Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) 2025 26(2):107-123
www.jzus.zju.edu.cn; www.springer.com/journal/11585
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Review

https://doi.org/10.1631/jzus.B2300607

Roles of lncRNA in the crosstalk between osteogenesis and angiogenesis in the bone microenvironment

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Abstract: Bone is a highly calcified and vascularized tissue. The vascular system plays a vital role in supporting bone growth and repair, such as the provision of nutrients, growth factors, and metabolic waste transfer. Moreover, the additional functions of the bone vasculature, such as the secretion of various factors and the regulation of bone-related signaling pathways, are essential for maintaining bone health. In the bone microenvironment, bone tissue cells play a critical role in regulating angiogenesis, including osteoblasts, bone marrow mesenchymal stem cells (BMSCs), and osteoclasts. Osteogenesis and bone angiogenesis are closely linked. The decrease in osteogenesis and bone angiogenesis caused by aging leads to osteoporosis. Long noncoding RNAs (lncRNAs) are involved in various physiological processes, including osteogenesis and angiogenesis. Recent studies have shown that lncRNAs could mediate the crosstalk between angiogenesis and osteogenesis. However, the mechanism by which lncRNAs regulate angiogenesis–osteogenesis crosstalk remains unclear. In this review, we describe in detail the ways in which lncRNAs regulate the crosstalk between osteogenesis and angiogenesis to promote bone health, aiming to provide new directions for the study of the mechanism by which lncRNAs regulate bone metabolism.

Key words: Long noncoding RNA (lncRNA); Osteogenesis; Bone angiogenesis; Osteoporosis; Bone microenvironment

1 Introduction

Long noncoding RNAs (lncRNAs) are involved in a wide range of aspects of gene expression regulation, including epigenetic, transcriptional, and post-transcriptional regulations. In addition to this, they also participate in the biological regulations of cell growth, migration, differentiation, reprogramming, and stress responses (Herman et al., 2022; Nojima and Proudfoot, 2022). LncRNA abnormalities lead to deficiencies in protein-coding capacity. At the epigenetic level, lncRNAs regulate DNA methylation and histone modification (Allas et al., 2019). Recently, many researchers have shown interest in studying bone diseases at the genetic level and discovering new bone disease-associated lncRNAs using high-throughput sequencing or microarray studies. LncRNAs are able to regulate osteogenesis, adipogenesis, and osteoclast differentiation through epigenetic modifications and microRNA (miRNA) adsorption, which can affect bone metabolism (Ghafouri-Fard et al., 2021; Wang SL et al., 2022). The vasculature, another essential factor that directly influences osteogenesis in the bone microenvironment, plays a crucial role in bone development, remodeling, and the maintenance of bone homeostasis (Chim et al., 2013; Dirckx et al., 2013; He et al., 2013). The continuing process of bone resorption and formation is cyclic during the bone life cycle, and neoangiogenesis is an integral part of this process. Additionally, angiogenesis occurs prior to osteogenesis, and new blood vessels ensure the transit of osteoblast precursors and osteoclasts to specific sites (Zhang et al.,

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Received Aug. 29, 2023; Revision accepted Jan. 16, 2024; Crosschecked Feb. 11, 2025

2021; Zheng et al., 2022), suggesting that osteogenesis is a vessel-dependent process. It has been reported that angiogenesis and osteogenesis are closely related, spatially and temporally, and have activation and interactions between signaling molecules and signaling pathways, known as the "crosstalk between angiogenesis and osteogenesis" (Schipani et al., 2009; Lafage-Proust et al., 2010; Maes, 2013; Saran et al., 2014; Grosso et al., 2017). The crosstalk between angiogenesis and osteogenesis is a necessary pathway for the co-growth of the vascular and bone phases in the bone microenvironment and a catalyst for both. Many scholars have devoted themselves to the study of mechanisms for the treatment of osteoporosis and other related diseases. Among them, the crosstalk between angiogenesis and osteogenesis is essential. For example, it has been shown that mechanical stimulation can couple osteogenesis and angiogenesis and promote the interactive effects of vascular and osteogenic factors (Ma et al., 2023). In addition, the exogenous supplementation of angiogenic factors can be achieved through hydrogel delivery systems to promote bone disease recovery (Tsai et al., 2023). In recent years, lncRNAs have been shown to play crucial roles as endogenous regulators in the crosstalk between angiogenesis and osteogenesis, including regulating various cell proliferation and differentiation processes and regulating the expression of osteogenic and angiogenic factors. However, the mechanism by which lncRNAs regulate the crosstalk between angiogenesis and osteogenesis is still unclear. Therefore, we summarize the latest studies on the involvement of lncRNAs in the regulation of angiogenesis and osteogenesis, as well as those on the pathways by which lncRNAs regulate the crosstalk between angiogenesis and osteogenesis, to provide support for the treatment of pathologic bone-related disorders and to provide new ideas for the study of the mechanism of lncRNA-regulated bone metabolism.

2 Overview of lncRNAs

More than 90% of the DNA sequences in the human genome are involved in transcription, and only 2% of the human DNA sequences code for proteins. RNAs that do not encode any proteins are referred to as noncoding RNAs (Dangwal et al., 2017). LncRNAs, widely distributed in mammalian cells, are more than 200 nucleotides long (Wilusz et al., 2009). Most of the lncRNAs identified so far are produced by the transcription of RNA polymerase II (pol-II) or RNA polymerase III (pol-III) (Kung et al., 2013). Initially, lncRNAs were considered to lack protein-coding capacity and to not have biological functions. However, increasing studies have shown that lncRNAs, an important class of regulatory molecules in the human genome, play a crucial role in various biological functions, such as cell proliferation and differentiation, cellular autophagy, embryonic development, substance metabolism, and tumorigenesis (Duret et al., 2006; Wang MQ et al., 2021). Although lncRNAs have no protein-coding ability, they can regulate gene expression at various levels, including epigenetic regulation, transcriptional level regulation, and post-transcriptional level regulation. Thus, there are various mechanisms by which lncRNAs perform their biological functions.

Currently, there is no uniform standard for classifying lncRNAs, mainly based on the indicators of genomic localization, mediated phenotype, mechanism of action, and subcellular localization. LncRNAs can be classified into positive lncRNAs, antisense lncRNAs, intronic lncRNAs, bi-directional lncRNAs, and intergenic lncRNAs according to the positional relationship of their neighboring protein-coding genes. Meanwhile, depending on their functions, lncRNAs can also be categorized as backbone molecules, signaling molecules, decoy molecules, and primers (St. Laurent et al., 2015; Mattick, 2018). LncRNAs are closely associated with their subcellular localization. A few lncRNAs are localized in the cytoplasm and regulate biological functions by affecting the stability of messenger RNAs (mRNAs), participating in translational regulation, and competing for binding miRNAs (Han et al., 2014; Kim et al., 2015) to regulate cellular biological functions. The diverse subcellular localization of lncRNAs makes their functions even more complex.

