	Upregulation	miR-204-5p/NF-kB axis	[74]
	H19	Upregulation	TAK1/NF-kB or TAK1/JNK/p38/MAPK pathway	[75]
	MEG3	Downregulation	Not explored	[76]
	LOC645166	Downregulation	TLR/IKK2/IkB/NF-kB axis	[77]
Ankylosing spondylitis	H19	Upregulation	Sponge for miR-22-5p and miR-675-5p	[45]

thereby mediating the progression of OS [48]. Similarly, *LncRNA-ROR* competitively binds *miR-185-3p* and upregulates the expression of Yes-associated protein 1 (YAP1), which, in turn, affects the aggressiveness of OS cells [49]. The inhibitory effect of *YAP1* gene knockout on OS cell proliferation has been clearly confirmed [50]. In addition to the ceRNA effect, certain lncRNAs have been shown to alter OS via established signaling pathways. *H19* gene knockout can lead to inactivation of the PI3K/AKT signaling pathway, which in turn results in ineffectiveness of the NF-kB pathway, thus inhibiting the migration of osteosarcoma cells and enhancing the invasion ability [47]. In contrast, the expression of *Gas5* is decreased in OS tissues and cell lines. It acts as a ceRNA that engulfs *miR-23a-3p* and regulates PTEN, which, through its lipid phosphatase activity and PI3K downstream targeting molecule PIP3, blocks the PI3K/ATK pathway and produces a tumor suppressor effect [51].

LncRNAs in OA

OA is a chronic joint disease characterized by progressive deterioration of the structure and function of articular cartilage. The occurrence and development of OA are closely related to the apoptosis of chondrocytes, the degradation of extracellular matrix, abnormal inflammation, and synovial angiogenesis [52]. We summarized the lncRNAs associated with OA and distinguished them according to the following levels:

1. LncRNAs that regulate cell proliferation and apoptosis. Compared with that in normal bones and joints, the expression of *MFI2-AS1* in OA is upregulated [41]. Overexpression of *MFI2-AS1* significantly promotes the inhibition of chondrocyte viability and the formation of apoptosis induced by lipopolysaccharide (LPS). This lncRNA acts as a ceRNA that targets and negatively regulates *miR-130a-3p*, weakening the inhibitory effect of *miR-130a-3p* on transcription factor 4 (TCF4) [41]. *Gas5* and *PVT1* are also highly expressed in OA chondrocytes. They sponge *miR-21* and *miR-488-3p*, respectively, thus stimulating chondrocyte apoptosis [53, 54]. *ZFAS1* is different from *MFI2-AS1*, *Gas5*, and *PVT1*, ceRNAs involved in regulation. It may be involved in the proliferation, migration, and apoptosis of chondrocytes by targeting the canonical Wnt signaling pathway [55]. Furthermore, *SNHG5* expressed in OA chondrocytes upregulates H3F3B through sponging *miR-10a-5p*, thereby inhibiting IL-β-stimulated chondrocyte apoptosis [56].
2. LncRNAs that regulate the degradation of extracellular matrix. *MALAT1* is highly expressed in OA tissues, and indirectly promotes the expression of AKT3 through sponging *miR-150-5p*, thus leading to the synthesis of cartilage degrading enzymes such as matrix metalloproteinase-13 (MPP-13) and a disintegrin

and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) [42]. *MEG3* interacts with *miR-93*, thus forming a CERNA network and regulating transforming growth factor β (TGF-β) receptor 2 (TGFBR2). Its overexpression decreases the expression of *miR-93* by increasing the activation of TGFBR2-induced TGF-β signaling pathway, thereby decreasing chondrocyte apoptosis and matrix degradation [57]. Similarly to *MEG3*, *SNHG5* regulates TGFBR3 by interacting with *miR-181a-5p*, induces the activation of the TGF-β signaling pathway and promotes the expression of MMP-13 and ADAMTS-5, thereby regulating the degradation of the extracellular matrix [58].

3. LncRNAs that regulate inflammation. *HOTAIR* is decreased in LPS-induced chondrocytes. Its overexpression results in sponging *miR-138* and targets its downstream NF-kB pathway, thus preventing the synthesis and release of pro-inflammatory cytokines; it additionally acts as a protective agent in LPS-induced chondrocyte inflammation [59]. Overexpression of the *Gas5* gene upregulates Kruppel-like factor 2 (KLF2) in LPS-induced chondrocytes, reversing inflammatory damage [60].
4. LncRNAs that regulate synovial angiogenesis. Compared with normal articular cartilage, *MEG3* expression is downregulated in human OA cartilage, thus increasing and the level of vascular endothelial growth factor (VEGF). *MEG3* gene knockout significantly weakens VEGF-mediated angiogenesis [61].

