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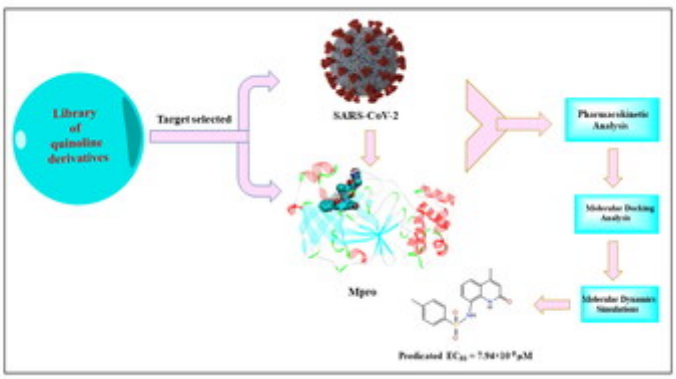

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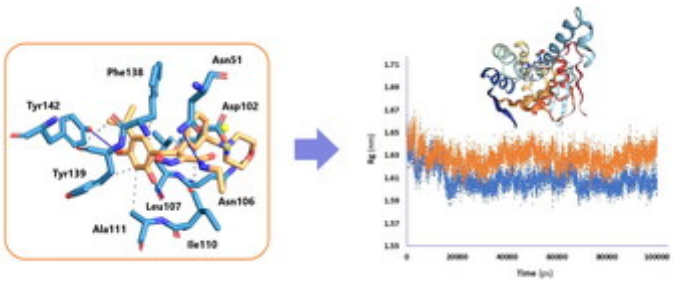

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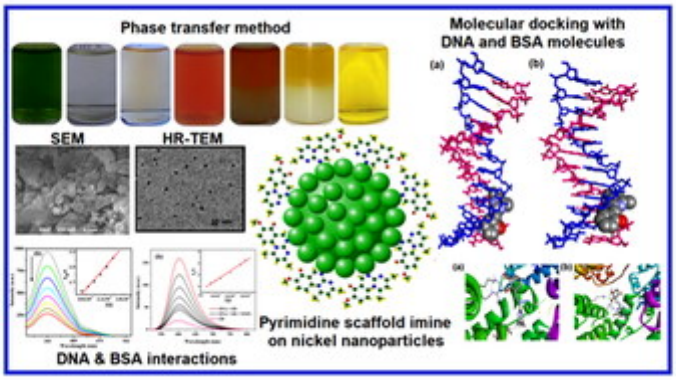

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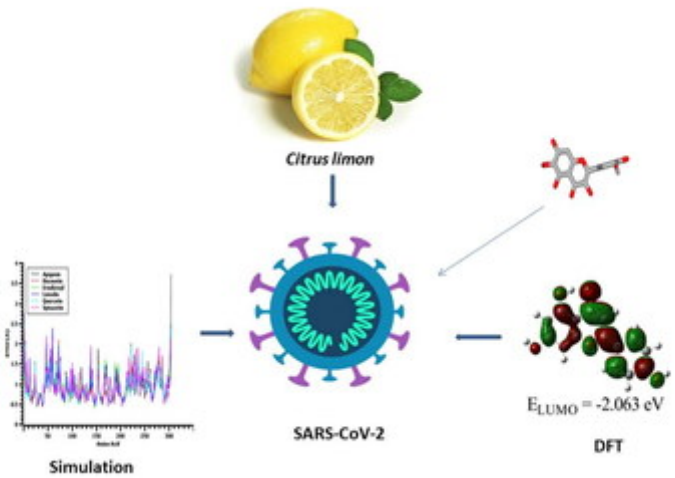

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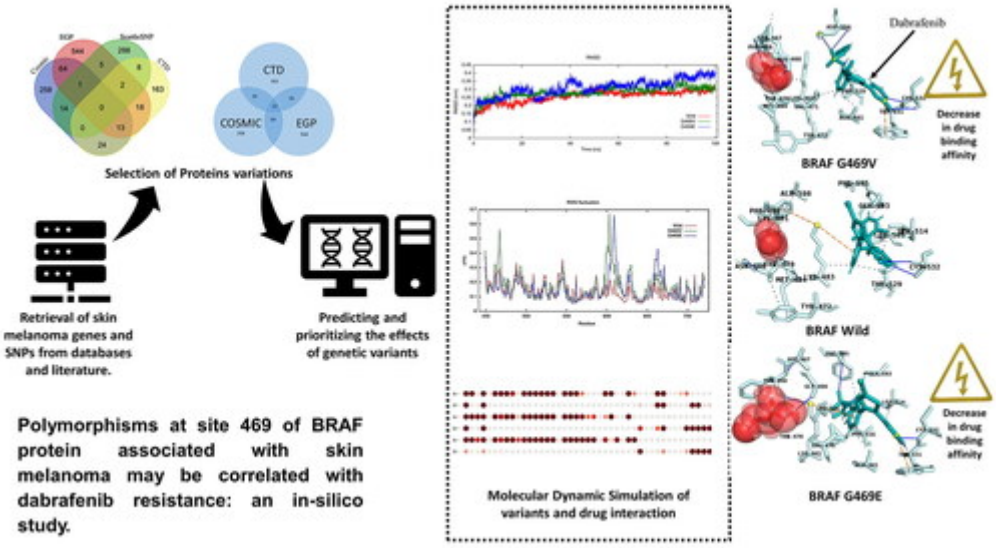

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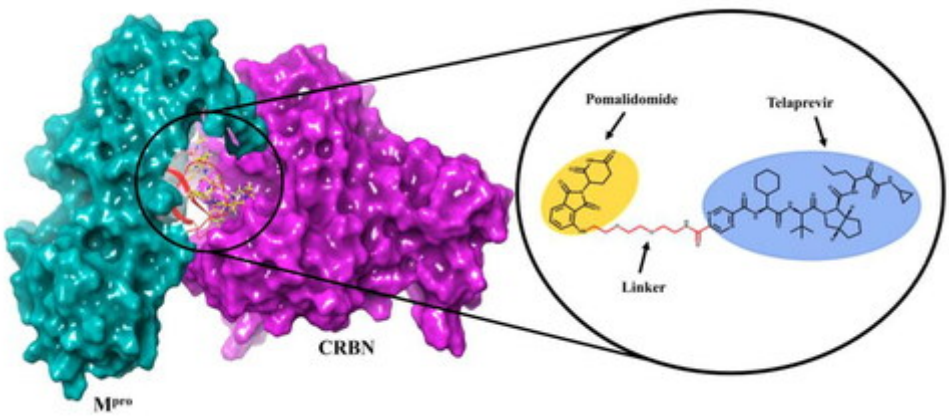

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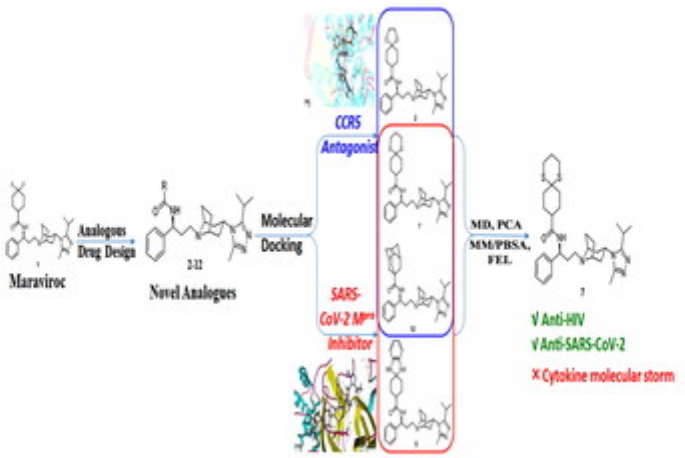