Numerous studies have confirmed that lncRNAs participate in the regulation of gene expression in three main ways. Firstly, at the transcriptional level, lncRNAs can control the transcription of other genes by regulating the binding and assembly of transcription factors, forming triple-stranded complexes with regulatory sequences, or interfering with the transcription process through binding with pol-II. Secondly, lncRNAs are more complex in epigenetic regulation because lncRNAs

can control chromatin remodeling by recruiting chromatin modifiers to DNA targets or acting as carriers of histone modification complexes by inducing their DNA methylation (Zhu et al., 2019). Finally, the function of lncRNAs relies on interactions with RNA-binding proteins (RBPs), which are highly expressed in the brain in terms of regulation at the post-transcriptional level (Smart et al., 2007). LncRNAs bind to RBPs to form a large number of lncRNA/RBP complexes, which can recruit various protein complexes and activate downstream molecules. For example, lncRNA regulates the expression of osteogenic genes during post-transcriptional mRNA modification as a competing endogenous RNA (ceRNA) (Chen K et al., 2021).

It has been shown that the subcellular equilibrium between ceRNA, miRNA, and mRNA targets constitutes a complex network that can fine-tune the regulation of gene expression during adaptation, stress response, and development (Mattick, 2018). Here, we emphasize the significance of lncRNA and miRNA interactions in this network. They regulate each other by competing for binding to the corresponding miRNA response elements (MREs), effectively controlling the post-transcriptional regulation of miRNAs (Karreth et al., 2011; Tay et al., 2011). In a cancer biology study, the lncRNA small nucleolar RNA host gene 1 (*SNHG1*) was found to regulate cancer cell metabolism by way of the sponge adsorption of multiple miRNAs (Yan et al., 2017; Li et al., 2018; Tian et al., 2018; Xu et al., 2018; Zhang N et al., 2018). MiRNAs are endogenous noncoding RNAs consisting of 21–25 nucleotides, which regulate the stability, translation, and degradation of mRNAs, leading to the modulation of physiological processes or signaling pathways. The function of miRNAs is related to tissue and organ formation, apoptosis, cell proliferation, differentiation, embryonic development, and various diseases. They can regulate the expression of more than 30% of the genes in the body (Bartel, 2004). MiRNAs have been demonstrated to regulate osteogenesis and angiogenesis in a variety of studies and are strongly correlated with the differentiation of bone marrow mesenchymal stem cells (BMSCs), osteoblasts, and osteoclasts (Bellavia et al., 2019). For example, microRNA-188 (miR-188) is significantly elevated in human mesenchymal stem/stromal cells (hMSCs) from senescent mice, leading to defective differentiation of hMSCs (Li et al., 2015), and miR-214 is significantly up-regulated in osteoblasts from older adults, inhibiting bone formation by suppressing the transcription factor 4 (TCF4) (Wang et al., 2013). Notably, the specific expression of miRNAs in blood vessels is a crucial regulator of angiogenesis. LncRNAs have been shown to activate the relevant pathways by targeting miRNAs to promote angiogenesis and osteogenic differentiation (Ding et al., 2021), suggesting that lncRNAs can regulate osteogenic/angiogenic coupling by adsorbing miRNAs. It has also been proved that lncRNAs can improve the process of crosstalk between osteogenesis and angiogenesis by enhancing the expression of vascular endothelial growth factor (VEGF) during the osteogenic differentiation of BMSCs (Zhang et al., 2020). It is worth noting that the structure and function of lncRNAs define the way they exert their biological regulatory roles. Much research indicates that lncRNAs, together with miRNAs, have participated in the crosstalk between osteogenesis and angiogenesis (Ouyang et al., 2020; Behera et al., 2021; Liu et al., 2024).

3 Angiogenesis-coupled osteogenesis in the bone microenvironment

There is a close relationship between bone blood flow and bone density; people with osteoporosis tend to have a lower bone blood supply than healthy individuals (Alagiakrishnan et al., 2003). Furthermore, animal studies have revealed that a reduction in bone mass in osteoporotic mice is accompanied by a corresponding decrease in the amount of blood supplied to the bones (Ding et al., 2011). Bone angiogenesis and osteogenesis are mutually coupled processes; on the one hand, bone angiogenesis promotes osteogenesis, and a decline in bone angiogenesis capacity decreases osteogenesis ability (Xiao et al., 2018). On the other hand, in the bone microenvironment, osteoblasts can secrete angiogenic factors to regulate the proliferation and vascularization of vascular endothelial cells, thereby promoting bone angiogenesis (Maes et al., 2010).

3.1 Influence of angiogenesis on osteogenesis in the bone microenvironment

Bone vasculature plays an important regulatory role in the occurrence, development, and rehabilitation of various bone-related diseases. At the time of fracture, the blood vessels in the bone will rapidly gather

and grow toward the injury site, delivering various growth factors and cells that promote osteogenesis and participate in the repair of the fracture (Baker et al., 2018; Bahney et al., 2019). Osteoporosis can be caused by various factors, including vascular anomalies that disrupt blood flow to the bone, reduce the number of blood vessels in the bone, and lead to abnormal blood vessel structure. Fortunately, several strategies can help alleviate osteoporosis symptoms, including improving blood flow to the bone (Peng et al., 2014; Jing et al., 2017). The type, spatial structure, and function of blood vessels in the bone microenvironment underlie the vascular effects on osteogenesis. Bone is a highly vascularized tissue, similar to other organs, but with some inconsistencies with the vasculature of other organs, such as growth plates and articular cartilage. Simultaneously, the skeletal system functions as an adaptable feedback regulatory mechanism that continuously integrates mechanical, biochemical, and neural signals (Harada and Rodan, 2003). The vascular system in bone exhibits a typical hierarchical structure, with branches of the arterial trunk flowing into an extensive network of capillaries before converging into large veins in the center of the backbone (Kusumbe et al., 2014). Although bone is the primary site for bone marrow storage, a sophisticated vascular system consisting of arteries, veins, and capillaries also exists. The capillaries are particularly specialized and have been shown to play a crucial role in maintaining bone health.