LncRNAs in OP

In recent years, many lncRNAs have been regarded as new regulators of OP. OP is one of the most prevalent systemic metabolic bone disorders, characterized by bone loss, degradation of bone microstructure, bone fragility, and increased fracture risk [62].

Disuse OP (DOP) is caused by a long-term lack of mechanical load or after the limb is stopped for a long time, thus leading to changes in bone structure and integrity and ultimately causing bone loss in the limb. Dkk4 is *H19*'s downstream target, and mechanical unloading enhances Dkk4 expression by lowering *H19* expression [63]. The upregulation of Dkk4 suppresses the Wnt/β-catenin signaling pathway, thus decreasing osteogenic differentiation and the onset and progression of DOP [63]. Another study has also confirmed the role of H19 in DOP. In DOP bone tissue, the expression of DNA methyltransferase-1 (DNMT1) is over-regulated, thus promoting the methylation of the *H19* promoter and inhibiting the downstream target ERK [64]. The ERK-MAPK signaling pathway involved in ERK has been demonstrated to play a key role in bone homeostasis and bone development [65].

Postmenopausal OP (PMOP) is a metabolic bone disease. The basic pathogenesis is abnormal bone metabolism caused by a significant decrease in estrogen levels in the body. In PMOP-derived BMSCs, the levels of *MEG3* and its downstream target *miR-133a-3p* are abnormally increased. When the expression of *miR-133a-3p*, which is positively regulated by *MEG3*, is upregulated, it significantly inhibits the formation of osteogenic markers and mineralized nodules [66]. Therefore, decreasing the expression of *MEG3* is expected to be a treatment to improve the progression of PMOP. Abnormal accumulation of iron can accelerate bone mineral loss in healthy postmenopausal women [67]. In the iron accumulation model, the expression of *XIST* and caspase 3 increases, and the expression of *miR-785-3p* decreases [68]. Therefore, *XIST* may act as the ceRNA of *miR-758-3p*, regulate caspase 3, and facilitate the formation of PMOP mediated by iron abnormality. In patients with PMOP, the expression of *H19* and SIRT1 is downregulated, whereas *miR-532-3p* is upregulated. *H19* interacts directly with *miR-532-3p*, upregulating the expression of SIRT1, and induces osteogenic differentiation of BMSCs; estrogen reverses the low expression of *H19* in bone tissue [69]. In addition, *H19* directly binds to forkhead box C2 (FOXC2), enhances the binding ability of FOXC2 and WNT4 promoter, promotes the osteogenic differentiation of BMSCs through the Wnt/β-catenin signaling pathway, and alleviates the progress of PMOP [70]. Furthermore, some other lncRNAs are also involved in PMOP regulation, including *ANCR* and *LOXL1-AS1*. The specific binding of *ANCR* and EZH2 inhibits the expression of Runx2, thereby inhibiting the osteogenesis of PMOP osteoblasts and the formation of osteoid in vivo [71]. In the serum of patients with PMOP, *LOXL1-AS1* and Hmga2 levels are elevated, and *miR-196a-5p* levels are diminished. *LOXL1-AS* regulates Hmga2 as a sponge of *miR-196a-5p*, inhibits the osteogenic differentiation of BMSCs by activating C/EBP-β-mediated PPARγ expression, and aggravates the progression of PMOP [44].

Glucocorticoid-induced OP is a type of OP caused by long-term use of glucocorticoids, such as dexamethasone (Dex). Studies have indicated that *EPIC1* effectively protects osteoblasts from Dex-induced cytotoxicity [72]. *EPIC1* targets Myc, thus supporting cell survival, whereas gene silencing increases the toxicity of Dex in cells [72]. The expression of *MALAT1* decreases in the hFOB1.19 osteoblast cell line treated with Dex. This lncRNA activates AMPK signal transduction by inhibiting PPM1E (protein phosphatase, Mg^{2+}/Mn^{2+}-dependent 1E) [73]. Meanwhile, *MALAT1* increases the activity of nicotinamide adenine dinucleotide phosphate and the activation of the Nrf2 signal [74].