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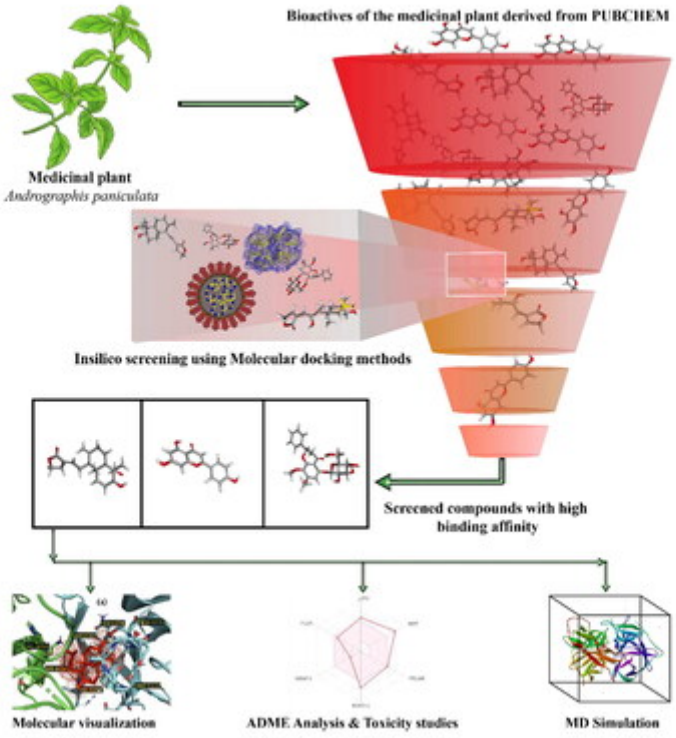

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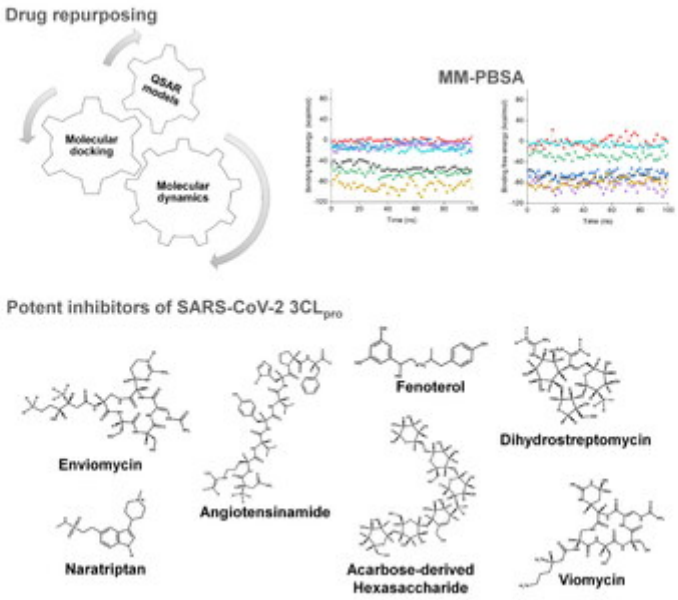

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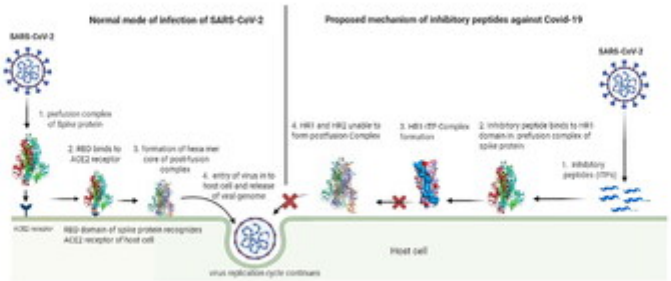

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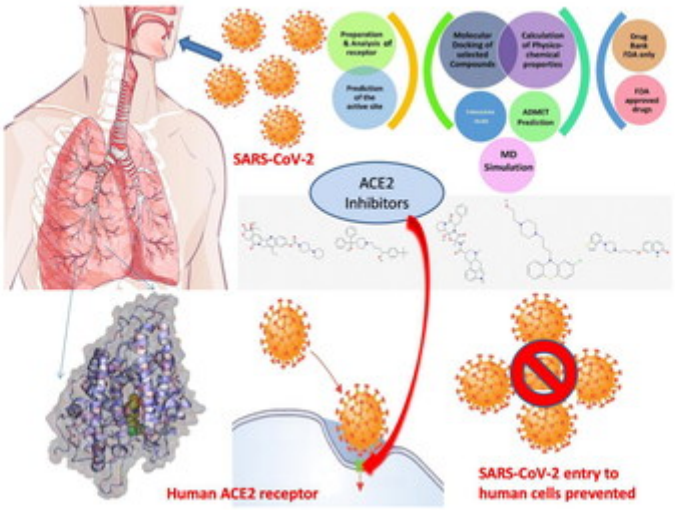

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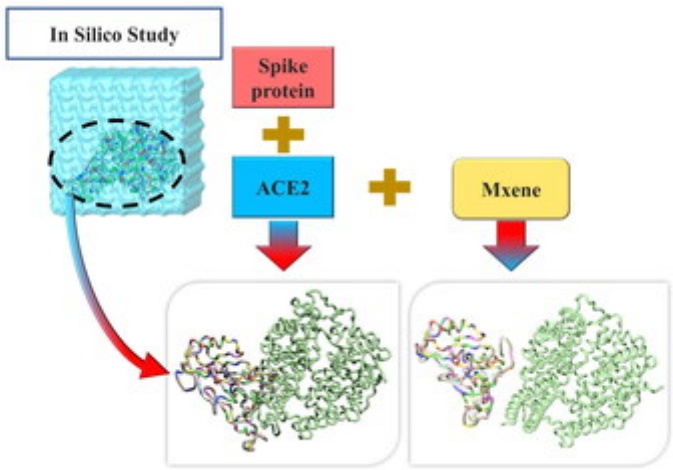

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Differentiation of osteoblasts: the links between essential transcription factors

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ABSTRACT

Osteoblasts, cells derived from mesenchymal stem cells (MSCs) in the bone marrow, are cells responsible for bone formation and remodeling. The differentiation of osteoblasts from MSCs is triggered by the expression of specific genes, which are subsequently controlled by pro-osteogenic pathways. Mature osteoblasts then differentiate into osteocytes and are embedded in the bone matrix. Dysregulation of osteoblast function can cause inadequate bone formation, which leads to the development of bone disease. Various key molecules are involved in the regulation of osteoblastogenesis, which are transcription factors. Previous studies have heavily examined the role of factors that control gene expression during osteoblastogenesis, both in vitro and in vivo. However, the systematic relationship of these transcription factors remains unknown. The involvement of ncRNAs in this mechanism, particularly miRNAs, lncRNAs, and circRNAs, has been shown to influence transcriptional factor activity in the regulation of osteoblast differentiation. Here, we discuss nine essential transcription factors involved in osteoblast differentiation, including Runx2, Osx, Dlx5, β-catenin, ATF4, Ihh, Satb2, and Shn3. In addition, we summarize the role of ncRNAs and their relationship to these essential transcription factors in order to improve our understanding of the transcriptional regulation of osteoblast differentiation. Adequate exploration and understanding of the molecular mechanisms of osteoblastogenesis can be a critical strategy in the development of therapies for bone-related diseases.

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Introduction

Bone is a metabolically active organ that is dynamic in maintaining its strength and integrity through the actions of osteoblasts and osteoclasts (El-Ganzuri et al., 2016; Shahi et al., 2017). In vertebrates, bone formation (ossification) occurs in the craniofacial intramembrane and endochondral bones in other parts of the skeletal system. Endochondral ossification is the replacement of cartilage with mineralized bone affected by chondrocyte differentiation in the central cartilage anlagen. This is followed by the invasion of perichondrial osteoblast progenitors, osteoclasts, vascular endothelial cells, and hematopoietic cells into hypertrophic cartilage. Dense mesenchymal progenitor cells differentiate into osteoblasts and form bone directly during intramembranous ossification (Berendsen & Olsen, 2015; Iaquinta et al., 2019).