Kusumbe et al. (2014) identified new microvessels in the mouse skeletal system with distinct morphological, molecular, and functional properties. They distinguished them based on the expression levels of platelet endothelial cell adhesion molecule-1 (PECAM1) (known as cluster of differentiation 31 (CD31)) and endomucin (EMCN) as a distinguishing criterion, referring to the $CD31^{hi}EMCN^{hi}$ subpopulation as H-type blood vessels, and the $CD31^{lo}EMCN^{lo}$ sinusoidal capillaries as L-type blood vessels (Kusumbe et al., 2014). H-type capillaries are located in the vicinity of the metaphyseal growth plate and are interconnected with one another as vascular columns. High levels of CD31 and EMCN are expressed. The L-type connects to the central vein and is surrounded by dense hematopoietic cells expressing low levels of CD31 and EMCN (Ramasamy et al., 2014). Recently, the capillary network was first observed in the long bones of mice. These bone marrow-derived capillaries, which run vertically across the cortical bone and connect the bone marrow to the periosteal circulatory system, are known as trans-cortical vessels (TCVs) and play a crucial role in the endoskeletal circulatory system of mice. In fact, TCVs account for more than 80% of arterial blood flow and 59% of venous blood flow in the mouse tibia. In addition, this study also found that capillaries similar in structure to TCVs also exist in human long bones (Grüneboom et al., 2019). The complex and dense network of vascular tissue is the basis, as well as a facilitator, of osteogenesis in the bone microenvironment (Fig. 1).

3.2 Angiogenesis and neovascularization regulated by lncRNAs in the bone microenvironment

Bone growth is accompanied by the formation of new blood vessels, otherwise known as neovascularization, which occurs in two ways—angiogenesis and neovascularization. Angiogenesis is the process of growing new blood vessels from the existing vascular system by recruiting endothelial cells, while neovascularization is the process of the re-formation of blood vessels from bone marrow-derived endothelial progenitor cells (EPCs) (Carmeliet and Jain, 2011; Laschke et al., 2011). EPCs are precursor cells of endothelial cells and belong to the class of pluripotent stem cells (Chopra et al., 2018). The main area of vascular endothelial cell proliferation in the bone microenvironment is the metaphysis of long bones (Ramasamy et al., 2014). Both angiogenesis and neovascularization participate in embryonic vascular development and formation and play important roles in blood vessel regeneration, repair, and reconstruction (Patschan et al., 2018). Angiogenesis is a complex process including vasodilation, basement membrane degradation, endothelial cell migration, chemotaxis, increased vascular permeability, endothelial cell proliferation, and blood vessel formation (Krüger-Genge et al., 2019).

The initiation of angiogenesis is primarily triggered by VEGF. VEGF recruits and mobilizes EPCs, increases endothelial cell differentiation and proliferation, and promotes vascular tube formation (Asahara et al., 1999). Numerous studies have found that VEGF promotes the proliferation, migration, and chemotaxis of vascular endothelial cells in a variety of tissues and organs (Ferrara et al., 2003; Coultas et al., 2005; Apte et al., 2019). It has three isoforms, i.e., A, B, and C, which form homo- and heterodimers and bind to the

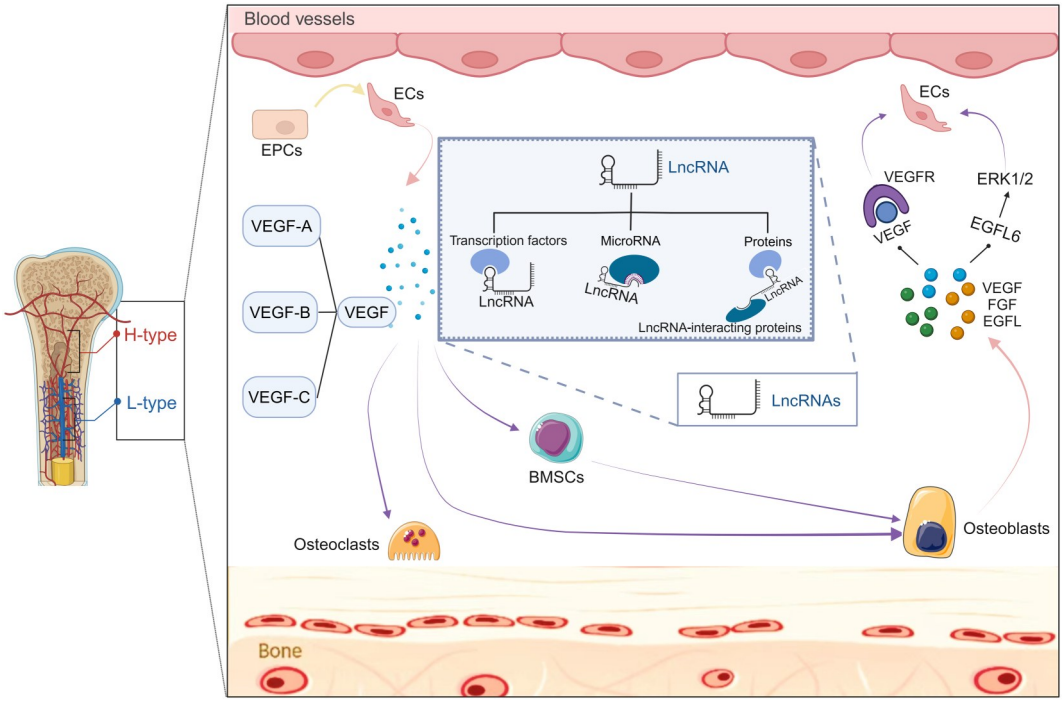

Fig. 1 Crosstalk between osteogenesis and angiogenesis in the bone microenvironment. A complex vascular network exists in the microenvironment of bone. Long noncoding RNAs (lncRNAs) play a crucial role in regulating interactions between endothelial cells (ECs), endothelial progenitor cells (EPCs), osteoclasts, osteoblasts, and bone marrow mesenchymal stem cells (BMSCs) in the bone microenvironment. "→" indicates promoting effect. EGFL: epidermal growth factor-like protein; ERK1/2: extracellular signal-regulated kinase 1/2; FGF: fibroblast growth factor; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor.

dimeric complexes of the two receptors, VEGF receptor-1 (VEGFR-1) (Fms-like tyrosine kinase 1 (Flt-1)) and VEGFR-2 (fetal liver kinase 1 (Flk-1)) (Ferrara, 1999; Shineh et al., 2023). EPC recruitment induces endothelial cell differentiation into stem tip cells by binding to VEGFR-2 (Carmeliet and Jain, 2011). Endothelial cells are the most sensitive to VEGF, which is determined by their higher expression of VEGFR-2 than that of other neighboring cells (Shimizu et al., 2023).