LncRNAs in other bone diseases

RA is an autoimmune disease characterized by chronic inflammation of joint synovium. Its main pathological feature is that the hyperplastic synovial lining tissue contains a large number of activated fibroblast-like synovial cells (FLSS), which interact with a variety of cells and pro-inflammatory cytokines. In RA synovial fluid and RA-FLSS, *PICSAR* is significantly higher than that in the normal control group. As the targeting ceRNA of *miR-4701-5p*, this lncRNA promotes the proliferation, migration, and invasion of RA-FLSS cells and also increases and decreases the secretion of pro-inflammatory cytokines and certain proteases, respectively [46]. *NEAT1* promotes the proliferation and apoptosis of RA-FLSS cells induced by TNF-α by targeting *miR-204-5p* and activates the NF-kB signaling pathway, thus mediating the secretion of pro-inflammatory

cytokines, thereby promoting the progression of RA [74]. TNF-α is responsible for the high expression of *H19* in RA, and the increased expression of *H19* promotes the phosphorylation of TGF-β-activated kinase 1 (TAK1), which activates the NF-kB and JNK/p38MAPK signaling pathways and promotes the expression of inflammatory cytokines [75]. Unlike the previous lncRNAs, *MEG3* is downregulated in RA tissues and is negatively correlated with NOD-like receptor 5 (NLRC5) [76]. NLRC5 is involved in the hypermethylation of the *MEG3* gene promoter, which inhibits *MEG3* gene transcription, whereas high *MEG3* expression lowers NLRC5 and inflammatory cytokines, preventing the development of RA [76].

AS is a chronic systemic inflammatory disease, mainly manifested by arthritis of the spine and sacroiliitis. One study has found that the expression of lncRNA LOC645166 is downregulated in patients with AS [77]. LOC645166 inhibits TLR-mediated activation of IKK2 by binding to the K63-linked polyubiquitin chain, thus resulting in downregulation of IkB phosphorylation. The stable IkB binds to NF-kB, decreases the transfer of NF-kB/IkB complex to the nucleus, and prevents NF-kB from entering the nucleus and subsequently facilitating the transcription of inflammatory cytokine target genes [77]. In 49 patients with AS, compared with healthy controls (49 cases), H19 was significantly expressed in peripheral blood mononuclear cells (PBMC) [45]. H19 acts as a ceRNA targeting miR-22-5p and miR-675-5p, and it significantly increases the expression of vitamin D receptor, TGF-β, and pro-inflammatory factors, such as IL-17A and IL-23 [45].

Summary and outlook

LncRNA research has yielded promising findings in recent years; however, for lncRNAs, compared with miRNAs, further studies are needed. LncRNAs were initially identified in cancer research, but have now been revealed to play a key role in stem cell research across a wide range of fields, including BMSCs. This article reviews the roles of lncRNAs in the osteogenic differentiation of BMSCs. Many studies have identified various processes that govern osteogenic differentiation, including miRNA precursors, signal pathways, and ceRNA mechanisms, by using in situ hybridization technology, luciferase reporter gene experiments, gene chips, and microarray expression profiling. The discovery of these mechanisms helps understand the regulatory role of lncRNAs in osteogenic differentiation.

We further discussed the role of lncRNAs in the pathogenesis of related bone diseases, including bone tumors, OA, OP, RA, and mandatory spondylitis. LncRNAs have multiple regulatory effects through different molecular mechanisms during the occurrence and development of these diseases. The expression of lncRNAs that positively regulate osteogenic differentiation could be promoted in order to improve osteogenic differentiation, or lncRNAs that inhibit osteogenic differentiation could be knocked out to improve bone regeneration. In addition, bone mineral loss after spinal cord injury can also cause OP, which is usually referred to as "fixed OP," a special type of OP. Although no reports have indicated which type of effect lncRNAs have on this type of OP, the current single-brake disuse theory cannot fully explain this severe bone loss and decline in bone structure degeneration [78]. Therefore, in future research in this field, lncRNAs may serve as a research focus to provide us with new research directions.

Despite the importance of lncRNAs in the regulation of osteogenic differentiation and bone diseases is considerable, future research in this area must be further advanced in order to guide the treatment of orthopedic clinical diseases.

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Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Data Availability

Not applicable.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

Authors' Contributions

S.Q. drafted and wrote the manuscript. S.C. and Z.Z. assisted with writing the manuscript and provided helpful suggestions. D.L. reviewed the final manuscript and provided advice on writing the manuscript. All authors read and approved the final manuscript.

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