Bone tissue has an amazing ability to repair itself and generally heals through regeneration. Under homeostatic conditions, the balance between bone formation (mediated by osteoblasts) and bone resorption (mediated by osteoclasts) is tightly regulated without major changes in net bone mass or mechanical strength, a process known as bone remodeling (Kim et al., 2020). Osteoclasts degrade bone by secreting polarized proteolytic enzymes, such as cathepsin K, and acids, such as HCl, which dissolve collagen and matrix proteins during bone resorption. Meanwhile, osteoblasts generate an extracellular collagen matrix with specific properties that will be mineralized following hydroxyapatite ($Ca_5(PO_4)_3(OH)$) crystal deposition (Kim et al., 2020; Shahi et al., 2017; Zhang, 2010). Once this balance is disrupted, abnormal bone remodeling occurs, resulting in bone deformities and a variety of bone diseases (Chan et al., 2021).

Osteoblast differentiation, also known as osteoblastogenesis, is a major component of bone formation due to the initial very rapid cell proliferation followed by extracellular matrix maturation and mineralization (Huang et al., 2007; Shahi et al., 2017). Classically, osteoblast differentiation is governed by a complex activity involving signal transduction and transcriptional regulation of gene expression (Huang et al., 2007). Runx2 has been identified as the master regulatory switch in osteoblast differentiation, with Osx acting as the 'downstream' regulator of Runx2 (Baldini et al., 2009; Komori, 2019). Furthermore, Dlx5, β-catenin, ATF4, Ihh, Satb2, and Shn3 are other essential transcription factors known to be involved in osteoblast differentiation (Bialek et al., 2004;

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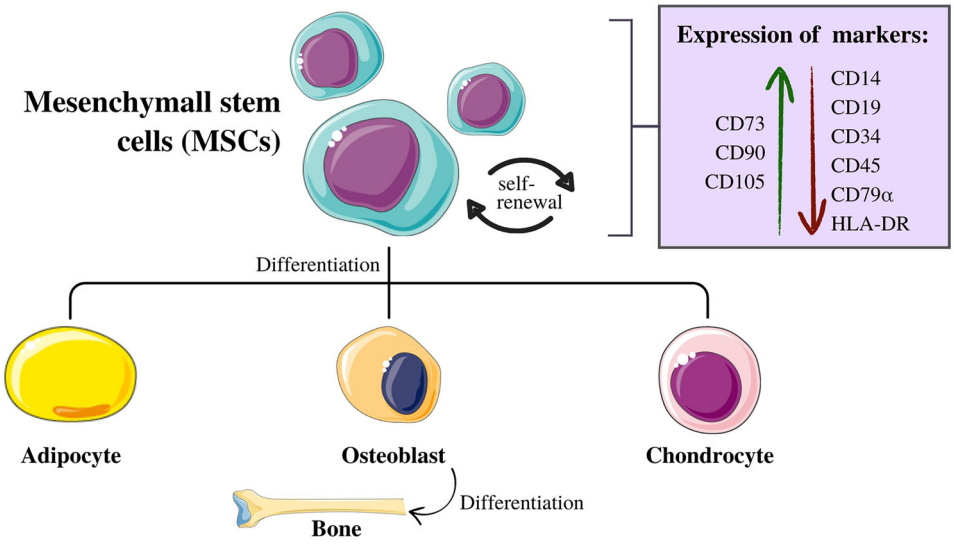

Figure 1. Schematic representation of multilineage mesenchymal stem cell (MSC) differentiation. Adipocyte, osteoblasts, and chondrocyte are all part of multilineage differentiation. The progression of osteoblast differentiation toward a mature cell phenotype will result in bone formation.

Lee et al., 2003a; Long et al., 2004; Okamoto et al., 2014; Shim et al., 2013; Tang et al., 2011; Yang & Karsenty, 2004). The discovery of new molecules, known as ncRNAs, that control transcription of osteoblast differentiation and function has recently opened up new avenues to understanding bone pathogenesis (Aurilia et al., 2021; Beermann et al., 2016). Thus, a better understanding of the regulatory mechanisms of osteoblast differentiation provides valuable opportunities for preventing or treating bone-related diseases.

This review looks at recent advances in the regulation of signaling and transcription in osteoblast differentiation. We also discuss about the utilization of these novel molecular players in this mechanism for future clinical applications.

Mesenchymal stem cells in osteoblast differentiation

Stem cells are cells with specific functions that can renew themselves, have varying potentials, and differentiate into multiple lineages. Mesenchymal stem cells (MSCs) are stem cells that develop from mesoderm (Ullah et al., 2015). MSCs were first isolated by Friedenstein et al. in the bone marrow and described as adherent cells capable of forming fibroblastic colonies (Friedenstein et al., 1970). Extensive MSC evaluations in recent decades have revealed that MSCs can be isolated from a variety of locations throughout the body. Furthermore, MSCs are multipotent due to their ability to differentiate into specific functional cells such as osteoblasts, adipocytes, or chondrocytes in response to specific factors and signaling cascades in the microenvironment (Knight & Hankenson, 2013; Pino et al., 2012). MSCs are also reported to be capable of expressing CD73, CD90, and CD105, as well as having a lack of expression of surface molecules CD11b, CD14, CD19, CD34, CD45, CD79α, and human leukocyte antigen-related D antigen (HLA-DR) (Hu et al., 2018). MSCs can be found in the bone compartment in the bone marrow, periosteum, and endosteum, as well as thin layers of connective tissue on the bone surface and the bone itself. They are also a major source of cellular renewal during bone repair. The capacity of MSCs to differentiate into functional osteoblasts is regulated by osteoblast-specific transcription factors that trigger osteoblast commitment and differentiation, as shown in Figure 1 (Capulli et al., 2014; Hu et al., 2018; Zhang, 2010). The roles of each essential transcription factor involved in osteoblast differentiation are shown in Table 1.

Osteoprogenitor cells

Osteoprogenitor cells (OPCs), also known as osteoblast progenitors (preosteoblasts), are bone stem cells that help with tissue formation and bone repair. OPCs are more common during bone development and can activate a multifunctional stage for bone reconstruction. OPCs can be found in the endosteum, the periosteum's cellular layer, and the osteogenic cell layer (Nahian & Davis, 2021). A large number of OPCs can also be found in bone marrow stromal cells, which are multidirectional. Periosteum and bone marrow-derived osteoprogenitors differentiate directly into osteogenic bone without involving other inducers. These properties of OPCs are known as determined OPCs (DOPCs). While OPCs are found only in pathological situations, such as heterotopic ossification and fracture repair, they are derived from undifferentiated mesenchymal cells found throughout the body. These OPCs can differentiate into osteoblasts via cartilage osteogenesis, hence the name osteoprogenitor-induced OPCs (Qiu et al., 2019). Alpha smooth muscle actin (αSMA) has recently been identified as a marker of OPCs in bone and periodontium, as well as a progenitor of osteochondral in the periosteum that contributes to fracture healing (Matthews et al., 2014). SMA-expressing osteoprogenitors have also been proven to improve site-specific periosteal osteoblast differentiation induced by mechanical loading (Matthews et al., 2020).

OPCs have been shown to divide, propagate, and differentiate further into functionally specialized cells. The majority of OPCs differentiate as osteoblasts during bone development. OPCs attach to the bone surface and are known as inactive osteoblasts

Table 1. Essential transcription factors in osteoblast differentiation.