In recent years, numerous studies have proved that lncRNA is able to participate in the regulation of angiogenesis and neovascularization in the bone microenvironment. Among all lncRNA-regulated angiogenic signaling pathways, VEGF plays an important role and is the pivot of most signaling pathways. LncRNA taurine-upregulated gene 1 (*TUG1*) functions as a ceRNA for miR-6321, and miR-6321 inhibits EPC migration and differentiation through its target, activating transcription factor 2 (ATF2) (Yu et al., 2020). LncRNAs play important roles during angiogenesis, and the lncRNA-miRNA-mRNA regulatory pathway is a common way in which they function. Similarly, lncRNA *SNHG1* is a competitive endogenous RNA for miR-140-3p, while hypoxia-inducible factor-1α (*HIF-1α*) has been identified as a target of miR-140-3p. LncRNA *SNHG1* promotes cell proliferation, tube formation, and the expression of VEGF, vascular endothelial cell calreticulin, and matrix metalloproteinase 2 (MMP2), while *SNHG1* knockdown showed the opposite effect (Liang et al., 2020).

In addition, lncRNAs can directly regulate the expression of angiogenic factors to affect angiogenesis. Ac103746.1 is one of the highly expressed lncRNAs among genes detected in human embryonic stem cell-derived mesenchymal stem cells (HES-MSCs) and human bone marrow-derived MSCs (HBM-MSCs), and is named *SCDAL* (stem cell-derived angiogenic lncRNA) (Wu et al., 2021). Knockdown of *SCDAL* significantly reduces the angiogenic potential and repair of HES-MSCs after myocardial infarction. In contrast, *SCDAL* overexpression in HES-MSCs and HBM-MSCs promotes angiogenesis and cardiac function recovery. Mechanistically, *SCDAL* induces growth/differentiation factor 6 (GDF6) expression through

direct interaction with SNF5 on the GDF6 promoter. Secreted GDF6 promotes vascular endothelial cell production by activating non-canonical VEGFR-2 (Wu et al., 2021). Furthermore, SCDAL-GDF6 is expressed in human endothelial cells and directly promotes endothelial cell angiogenesis (Wu et al., 2021). The studies above indicate that lncRNA is essential in regulating angiogenesis and neovascularization in the bone microenvironment.

4 Effects of lncRNAs on the crosstalk between angiogenesis and osteogenesis in the bone microenvironment

4.1 LncRNA-regulated osteogenic differentiation underlying the crosstalk between angiogenesis and osteogenesis

BMSCs are tissue repair cells that play an essential role in tissue engineering and bone development strategies. The development of osteoporosis is associated with a balance of the multidirectional differentiation of BMSCs, which are mesoderm-derived pluripotent stem cells that can differentiate into osteoblasts, chondrocytes, adipocytes, and even myoblasts. In the bone microenvironment, osteoblasts secrete angiogenic factors to regulate the proliferation and vascularization of vascular endothelial cells (Maes et al., 2010). Osteoblasts and their precursor cells are mainly distributed around H-type vascular endothelial cells and are involved in the regulation of bone angiogenesis through the secretion of angiogenic factors such as VEGF, fibroblast growth factor (FGF), and epidermal growth factor-like protein (EGFL). Osteoblasts can secrete the VEGFR to promote the proliferation and vascularization of vascular endothelial cells and bone angiogenesis (Potente et al., 2011). The FGF signaling pathway can also be involved in the regulation of angiogenesis and bone formation. FGF has been shown to induce the expression of VEGF-A and VEGFR-2 to stimulate bone arteriolar vasodilatation, and the knockdown of FGF2 in mice leads to a decrease in the rate of bone formation and the volume of bone trabeculae (Byun et al., 2014). Knockdown of FGF9 and FGF18 has been shown to reduce VEGF-A expression and decrease angiogenesis (Hung et al., 2016). Osteoblasts also regulate bone angiogenesis through the EGFL signaling pathway. For example, osteoblasts secrete EGFL6 to promote endothelial cell proliferation and vascularization by activating extracellular signal-regulated kinase 1/2 (ERK1/2) (Chim et al., 2011). It is widely accepted that osteoblasts are essential for the promotion of bone angiogenesis, and they primarily originate from BMSCs. The osteogenic differentiation of BMSCs is an essential process of bone formation, and lncRNA is an important regulator in this process.

Meanwhile, bone angiogenesis is highly correlated with osteogenesis. From a microscopic point of view, lncRNAs can affect angiogenesis by regulating the osteogenic differentiation of BMSCs. Recently, several studies have indicated that lncRNAs are able to modulate the proliferation and differentiation of BMSCs and regulate the balance of the multidirectional differentiation of BMSCs (Guo et al., 2020; Yu et al., 2022; Kieu Nguyen et al., 2023). The effects of lncRNAs on the osteogenic differentiation of BMSCs primarily occur in two respects, by promoting and inhibiting differentiation. Additionally, the regulatory role of specific lncRNAs in osteogenic differentiation is inconsistent across different studies.

LncRNAs regulate the osteogenic differentiation of BMSCs by targeting miRNA, the target genes of which are osteogenic factors. LncRNA maternally expressed gene 3 (*MEG3*) is a tumor suppressor (Zhou et al., 2012; Mitra et al., 2017) that promotes the osteogenic differentiation of MSCs in multiple myeloma patients (Zhuang et al., 2015; Li et al., 2017). LncRNA *MEG3* is shown to inhibit the osteogenesis of BMSCs in postmenopausal osteoporosis by binding to miR-133a-3p to up-regulate miR-133a-3p expression, thereby down-regulating solute carrier family 39 member 1 (*SLC39A1*) expression (Wang et al., 2017). It has also been suggested that *MEG3* works in conjunction with DEP domain-containing mammalian target of rapamycin (mTOR)-interacting protein (*DEPTOR*). *DEPTOR* is highly expressed in the cancellous bone and BMSCs of osteoporotic mice, and continuously decreases during the osteogenic differentiation of BMSCs. The down-regulation of *DEPTOR* by lentiviral transfection can promote the osteogenic differentiation of BMSCs, as shown from the results of in vivo and in vitro experiments (Chen et al., 2018). Furthermore, lncRNA and mRNA sequencing indicated that the reduction of *DEPTOR* up-regulated the expression of *MEG3*, which subsequently activated bone