No.	Transcription factors	Role	Model		References
			In vivo	In vitro	
1.	Runx2	Regulates osteoprogenitor proliferation and functions as a master switch in the induction of osteoblast differentiation.	Knockout of Runx2 causes osteoblast and oscillation defects and inhibits chondrocyte maturation.	Knockout of Runx2 causes an increased proliferation of osteoblast progenitors.	Kawane et al., 2018; Komori, 2019
2.	Osx	Promotes the differentiation of preosteoblasts into osteoblasts, the maturation and function of osteocytes, and cartilage resorption.	Osx inactivation leads to the cessation of osteoblast differentiation and new bone formation.	Silencing Osx decreases the regulation of Col-X expression, Dlx5, and ALP.	Zhang et al. 2008a; Zhou et al., 2010; Martin et al., 2011; Omoteyama & Takagi, 2010
3.	Dlx5	Promotes osteoblast proliferation and differentiation, and is involved in the later stages of osteogenesis.	Dlx5-null showed a significant decrease in bone volume, proliferation and differentiation of osteoblasts, and potentially induced osteoclastogenesis.	Dlx5 is a direct transcription activator of Runx2.	Holleville et al., 2007; Samee et al., 2008
4.	β-catenin	An important component in canonical Wnt signaling.	The knockdown of β-catenin inhibits osteoblast differentiation and induces chondrocyte differentiation.	Cells with low β-catenin activity enter the chondrocyte lineage.	Day et al., 2005; Hill et al., 2005
5.	ATF4	Regulates terminal osteoblast differentiation as well as chondrocyte proliferation and differentiation during skeletal development.	Ablation of ATF4 causes growth defects and osteogenesis as well as a reduction in bone mass. ATF4 deficiency causes delayed bone formation during embryonic development and low postnatal bone mass.	Knockout of ATF4 shows severe cell proliferative defects and increases cell apoptosis.	Yang et al., 2004; Yang & Karsenty, 2004; Wang et al., 2009; Zhang et al., 2008b; Zhang et al., 2019
6.	Ihh	Promotes MSC differentiation and is involved in bone formation.	Ihh deficiency causes decreased proliferation and maturation of chondrocytes as well as failure of osteoblast development in endochondral bone.	Knockdown of Ihh causes inhibition of osteoblast growth, increased apoptosis, termination of the cell cycle, decreased ALP activity and deposition of osteoblast minerals.	Nakamura et al., 1997; Deng et al., 2017; Long et al., 2004; Wang et al., 2012; Yang et al., 2015
7.	Satb2	Multifunctional determinants of craniofacial pattern and osteoblast differentiation.	Knockout of Satb2 causes craniofacial disability as well as defects in differentiation and function of osteoblasts. Double heterozygous mutants, Satb2/Runx2 and Satb2/ATF4, showed defects in bone formation.	Knockout of Satb2 shows a decrease in BSP and OCN regulation.	Dobreva et al., 2006; Mouillé et al., 2022
8.	Shn3	Negative regulator of Runx2.	Knockout of Shn3 causes an increase in bone time phenotype and bone formation.	Knockout of Shn3 causes an increase in the number of terminalized nodules as well as the expression of BSP, OCN, Osx, and ATF4.	Jones et al., 2006
9.	Twist1	Inhibits osteoblast differentiation.	Twist-1 hypoinsufficiency causes Saethre-Chotxen syndrome.	Twist-1 haploinsufficiency leads to increased regulation of osteogenic markers, including ALP and COL1A1.	Bialek et al., 2004; Quarto et al., 2015; Zhang et al., 2014

Col-X, X-type collagen.

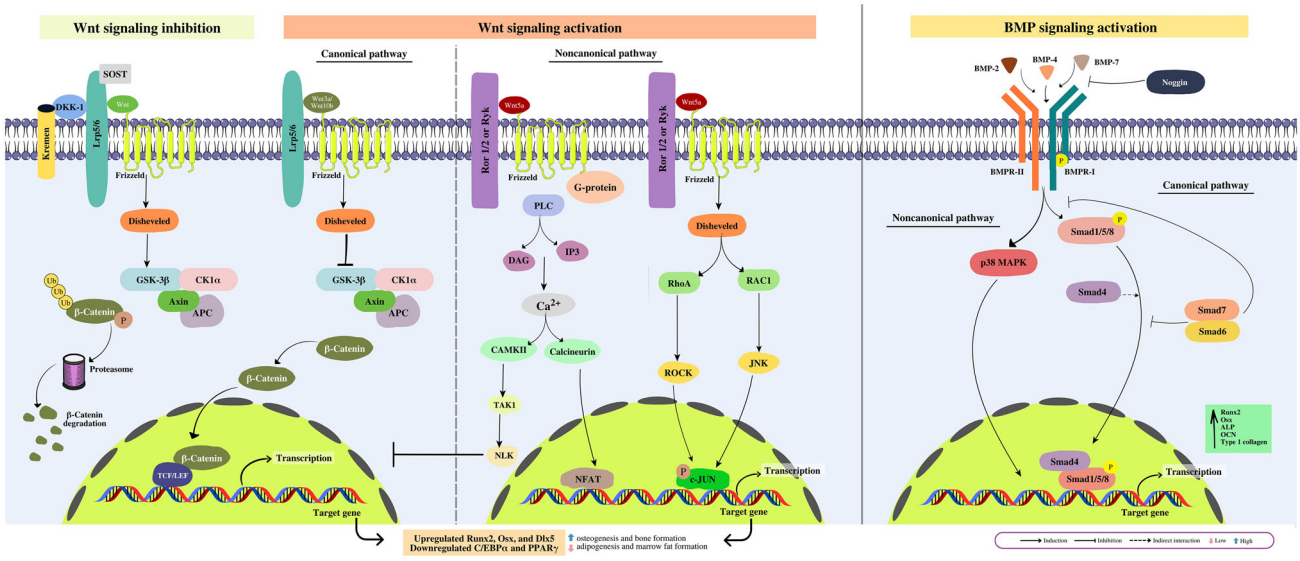

Figure 2. The Wnt and BMP signaling cascades. Both can be activated via canonical and noncanonical pathways, causing osteoblastic transcription factors to be expressed.

in mature bone (Qiu et al., 2019). The recruitment of OPCs initiates the process of new bone formation via a complex and highly regulated interaction between signaling from the systemic and local biomechanical and biophysical environments. This signaling regulates the activation and maturation of OPCs into osteoblasts, which produce and form the extracellular bone matrix (Ibrahim et al., 2016). Age can have a significant impact on OPC regenerative capacity. The accumulation of marrow adipose tissue (MAT) in the bone marrow cavity due to aging contributes to a pathological process that interferes with the maintenance of proper bone tissue repair and the hematopoietic system, increasing the risk of fractures and complications (Ambrosi et al., 2017). Furthermore, estrogen deficiency contributes to increased bone resorption, which results in bone loss (Manolagas, 2000; Syed et al., 2008). The estrogen receptor α (ERα) in osteoblast progenitors has been shown to promote bone formation on the cortex's periosteal surface and prevent resorption on the endocortical surface (Almeida et al., 2013).

Several studies utilizing OPCs as therapy for bone defects have been developed due to their promising role in bone development and healing. Autogenous OPC transplantation into a porous calcium phosphate scaffold can improve mandibular segmental defect repair (Schliephake et al., 2001). In another study, exogenous murine MC3T3-E1 OPCs with a high propensity for osteoblast differentiation demonstrated the ability to migrate systemically to the femoral bone defect and accelerate bone healing (Gibon et al., 2012). Thus, additional research on this topic may provide a potential therapeutic alternative for bone repair in clinical practice.

Osteoblasts

Osteoblasts are mononuclear cuboid cells derived from OPCs in the bone marrow that differentiate from MSCs. Osteoblasts are responsible for bone formation. This cell is distinguished from mesenchymal progenitor cells at the site of membrane and endochondral bone formation (Kobayashi et al., 2008; Ponzetti & Rucci, 2021). Osteoblasts occupy 4–6% of the total resident cells in bone and play an important role in the fulfilment and maintenance of bone mass along with osteoclasts and osteocytes. In addition, osteoblasts can also differentiate into osteocytes (Capulli et al., 2014; Rutkovskiy et al., 2016). Osteoblasts can site and secrete bone matrix and contribute to bone mineralization to regulate the balance of calcium and phosphate ions in bone formation. Once the OPCs differentiate into osteoblasts, they will be followed by the secretion of collagen I to form osteoid, followed by the precipitation of calcium and phosphorus salts from the blood by osteoblasts and the formation of bonds with osteoid for the mineralization of bone tissue. Furthermore, the presence of estrogen receptors in osteoblasts promotes an increase in the number of osteoblasts, which leads to an increase in collagen production. ALP, an enzyme involved in bone mineralization and an early marker of osteoblast differentiation, is also produced by osteoblasts. Increased ALP expression is associated with osteoblast differentiation (Bassi et al., 2011).

The key role of signalling pathways in osteoblast differentiation

The differentiation of osteoblasts from MSCs is triggered by the expression of specific genes, which are subsequently controlled by pro-osteogenic pathways. The wingless-related integration site (Wnt)/β-catenin and bone morphogenetic proteins (BMPs) pathways are the main pathways that play an important role in promoting MSC's commitment to osteo/chondroprogenitor cells in the initial steps of osteoblastogenesis. Figure 2 illustrates schematically how the Wnt and BMP signaling pathways regulate osteoblast differentiation.

Wnt signaling pathway in osteoblast differentiation

The wingless-related integration site (Wnt) signaling pathway is divided into two parts: a canonical pathway that mediates

signaling via β-catenin stabilization, which is involved in increased bone formation, and a noncanonical pathway that works independently of β-catenin, which plays a role in regulation of cell migration and polarity during embryogenesis (Kim et al., 2013; Nemoto et al., 2012). Canonical Wnt, such as Wnt3a and Wnt10b, binds to Frizzled (Fzd) and low-density lipoprotein receptor-associated protein 5/6 (Lrp5/6) to inhibit glycogen synthase kinase-3β (GSK-3β) activations, an enzyme that phosphorylates β-catenin, causing it to ubiquitinate and degrade. This inhibition induces the accumulation of β-catenin in the target cell, which results in translocation into the nucleus. β-catenin will initiate the transcription of the target gene through its interaction with members of the T-cell family factor/lymphoid enhancer factor (Tcf/Lef). Meanwhile, noncanonical Wnt, such as Wnt5a, binds to the Fzd, Ror1/2 or Ryk receptor complexes. In addition, some Wnt antagonists, such as dikkopf-1 (DKK-1), sclerostin (SOST), kremen, and others, can inhibit this signaling.

Multipotential cells, as previously stated, can differentiate into osteoblasts and adipocytes. The balance of adipogenic and osteoblastogenic components via Wnt/-β-catenin signaling is thought to be a determinant of the differences in outcomes of these mesenchymal precursor cells. Previous research has shown that ectopic expression of Wnt10b, a subfamily of the canonical Wnt pathway, suppresses the expression of adipogenic transcription factors CCAAT/enhancer-binding protein α (C/EBPα) and peroxisome proliferator-activated receptor γ (PPARγ) in ST2 cells. Following this condition, osteoblastogenic transcription factors are activated, as evidenced by increased regulation of Runx2, Osx, and Dlx5. Meanwhile, in Wnt10b-expressing ST2 cells, partially forced expression of C/EBPα or PPARγ promotes lipid accumulation while decreasing mineralization. Thus, in Wnt/β-catenin signaling, C/EBPα or PPARγ repression is required to direct precursor cells into osteoblasts (Kang et al., 2007).

Furthermore, Okamoto et al. (2014) stated that good bone formation requires cooperation between Wnt5a-induced noncanonical signaling, a subfamily of Wnt noncanonical pathways, and Wnt/β-catenin signaling. Wnt5a has also been implicated in osteoblast differentiation. Through upregulation of Lrp 5/6 expression in osteoblast cell lineages, Wnt5a can suppress PPARγ and increase Wnt/β-catenin signaling (Nemoto et al., 2012; Okamoto et al., 2014). Wnt5a deficiency in osteoblast lineage cells reduces Lrp5/6 expression, lowering the sensitivity of canonical Wnt ligands such as Wnt3a and Wnt10b. This condition interferes with osteoblast differentiation while increasing adipocyte differentiation (Okamoto et al., 2014). TAZ, a Hippo pathway transcription factor, is also known to induce osteoblastogenesis and suppress canonical Wnt signaling semiconductor adipogenesis (Okamoto et al., 2014; Zarka et al., 2022). Thus, during osteoblast differentiation, Wnt5a can play a role in increasing Wnt/β-catenin and Wnt/TAZ signaling by upregulating Lrp5/6 (Okamoto et al., 2014). The receptor tyrosine kinase-like orphan receptor 2 (Ror2) has been known as the Wnt5a receptor or co-receptor. Nemoto et al. (2012) has proven that the Wnt5a/Ror2 signaling pathway is involved in BMP-2-mediated osteoblast differentiation in Smad-independent pathways. The suppression of Wnt5a/Ror2 expression resulted in the suppression of osteoblast differentiation marker gene expression, specifically ALP and OCN, induced by BMP-2 (Nemoto et al., 2012).

BMP signaling in osteoblast differentiation

BMPs are members of the transforming growth factor β (TGF-β) superfamily that play a role in regulating osteoblast differentiation and inducing bone formation. During development, genetic interventions in the BMP gene cause a variety of extracellular and bone abnormalities (Kim et al., 2017). BMP signaling is mediated by BMP receptors type I (BMPR-I) and type II (BMPR-II) (BMPR-II). Both are serine-threonine receptors that are required for BMP signaling. BMPR-I is consisting of three receptors: BMPR type IA (BMPR-IA), which binds BMP-2 and BMP-4 efficiently; BMPR type IB (BMPR-IB), which binds BMP-4 and BMP-7 efficiently; and activin type I receptor (ActRI), which binds activins, proteins from TGF-β/BMP family members, and BMP-7 (Nohno et al., 1995; Chen et al., 2012). Meanwhile, type II receptors include BMPR-II, which binds to BMP-4 and BMP-7, and activin type II receptors (ActR-II) and ActR-IIb, which bind to activin and BMP-7 (Rosenzweig et al., 1995; Yamaguchi et al., 2008). Unlike the TGF-β receptor, BMPR-I binds BMP directly without the involvement of BMPR-II, which only binds BMPR-I on the extracellular N-terminus. Furthermore, BMPR-I has a GS domain, which is a cytoplasmic juxta-membrane area made up of glycine and serine that serves as a site for phosphorylation of serine and threonine after the receptor binds to a ligand, activating BMPR-II. This dynamic interaction directs downstream BMP signals via BMP-specific Smad (Smad 1, 5, or 8) or p38 MAPK. Activated receptor kinases, in collaboration with other co-factors, regulate the transcription of specific target genes by forming heterodimeric complexes with nuclear Smad4 (Kim et al., 2017; Chen et al., 2012; Yamaguchi et al., 2008).

Based on its role, BMP-2 has been proven to promote the expression of Runx2, Osx, and osteoblast differentiation markers (ALP, OCN, and type I collagen) in a variety of cells (Yamaguchi et al., 2008 ; Ogasawara et al., 2004). Furthermore, BMP-2 and BMP-4 are involved in the formation of bone nodules (Wada et al., 1998). The application of recombinant human bone morphogenetic protein-2 (rhBMP-2) therapy has shown promising results both preclinically and clinically. rhBMP-2 has the ability to stimulate bone repair and regeneration (Chen et al., 2012; Ueyama et al., 2021). BMP-7 is well-known for its osteogenic activity (Chen et al., 2019; Lavery et al., 2009). It was recently discovered that immature BMP-7, also known as bone-forming peptide-2 (BFP-2), has higher osteogenic activity than mature BMP-7 and induces bone formation in vitro and in vivo (Kim et al., 2017).