morphogenetic protein 4 (BMP4)/mothers against decapentaplegic homolog 1/5/8 (Smad1/5/8) signaling. Chen et al. (2018) discovered that *DEPTOR* could bind to a specific region of the *MEG3* promoter to regulate its transcription, and the inhibition of *MEG3* reduced BMP4 activation triggered by *DEPTOR* knockdown. The suppression of *MEG3* decreases the promotion of osteogenic differentiation by *DEPTOR* knockdown, showing that *DEPTOR* can inhibit the differentiation of BMSCs toward osteogenesis through *MEG3*. *SNHG5* promotes osteogenesis and attenuates the apoptosis of human BMSCs (hBMSCs) via regulating runt-related transcription factor 3 (RUNX3) expression through the sponge adsorption of miR-582-5p (Zheng et al., 2024). The expression of lncRNA growth arrest-specific transcript 5 (*GAS5*) was reduced in the hMSCs of osteoporosis patients, and the overexpression of *GAS5* was able to up-regulate RUNX2 expression by regulating miR-498 and thus promoted the osteogenic differentiation of hMSCs, which attenuates the development of osteoporosis (Feng et al., 2019). Some studies have demonstrated that lncRNA metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) regulates the osteogenic differentiation of BMSCs by raising the expression of osterix through the sponge adsorption of miR-143 and miR-96 (Gao et al., 2018; Zang et al., 2022).

In addition to *MEG3*, *SNHG5*, *GAS5*, and *MALAT1*, many lncRNAs can regulate the osteogenic differentiation of BMSCs, such as HOXA transcript at the distal tip (*HOTTIP*), differentiation antagonizing non-protein coding RNA (*DANCR*), and *SNHG1*. LncRNA *HOTTIP* enhances osteogenic differentiation by interacting with WD40 repeat domain protein 5 (WDR5), activating the Wnt/β-catenin signaling pathway, and up-regulating β-catenin gene expression (Liu et al., 2020). In contrast, lncRNAs *DANCR* and *SNHG1* play different roles in osteogenesis. Yu et al. (2021) showed in their latest findings that lncRNA *SNHG1* can bind to miR-181c-5p as a sponge and down-regulate the expression of miR-181c-5p, which in turn regulates the secreted frizzled-related protein 1 (SFRP1)/Wnt/β-catenin signaling pathway, inhibiting the osteogenic differentiation of BMSCs and promoting the pathological development of osteoporosis. In addition, in an experimental study of a postmenopausal osteoporosis mouse model, Wang et al. (2020) discovered that lncRNA *DANCR* was capable of inhibiting the Wnt/β-catenin signaling pathway during the differentiation of osteoporotic BMSCs by down-regulating the expression of catenin β1 (*CTNNB1*) and eliminating the up-regulatory effect of miR-320a on *CTNNB1*. This negative regulation of the osteogenic process has significant implications for understanding the role of lncRNAs in regulating bone metabolism in vivo.

Some lncRNAs are shown to regulate osteogenesis by signaling pathways such as the BMP2/Smad signaling pathway, the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, and the p38/mitogen-activated protein kinase (MAPK) signaling pathway. For example, lncRNA musculin antisense RNA 1 (*MSC-AS1*) could act as a miR-140e-5p sponge and bind to it to up-regulate the expression of BMP2, which promotes the osteogenic differentiation of BMSCs and delays the progression of osteoporosis through the miR-140e-5p/BMP2/Smad signaling pathway (Zhang ND et al., 2019). LNC_000052 inhibits apoptosis and promotes the proliferation and osteogenic differentiation of BMSCs through the miR-96-5p/PI3K/AKT signaling pathway axis (Li et al., 2020). In ovariectomized mice, lncRNA *SNHG1* negatively regulates the neuronally expressed developmentally downregulated 4 (Nedd4)-mediated p38/MAPK signaling pathway, thereby inhibiting the osteogenic differentiation of BMSCs (Jiang et al., 2019). LncRNA *DANCR* is considered to reverse the osteogenic differentiation fate of BMSCs in osteoporosis and accelerate the development of osteoporosis. It could inactivate the p38/MAPK pathway, thus significantly inhibiting the proliferation and osteogenic differentiation of BMSCs (Zhang JL et al., 2018).

Additionally, there are also individual lncRNAs whose role in regulating the osteogenic differentiation of BMSCs is controversial, such as lncRNA *TUG1* and lncRNA *MEG3*. Some researchers analyzed plasma from osteoporosis patients by assay and found that lncRNA *TUG1* expression was decreased and miR-23b expression was increased. They indicated that the down-regulation of lncRNA *TUG1* could inhibit the differentiation of BMSCs by targeting the miR-23b/RUNX2 pathway (Teng et al., 2021). However, another study suggested that lncRNA *TUG1* could promote the differentiation of BMSCs and inhibit cell apoptosis by targeting the miR-34a/FGF receptor 1 (FGFR1) pathway, providing a potential therapeutic target for osteoporosis (Wang XW et al., 2021). As

mentioned earlier, lncRNA *MEG3* can inhibit the transformation of BMSCs into osteoblasts in postmenopausal osteoporosis. For these controversial lncRNAs, although earlier studies have been conducted to investigate their role in BMSC transformation, more and more studies have been undertaken in recent years with opposite conclusions.

We concluded that the main reason for the effects of the opposed regulation of the same lncRNAs is that they exert their regulatory effects through different signaling pathways. LncRNA *MALAT1* in exosomes derived from BMSCs in ovariectomized osteoporotic mice can be transferred to osteoblasts, which in turn act as miR-34c sponge for and up-regulate the expression of special AT-rich sequence-binding protein 2 (SATB2) in osteoblasts, and enhance the activity of osteoblasts, thus alleviating osteoporosis (Yang et al., 2019). However, some scholars have come to a contrary conclusion. Zheng et al. (2019) found that lncRNA *MALAT1* could enhance the MAPK signaling pathway to reduce the osteogenic differentiation of BMSCs, thus accelerating the progression of osteoporosis in the osteoporosis model mice. In addition, some other lncRNAs are not discussed in detail regarding their functions, but are rather organized in Table 1.