The osteoblast differentiation regulation, essential transcription factors involved, and their links

The osteoblast differentiation begins with the commitment of MSCs into osteoblast lineage progenitor cells, later known as preosteoblasts. Preosteoblasts then undergo proliferation,

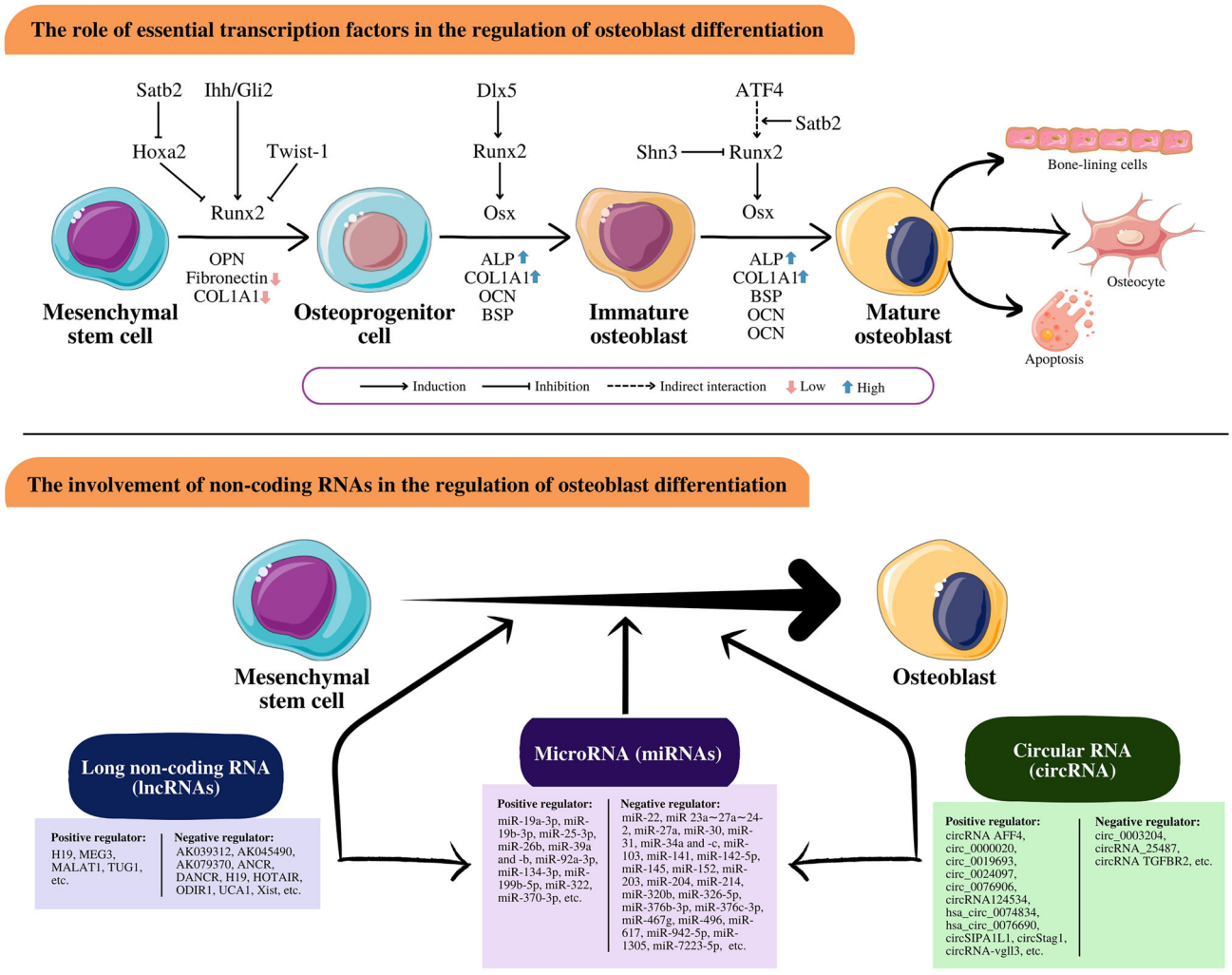

Figure 3. Regulation of osteoblast differentiation by essential transcription factors. ncRNAs (miRNAs, lncRNAs, and circRNAs) are novel players that can influence the molecular regulation of osteoblast differentiation by targeting essential transcription factors.

extracellular matrix (ECM) secretion, matrix maturation, and matrix mineralization, which are complexly regulated by various transcription factors (Figure 3). Runx2 is a transcription factor that is required for osteoprogenitor proliferation and osteoblast differentiation. Runx2 expression is known to be low in MSCs, but it increases throughout cell proliferation and then decreases in maturing osteoblasts. Regulation of Runx2 expression in osteoprogenitors requires Ihh at the stage of MSC's commitment formation into preosteoblasts (Amarasekara et al., 2021; Nakashima & De Crombrugghe, 2003; Shimoyama et al., 2007). In this regard, the upstream of Runx2 is involved in controlling the early stages of osteoblast differentiation, including Twist-1 and Satb2. Twist-1, through its physical interaction with Runx2, functions as a switch that blocks Runx2 function, delaying osteoblast differentiation and preventing premature osteoblast formation. Twist-1 expression is also downregulated when osteogenesis begins. Satb2 regulates the expression of BSP and OCN, the osteoblast-forming components during the cell differentiation phase, as well as inhibiting Hoxa2, a bone formation-inhibiting gene (Bialek et al., 2004; Liu & Lee, 2013). Following cell commitment, preosteoblasts proliferate and express OPN, fibronectin, collagen, and TGF-β1 receptors (Rutkovskiy et al. 2016). The proliferation phase is regulated in order to induce maturation during osteogenesis (Vimalraj et al., 2015). Runx2 expression is still increasing at this stage, promoting Osx to mediate osteoblast commitment and differentiation. Moreover, Dlx5 is present to aid in early osteoblast differentiation and advanced stages of osteogenesis. Dlx5 has been shown to influence the expression of Osx, ALP, OCN, and BSP (Holleville et al., 2007; Samee et al., 2008). Following the proliferation phase, the formed osteoblasts begin to express the bone matrix protein gene at various levels depending on cell maturation. ATF4 is also involved in indirect interactions with Runx2 during cell maturation to increase OCN expression, a marker of terminal osteoblast differentiation (Xiao et al., 2005). Along with this, Satb2 also acts as a mediator to increase the synergy of both actions (Dobreva et al., 2006). Mature osteoblasts secrete COL1A1, a key component of ECM, as well as ALP, which aids in ECM maturation. This process is then followed by matrix mineralization. This step is triggered after osteoblasts

Table 2. Essential osteoblastic markers.

No.	Marker	Role	References
1.	ALP	ECM maturation.	Stein and Lian, 1993
2.	BSP-II	Promotes mineralization by regulating the formation of hydroxyapatite crystals.	Gordon et al., 2007; Kim et al., 1994; Lin et al., 2020
3.	COL1A1	ECM main constituents.	Stein and Lian, 1993
4.	OCN	Terminal osteoblast differentiation markers, which regulate calcium metabolism and promote mineral deposition in ECMs.	Xiao et al., 2005
5.	OPN	Increases MSC proliferation capacity in a dose-dependent manner and promotes bone formation and mineralization.	Lin et al., 2020

bind to the existing matrix via integrin β1, forming a single layer that is linked to cadherin. Furthermore, cells secreted the matrix by expressing OPN, OCN, and BSP, as well as maintaining ALP and COL1A1 expression (Table 2) (Huang et al., 2007; Stein & Lian, 1993). Runx2 protein levels decreased at the end of this stage, which could be regulated by Shn3, an adapter that induces Runx2 degradation via ubiquitination (Jonason et al., 2009; Jones et al., 2006; Shim et al., 2013). Additionally, osteoblasts that have completed their roles in bone homeostasis will undergo apoptosis, becoming bone-lining cells, or terminally differentiate osteocytes (Nakashima & De Crombrugghe, 2003; Amarasekara et al., 2021).

The following are reviews of the essential transcription factors involved in osteoblast differentiation:

Runt-related transcription factor 2

Runt-related transcription factor 2 (Runx2) is a transcription factor that is required for osteogenesis and is responsible for activating osteoblast differentiation marker genes. Runx2 specifically increases the expression of osteoblastogenic markers such as ALP, BSP-II, collagen1α1 chain (CoL1A1), OCN, and OPN, which leads to osteoblast commitment (Vimalraj et al., 2015; Ponzetti & Rucci, 2021). Furthermore, Runx2 regulates osteoblast progenitor proliferation by inducing fibroblast growth factor receptor (Fgfr)-2 and Fgfr3 expression. Both promote proliferation by activating the mitogen-activated protein kinase (MAPK) pathway (Kawane et al., 2018; Komori, 2019).