4.2 LncRNA-mediated angiogenesis regulating osteogenesis in the bone microenvironment

EPCs are thought to promote bone repair by stimulating neovascularization and osteogenesis (Atesok et al., 2010; Jules et al., 2012; Kamei et al., 2017). Pro-angiogenic factors secreted by osteoblasts, such as VEGF, can trigger signaling responses in various cells, including ECs and osteoblasts that express VEGF receptors (Novack and Teitelbaum, 2008). EPCs contribute to the formation of new blood vessels and indirectly promote new bone formation during bone repair, while

Table 1 Some lncRNAs in osteogenic differentiation of BMSCs

LncRNA	Target	Function	Reference
MEG3	miR-133a-3p/SLC39A1	Inhibition	Wang et al., 2017
SNHG5	miR-582-5p/RUNX3	Promotion	Zheng et al., 2024
GAS5	miR-498/RUNX2	Promotion	Feng et al., 2019
MALAT1	miR-96/osterix	Promotion	Zang et al., 2022
MALAT1	miR-143/osterix	Promotion	Gao et al., 2018
MEG3	BMP4/Smad	Inhibition	Tsuji et al., 2008; Wu et al., 2016; Chen et al., 2018
HOTTIP	WDR5/Wnt/β-catenin signaling pathway	Promotion	Liu et al., 2020
SNHG1	miR-181c-5p, SFRP1/Wnt/β-catenin signaling pathway	Inhibition	Yu et al., 2021
DANCR	CTNNB1/Wnt/β-catenin signaling pathway	Inhibition	Wang et al., 2020
MSC-AS1	miR-140e-5p/BMP2/Smad signaling pathway	Promotion	Zhang ND et al., 2019
LNC_000052	miR-96-5p/PI3K/AKT signaling pathway	Inhibition	Li et al., 2020
SNHG1	Nedd4/p38/MAPK signaling pathway	Inhibition	Jiang et al., 2019
DANCR	p38/MAPK signaling pathway	Inhibition	Zhang JL et al., 2018
TUG1	miR-23b/RUNX2	Inhibition	Teng et al., 2021
TUG1	miR-34a/FGFR1	Promotion	Wang XW et al., 2021
MALAT1	miR-34c/SATB2	Promotion	Yang et al., 2019
MALAT1	MAPK signaling pathway	Inhibition	Zheng et al., 2019
ANCR	RUNX2	Inhibition	Cai et al., 2019
DANCR	FOXO1	Inhibition	Tang et al., 2018

LncRNA: long noncoding RNA; BMSCs: bone marrow mesenchymal stem cells; *MEG3*: maternally expressed gene 3; *SNHG*: small nucleolar RNA host gene; *GAS5*: growth arrest-specific transcript 5; *MALAT1*: metastasis-associated lung adenocarcinoma transcript 1; *HOTTIP*: HOXA transcript at the distal tip; *DANCR*: differentiation antagonizing non-protein coding RNA; *MSC-AS1*: musculin antisense RNA 1; *TUG1*: taurine-upregulated gene 1; *ANCR*: anti-differentiation non-coding RNA; miR: microRNA; SLC39A1: solute carrier family 39 member 1; RUNX: runt-related transcription factor; BMP: bone morphogenetic protein; Smad: mothers against decapentaplegic homolog; WDR5: WD40 repeat domain protein 5; SFRP1: secreted frizzled-related protein 1; CTNNB1: catenin β1; PI3K: phosphatidylinositol 3-kinase: AKT: protein kinase B; Nedd4: neuronally expressed developmentally downregulated 4; MAPK: mitogen-activated protein kinase; FGFR1: fibroblast growth factor receptor 1; SATB2: special AT-rich sequence-binding protein 2; FOXO1: forkhead box protein O1.

VEGF has a strong chemotactic effect on osteoblasts and osteoclasts (Mayr-Wohlfart et al., 2002; Henriksen et al., 2003; Bates et al., 2017).

EPC-derived exosomes are involved in the communication between EPCs and BMSCs and promote osteoblast differentiation by suppressing the expression of osteogenic genes and promoting proliferation in vitro (Qin and Zhang, 2017). It has been shown that lncRNA *MALAT1* from the exosomes of EPCs directly binds to miR-124 and negatively regulates miR-124 expression, while integrin β1 (ITGB1) is a target of miR-124. LncRNA *MALAT1* in EPCs-derived exosomes promotes bone repair by facilitating the recruitment and differentiation of osteoclast precursors through the lncRNA *MALAT1*/miR-124 pathway (Cui et al., 2019). Human umbilical vein endothelial cell (HUVEC)-derived exosomes can induce macrophage M2 polarization via the DEAD-box helicase 3X-linked (DDX3X)/NOD-like receptor protein 3 (NLRP3) regulatory axis, which delivers nuclear-enriched abundant transcript 1 (NEAT1) to attenuate inflammation and ultimately promotes osteogenesis in vivo with the help of alginate/gelatin methacryloyl (GelMA) interpenetrating polymer network (IPN) hydrogels (Chen et al., 2023). These studies demonstrate that exosomes are one of the ways in which lncRNAs regulate the crosstalk between osteogenesis and angiogenesis in the bone microenvironment (Fig. 2).

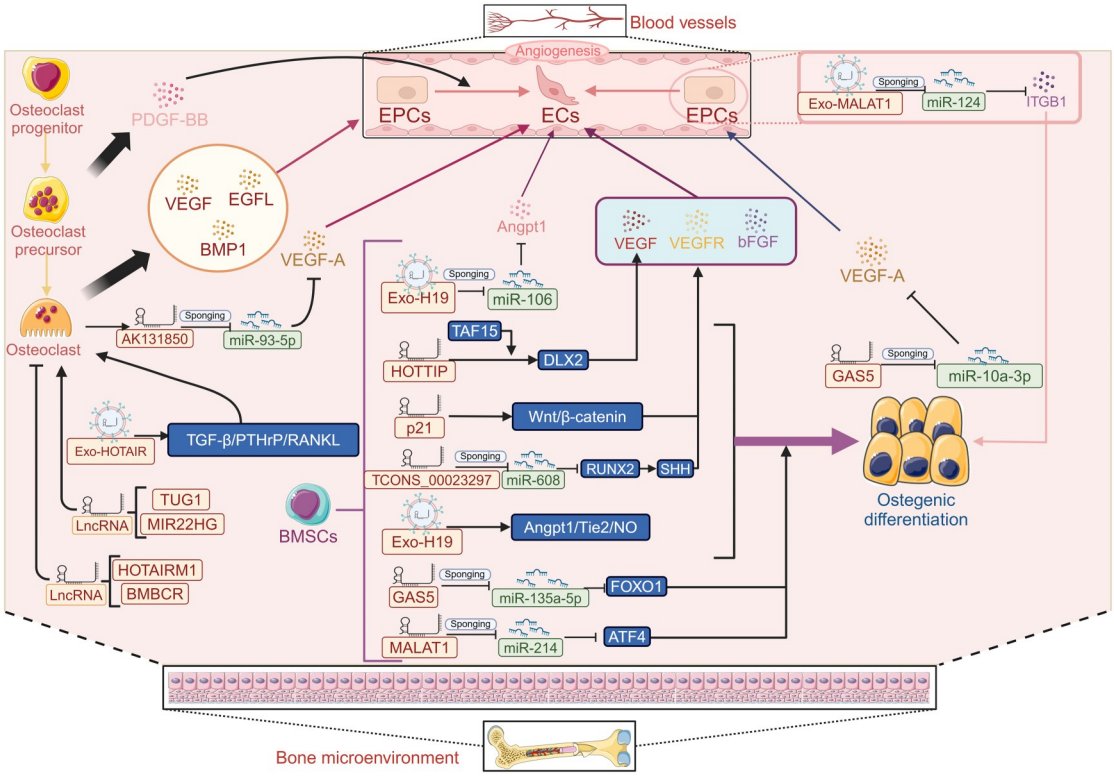

Fig. 2 Roles of long noncoding RNAs (lncRNAs) in regulating the crosstalk between angiogenesis and osteogenesis in the bone microenvironment. LncRNAs regulate the crosstalk between angiogenesis and osteogenesis coupling in the bone microenvironment through various modes of action. LncRNAs can regulate endothelial cell (EC) and endothelial progenitor cell (EPC)-dominated angiogenesis directly or indirectly by regulating the osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs). These processes are inseparable from angiogenic factors, e.g., vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR), VEGF-A, epidermal growth factor-like protein (EGFL), and basic fibroblast growth factor (bFGF). "→" indicates promoting effect. Angpt1: angiopoietin 1; ATF4: activating transcription factor 4; BMBCR: B-cell receptor; BMP1: bone morphogenetic protein 1; DLX2: distal-less homeobox 2; Exo: exosome; FOXO1: forkhead box protein O1; GAS5: growth arrest-specific transcript 5; HOTAIR: homeobox transcript antisense intergenic RNA; HOTAIRM1: HOTAIR-M1; HOTTIP: HOXA transcript at the distal tip; ITGB1: integrin β1; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; PDGF-BB: platelet-derived growth factor-BB; PTHrP: parathyroid hormone-related protein; RANKL: receptor activator of nuclear facto-κB ligand; RUNX2: runt-related transcription factor 2; SHH: sonic hedgehog signaling pathway; TAF15: TATA-box binding protein associated factor 15; TGF-β: transforming growth factor-β; TUG1: taurine-upregulated gene 1.

4.3 LncRNA-mediated crosstalk between angiogenesis and osteogenesis in bone diseases

4.3.1 Osteosarcoma

Osteosarcoma is extremely prevalent, especially malignant tumors occurring near the growth plate of the metaphysis of long bones or around the knee joint (Luetke et al., 2014; Huang et al., 2022). Over the last few years, an increasingly large number of studies have been focusing on the roles of angiogenesis in osteosarcoma progression, such as the imbalance between anti-angiogenic and pro-angiogenic effects including proliferation, migration, and metastasis (Chang and Yu, 2016). Vasculogenic mimicry is a new form of angiogenesis in tumor tissues that promotes angiogenesis, increases the supply of oxygen and nutrients to tumor tissues, and provides the basis for tumor cell metastasis (Qiao et al., 2015; Wei HL et al., 2017). LncRNAs participate in vasculogenic mimicry formation in a variety of tumors, including gastric, lung, and liver cancers (Luo et al., 2020). It is an unfavorable prognostic factor in cancer patients. LncRNAs are aberrantly expressed in osteosarcoma and are involved in vasculogenic mimicry in osteosarcoma (Ren et al., 2019). The suppression of n340532 exhibited potent anti-vasculogenic mimicry and anti-metastasis effects in vivo, suggesting its potential role in vasculogenic mimicry and metastasis in osteosarcoma (Ren et al., 2019).

VEGF-A is considered a key factor in tumor-induced angiogenesis (Claesson-Welsh and Welsh, 2013). Zhang et al. (2017) found that high expression of lncRNA *MALAT1* in MNNG/HOS cells resulted in the up-regulation of angiogenic factors, including VEGF-A. The LOC100129620/miR-335-3p/cyclin-dependent kinase 6 (CDK6) signaling axis contributes to osteosarcoma metastasis by regulating osteosarcoma cell proliferation, macrophage polarization, and angiogenesis (Chen Y et al., 2021). miR-335-3p mediates the regulation of CDK6 expression and achieves the indirect promotion of angiogenesis and macrophage polarization by LOC100129620. LINC00265 may promote the metastatic effects of LOC100129620 on angiogenesis and macrophage polarization in osteosarcoma by targeting miR-382-5p/spermine N1-acetyltransferase-1 (SAT1) and miR-382-5p/Vav guanine nucleotide exchange factor 3 (VAV3) to promote proliferation, migration, invasion, and angiogenesis in osteosarcoma (Xiao et al., 2020). Exosomes derived from serum transport lncRNA myocardial infarction-associated transcript (*MIAT*) carried by osteosarcoma patient serum-derived extracellular vesicles (EVs) (EV-MIAT) into osteosarcoma cells to compete for binding to miR-613, thus up-regulating GPR158 and promoting osteosarcoma cell proliferation and angiogenesis (Wang BD et al., 2022). Exosome-derived lncRNA noncoding RNA activated by DNA damage (*NORAD*), from BMSCs, regulates cAMP response element-binding protein (CREB)-binding protein (CREBBP) through miR-877-3p to promote osteosarcoma cell proliferation, invasion, migration, and angiogenesis (Feng et al., 2022). The Ewing sarcoma-associated transcript 1 (EWSAT1) regulates osteosarcoma-induced angiogenesis via two pathways, called the "double stacking effect," which is a combination of the increase in the sensitivity of vascular endothelial cells induced by exosomes carrying EWSAT1 and the EWSAT1-induced increase in angiogenic factor secretion from osteosarcoma cells (Tao et al., 2020). EWSAT1 regulates AKT and ERK signaling pathways through the EWSAT1/miR-326/Kirsten rat sarcoma viral oncogene homolog (KRAS) ceRNA pathway, significantly promoting osteosarcoma proliferation, migration, colony formation, and survival (Tao et al., 2020). The above-mentioned studies provide new ideas for the study of the pathogenesis of angiogenesis in osteosarcoma.