Osterix

Osterix (Osx) or Sp7 is an osteoblast-specific transcription factor that is involved in preosteoblast differentiation into osteoblasts and bone formation. Osx has a proline-rich region (PRR) transactivation domain near the N-terminus of the protein and a three-type DNA binding domain C2H2 zinc finger near the C-terminus with motifs similar to Sp1, Sp3, and Sp4 (Zhang et al., 2008a). Osx may play a role in the bone microenvironment during osteogenesis (Liu et al., 2020). As a downstream of Runx2, Osx is expressed specifically in osteoblasts of all endochondral bones and membranes, as well as at low levels in pre-hypertrophic chondrocytes (Zhang et al., 2010; Tang et al., 2011). Zhou et al. (2010) demonstrated that inactivating Osx during and after birth resulted in the cessation of osteoblast differentiation and new bone formation in mice. Furthermore, Osx is required for cartilage resorption, maturation, and osteocyte function. During the bone formation, osteoblasts are known to store osteoid, which are unmineralized matrixes containing type I collagen. In this case, osteocytes participate in the osteoid mineralization process by regulating extracellular matrix mineralization and Fgf23 production by bone via Dmp1 and Phex, gene products that are highly expressed in normal osteoblasts and osteocytes (Martin et al., 2011; Zhou et al., 2010). Osteocyte anomalies in $Osx^{postnatal}$ mutants revealed defects in the mineralization process due to decreased Dmp1 and Phex expression. Furthermore, terminalized cartilage resorption also defects $Osx^{postnatal}$ mutants due to a significant decrease in osteoclast density (Zhou et al., 2010).

Distal-less homeobox 5

Distal-less homeobox 5 (Dlx5) is a proliferation and early osteoblast differentiation driver that also influences the later stages of osteogenesis. This transcription factor is expressed specifically in osteogenic lineage cells, such as chondroprogenitor cells (Samee et al., 2008). Dlx5 can induce osteoblast differentiation from endochondral and membrane oscillating bone (Erceg et al., 2003). Furthermore, in vitro studies have reported that Dlx5 acts as a direct transcription activator of Runx2 by binding to the P1 promoter, which is the transcriptional regulator of the Runx2-II isoform. Dlx5 expression is specifically induced by BMP signaling pathways such as BMP-2 or BMP-4 stimulation (Holleville et al., 2007; Samee et al., 2008). Earlier studies have shown that the Dlx5 modulation of osteoblast differentiation mediates Runx2 expression via BMP-2 stimulation (Lee et al., 2003a; Holleville et al., 2007). Dlx5 has also been shown to promote ALP and Osx via a Runx2-independent pathway. Osx expression was also reduced in $Dlx5^{-/-}$ osteoblast cultures (Holleville et al., 2007; Samee et al., 2008). Osx, as previously stated, is a downstream of Runx2 (Samee et al., 2008; Lee et al., 2003b). Moreover, Dlx5 directly controls OCN and BSP transcription in in vitro studies due to a significant decrease in $Dlx5^{-/-}$ osteoblast culture (Samee et al., 2008).

β-catenin

β-catenin is an important component that transduces canonical Wnt signaling to determine the direction of mesenchymal progenitor differentiation, regardless of regional location or oscillation mechanism. Activation of β-catenin leads to increase oscillation and suppression of chondrocyte formation. In the meantime, its inactivation inhibits osteoblast differentiation during intramembranous and endochondral ossification and promotes chondrocyte differentiation (Day et al., 2005; Hill et al., 2005; Hu et al., 2005). Furthermore, β-catenin/TCF1 has been shown to increase Runx2 promoter expression and activity, causing osteoprogenitor cells to differentiate into preosteoblasts. β-catenin, along with Osx, regulates the differentiation of preosteoblasts into immature osteoblasts (Gaur et al., 2005).

Activating transcription factor 4

Activating transcription factor 4 (ATF4) is a leucine basic zipper (bZip) transcription factor from the ATF/cAMP family response element-binding protein (CREB). The ATF4 gene appears to be expressed in variety of cells during development and embryonic life. However, the accumulation of ATF4 protein is strongly inversely related to its gene expression because ATF4 protein is degraded in most cells, except osteoblasts, via ubiquitination mediated by β-TrCP1, ligase ubiquitin E3 (Yang & Karsenty, 2004; Zhang et al., 2019). ATF4 is required for terminal osteoblast differentiation via OCN activation, as well as regulation of chondrocyte proliferation and differentiation during skeletal development via Ihh activation (Wang et al., 2009; Yang & Karsenty, 2004; Zhang et al., 2019). ATF4 ablation has been linked to severe osteopenia, impaired terminal osteoblast differentiation, and decreased OCN expression and type I collagen production in mice (Yang et al., 2004). Previous studies demonstrate that ATF4 acts as a specific activator of osteocalcin-specific element 1 (OSE1) in an RSK2-dependent manner, and that it indirectly associates with Runx2 to increase OCN expression, which eventually leads to terminal osteoblast differentiation (Xiao et al., 2005; Yang et al., 2004). Satb2 mediates the synergistic action of both. Transcription factor general IIag (TFIIAg) has also been reported to increase OCN expression via interactions with Runx2 and ATF4 (Dobreva et al., 2006; Yu et al., 2008). Furthermore, Tominaga et al. (2008) stated that CCAAT/enhancer-binding proteins (C/EBPs), a bZip protein family, are responsible for increasing OCN promoter activity via a heterodimeric bond with ATF4 on OSE1. C/EBPβ is expressed in osteoblastic cells, and its regulation becomes more active during osteoblast differentiation. This heterodimerization also facilitates it to collaborate with Runx2 (Tominaga et al., 2008). Xiao et al. (2005) demonstrated that the physical interaction between C/EBPβ and Runx2 promotes OCN promoter gene expression. Thus, C/EBPβ promotes the formation of complexes and associations between ATF4 and Runx2 in order to encourage OCN expression during terminal osteoblast differentiation (Tominaga et al., 2008). Moreover, ATF4 also plays a role in the regulation of chondrocyte proliferation and differentiation during skeletal formation by involving Ihh transcription and signaling. ATF4 overexpression in mutant chondrocytes restored osteoblastic marker gene (OCN and BSP) expression in developing bone, according to studies using the ATF4$^{-/-}$;COL2A1-ATF4 mouse model, in which ATF4 was expressed in chondrocytes selectively in an ATF4-null background. This is followed by correction of the bone elongation defect as well as improvement in decreased Ihh expression and Hh signaling. As a result, ATF4 is involved in the autonomic role of chondrocytes in growth plate development and may also be involved in osteogenesis regulation during postnatal bone development and remodeling (Wang et al., 2009, 2012).