4.3.2 Osteoarthritis

Angiogenesis is involved in almost every process of osteoarthritis, including synovitis caused by the appearance of neovascularization in the synovium, cartilage destruction caused by the appearance of neovascularization at the osteochondral joint, and the formation of bone capillaries, all of which are closely related to angiogenesis (Ashraf et al., 2011). VEGF is considered a key factor in angiogenesis. Inflammatory factors (interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α)), hypoxia, and mechanical stress all increase the expression of VEGF in angiogenesis joints through multiple signaling pathways (Ashraf and Walsh, 2008). VEGF expression in the surface, middle, and deep layers of angiogenesis cartilage has been shown to be up-regulated, whereas angiogenesis occurs predominantly in the deeper cartilage (Mapp and Walsh, 2012). Angiogenesis is an important part of the cartilage's osteogenesis process, leading to

subchondral bone remodeling, synovial hyperplasia, and osteophytes (He et al., 2021). *MEG3* is significantly down-regulated in the articular cartilage of osteoarthritis patients, while VEGF expression is significantly increased (Su et al., 2015). *MEG3* promotes the transcription of p53, which inhibits VEGF expression by binding to Sp1, a transcription site on the VEGF promoter (Kim et al., 2011; Zhang Y et al., 2019). The down-regulation of *MEG3* may indirectly promote VEGF production and endochondral vascularization through this pathway. LncRNA *H19* is a gene that regulates chondrocyte and osteoblast growth as well as cellular anabolic processes (He et al., 2016). Some studies have shown that lncRNA *H19* is highly expressed in the peripheral blood of osteoarthritis patients, which is expected to be a new indicator for the diagnosis of osteoarthritis (Zhou et al., 2020). Exosomal H19 acts as a "sponge" to absorb miR-106, thereby up-regulating the expression of angiopoietin 1 (Angpt1), an angiogenic factor that activates H19/Tie2-NO signaling in mesenchymal and endothelial cells (Behera et al., 2021). In hypertrophic chondrocytes, hypertrophic chondrocyte angiogenesis-related lncRNA (*HCAR*) promotes endochondral bone repair by competitively binding to miR-15b-5p to increase the expression of matrix metallopeptidase 13 (MMP13) and VEGF-A (Bai et al., 2022). In a bone repair model, lncRNA *HCAR* knockdown in hypertrophied chondrocytes inhibited cartilage matrix remodeling and reduced the number of $CD31^{hi}EMCN^{hi}$ vessels (Bai et al., 2022).

4.3.3 Fractures

As a clinical diagnosis, fracture nonunion is characterized by patients with fractures exhibiting clinical signs of pain at the fracture site. At the same time, the radiologic findings are consistent with bone nonunion (Hankenson et al., 2011). New blood vessels bring oxygen and nutrients to the highly metabolically active regenerating bone scab, providing a pathway for inflammatory cells, cartilage, and bone precursor cells to reach the injury site (Hankenson et al., 2011). The normal development of blood vessels in the fracture scab is an important part of fracture rehabilitation. Spliced-transcript endothelial-enriched lncRNA (*STEEL*) expression and vascular density in bone scab tissues of fracture model mice were significantly lower than those of controls; meanwhile, it was verified with in vitro experiments that the proliferative capacity of HUVECs was significantly reduced after the low expression of *STEEL* in HUVECs (Zhang SZ et al., 2018). This is due to the fact that *STEEL* can promote angiogenesis by interacting with poly(ADP-ribose) polymerase 1 (PARP-1) and up-regulating the expression of VEGF (Zhang SZ et al., 2018). In a study on osteodysplasia, the expression of lncRNA ENST00000563492 was down-regulated in osteodysplasia tissues, which could promote the differentiation of BMSCs towards osteogenesis by up-regulating the expression of cadherin-11 (CDH11) and could also improve the process of osteogenic–angiogenic coupling by enhancing the expression of VEGF during the process of the osteogenic differentiation of BMSCs. *CDH11* and *VEGF* are the target genes of miR-205-5p, so lncRNA ENST00000563492 indirectly regulates the expression of both genes as the ceRNAs of miR-205-5p, and can promote the osteogenesis of BMSCs in vivo. Therefore, lncRNA ENST00000563492 may become a new target of osteodysplasia (Ouyang et al., 2020). The application of normal-source BMSC exosomal-lncRNA *H19* competitively binding to miR-467 regulated the expression of homeobox protein Hox-A10 (HoxA10) and inhibited poor fracture healing caused by a high-fat diet (Wang YJ et al., 2021). Wei BF et al. (2017) demonstrated, in a study related to non-traumatic femoral head necrosis, that lncRNA homeobox transcript antisense intergenic RNA (*HOTAIR*) was found to regulate the expression of miR-17-5p and its target gene *SMAD7* through the BMPs/transforming growth factor-β (TGF-β) pathway to inhibit osteogenic differentiation.

5 Summary and prospects

Angiogenesis is a continuous process that occurs throughout the life cycle of bone from generation to growth. Angiogenesis and osteogenesis in the bone microenvironment are not independent parts but interact with each other. LncRNAs regulate the crosstalk between angiogenesis and osteogenesis through multiple miRNAs, mRNAs, and signaling pathways, mainly in osteogenesis, osteoclastogenesis, and angiogenesis. Meanwhile, the roles of some lncRNAs in osteogenesis and angiogenesis are subject to controversy due to conflicting findings from various studies, resulting

from the progressively deeper research into lncRNAs. However, numerous queries necessitate further scientific and comprehensive investigations. For instance, can the findings in this field substantiate the clinical intervention for osteoporosis? It is suggested that more researchers concentrate on simulating the bone microenvironment in vitro to achieve multi-cell co-culture. It is even possible to incorporate the latest reactive biomaterials into encapsulating lncRNAs and stimulate their release at distinct stages of osteogenesis or angiogenesis, aiming to treat various bone-related diseases. Therefore, in the future, the advancement toward the modulation of bone-related illnesses through the use of lncRNAs promises a vibrant field of research.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81901430), the Guangdong Basic and Applied Basic Research Foundation (No. 2022A1515010379), the Science and Technology Projects in Guangzhou (No. 2023A04J0555), and the Guangdong Provincial Key Laboratory of Physical Activity and Health Promotion (No. 2021B121204 0014), China.

Author contributions

Shihua ZHANG: conceptualization, formal analysis, writing – original draft, and writing – review and editing. Jianmin GUO: writing – original draft and writing – review and editing. Yuting HE and Zhi'ang SU: validation and writing – review and editing. Yao FENG: formal analysis and writing – review and editing. Lan ZHANG and Jun ZOU: funding acquisition, supervision, writing – original draft, and writing – review and editing. Xiquan WENG and Yu YUAN: funding acquisition, supervision, writing – review and editing, and project administration. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Shihua ZHANG, Jianmin GUO, Yuting HE, Zhi'ang SU, Yao FENG, Lan ZHANG, Jun ZOU, Xiquan WENG, and Yu YUAN declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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