Indian hedgehog

The transcription factor Indian hedgehog (Ihh) is a *Drosophila hedgehog* (Hh) mammalian homologue that is important for osteoblast differentiation and bone formation. Ihh acts as the primary regulator in the longitudinal growth and development of the endochondral skeleton. It is primarily expressed by peritrophic chondrocytes that have recently exited the cell cycle and send signals to proliferative chondrocytes to divide and perichondrial mesenchymal cells to differentiate into osteoblasts. The dysfunctional regulation of Hh signaling causes problems with bone homeostasis and development, as well as the onset of several bone diseases such as progressive heteroplasia and osseous dysplasia (Long et al., 2004; Wang et al., 2012; Yang et al., 2015). In vivo studies revealed that Ihh gene deficiency reduced chondrocyte proliferation and maturation, as well as failed osteoblast development in endochondral bone (St-Jacques et al., 1999). In an in vitro study using MC3T3-E1 osteoblast cells, Ihh expression increases ALP activity through cooperation with BMP-2 (Nakamura et al., 1997). Meanwhile, knocking out Ihh causes an increase in apoptosis, cell cycle termination in the G1 to S phases in osteoblasts, as well as a decrease in ALP activity and osteoblast mineral deposition, which are associated with the TGF-β/Smad and OPG/RANKL signaling pathways (Deng et al., 2017). Furthermore, Hh proteins, including Ihh, exert biological effects via their receptor components, patched (PTCH) and smoothened (Smo). Ihh binding to PTCH activates Smo and transduces signals in the cytoplasm via the fusion of intracellular signal molecules and transcription factors from the Gli family with the zinc finger domain. Gli2 and Gli3 are direct Ihh signaling mediators. Ihh/Gli2 signaling promotes mesenchymal cell differentiation in osteoblastogenesis by regulating expression and stimulating Runx2 osteoblastogenic function. Gli2 physically increases Runx2 expression and Runx2 osteogenic activity (Shimoyama et al., 2007). Meanwhile, Gli3 functions as a transcriptional repressor of the Hh target gene (Hilton et al., 2005).

Special at-rich sequence binding protein 2

Special AT-rich sequence binding protein 2 (Satb2) is a gene derived from a family of special AT-rich binding proteins that bind nuclear matrix attachment regions (MARs), an AT-rich

DNA sequence involved in gene transcription regulation. MAR affects the organization of eukaryotic chromosomes by structurally defining the boundary of the chromatin domain and increasing the ability of enhancers to work over long distances. Satb2 is known to be located in the poor region of the 2q32-q33 gene, and its coding transcript consists of 11 exons and 191 kb of genomic DNA (FitzPatrick et al., 2003; Dobreva et al., 2006). Satb2 is thought to increase expression of gene differentiation-specific type cells by regulating chromatin recurrence in MAR (Dobreva et al., 2006). Satb2 has been proven to be a multifunctional determinant of craniofacial pattern and osteoblast differentiation. Activation of Satb2 by Osx overexpression is responsible for MSC differentiation into osteoblasts by targeting inhibition of several Hox genes (Hoxa13, Hoxa2, and Hoxb2) in osteoblasts. Hox is a gene that regulates branchial arch patterns by directly recognizing MAR-like sequences (Dobreva et al., 2006; Mouillé et al., 2022). Furthermore, Satb2 also targets BSP as an initial marker for osteoblast differentiation and OCN as a terminal marker for osteoblast differentiation (Dobreva et al., 2006). BSP is the main structural protein of the bone matrix that promotes osteoblast differentiation and thus increases the production of terminalized matrix (Gordon et al., 2007; Kim et al., 1994). Satb2 directly binds to the BSP promoter region associated with the three osteoblast-specific element sequences, according to ChIP and EMSA analysis of fully-differentiated osteoblasts (Dobreva et al., 2006; Kim et al., 1994). Meanwhile, OCN, which is involved in bone matrix mineralization, is the second most abundant protein in bone after collagen. OCN is highly expressed in matured osteoblasts, which initiate the bone formation (Li et al., 2016; Rutkovskiy et al., 2016). Existing literature has shown that Runx2 and ATF4, transcription factors that promote mineralization at different stages of the bone formation process, play a role in OCN regulation. In their functional synergy, Runx2 and ATF4 have indirect interactions. Satb2 acts as a synergistic activation mediator of Runx2 and ATF4 in this regard because double heterozygous mutant mice, Satb2/Runx2 and Satb2/ATF4, showed defects in bone formation. Thus, Satb2 physically interacts with Runx2 and ATF4, increasing their transactivation function; incorporates the specific-transcription factor at the OCN promoter, encouraging OCN expression indirectly (Bidwell et al., 1993; Dobreva et al., 2006; Ducy & Karsenty, 1995).

Schnurri-3

Schnurri-3 (Shn3) is a large zinc finger protein that plays an important role in embryogenesis as a cofactor for Decapentaplegic signaling (Dpp), a Drosophila homolog of the BMP/TGF-β signaling pathway. Shn3 is one of three Drosophila Shn mammalian homologs that act as essential regulators of bone formation, regulating osteoblast activity (Jones et al., 2006). Shn3 knockout mice had a higher bone tenure phenotype due to increased synthetic osteoblast activity and bone formation. In osteoblasts, a multimeric complex composed of Runx2, Shn3, and the Nedd4 family's E3 ubiquitin ligase WWP1 can inhibit Runx2 function. This is because Shn3 promotes Runx2 poly-ubiquitination and proteasome-dependent degradation via WWP1. Therefore, the absence of Shn3 in osteoblasts causes an increase in Runx2 protein levels, followed by an increase in Runx2 transcriptional activity and target gene, which increases extracellular matrix mineralization during the bone formation process (Jones et al., 2006). Furthermore, Shn3 mediates interaction and inhibition of ERK activity in the Wnt signaling pathway in osteoblasts. In vivo studies revealed that knockout in this section causes abnormal ERK activation, resulting in osteoblast hyperactivity and bone development problems (Shim et al., 2013).

Twist-associated protein 1

Twist-related protein 1 (Twist-1) is a basic helix-loop-helix (bHLH) transcription factor that acts as an anti-osteogenic and osteogenesis initiator (Komaki et al., 2007; Lee et al., 1999; Zhang et al., 2014). In humans and mice, heterozygous loss of Twist-1 functions causes Saethre-Chotxen syndrome, which is characterized by craniosynostosis, a condition caused by premature osteoblast differentiation in the skull (Quarto et al., 2015). Twist-1 has been shown to suppress osteoblast differentiation by inhibiting Runx2 function. The decreasing Twist-1 gene expression triggers osteoblast differentiation through increased expression of Runx2 downstream in vivo. Twist-1 overexpression also inhibits osteoblast differentiation while having no effect on Runx2 expression (Bialek et al., 2004; Zhang et al., 2014). Similar to Runx2, Twist-1 also inhibits ATF4 function without interfering with ATF4 protein levels (Danciu et al., 2012). In vitro experiments with C3H10T1/2 cells revealed that decreased Twist-1 gene expression resulted in increased ALP and COL1A1 expression. Moreover, Twist-1 has been shown to modulate Fgfr2 expression, activating ERK1/2 and PI3K signaling during osteoblastogenesis (Guenou et al., 2005; Miraoui et al., 2010). Twist-1 and Twist-2 haploinsufficient mouse models revealed that hereditary expression of Fgfr2 and Fgfr1-4 causes a decrease in bone formation, proliferative disorders, and osteoprogenitor differentiation (Huang et al., 2014).

Noncoding RNAs and their interplay with essential transcription factors: an advanced regulation concept for osteoblast differentiation

Noncoding RNAs (ncRNAs) are functional RNA molecules that do not have the ability to encode proteins, so they were initially considered 'evolutionary garbage'. However, emerging evidence has established the role of ncRNAs as potent and multifunctional regulators in all biological processes, including transcriptional regulation of osteoblast differentiation (Beermann et al., 2016; Aurilia et al., 2021). In parallel, these studies have discovered an association between ncRNA expression and disease progression in humans, including bone-related diseases. MicroRNAs (miRNAs), small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and other ncRNAs have been identified due to advances in RNA-Seq

Table 3. miRNAs involved in osteoblast differentiation regulation.

No.	miRNAs	Therapeutic prospects	Roles	References
1.	miR 23a–27a–24-2	Bone formation	Inhibits bone formation by targeting Runx2 and Satb2.	Hassan et al., 2010
2.	miR-39a and -b	Bone loss	Promotes osteoblast differentiation by decreasing the expression of Wnt signaling antagonists (DKK-1, Kremen2, and sFRP2) and AKT/β-catenin (PTEN).	Kapinas et al., 2010; Xia et al., 2020
3.	miR-214	Osteoporosis	Inhibits osteoblast differentiation by targeting ATF4.	Wang et al., 2013
4.	miR-34b and -c	Skeletogenesis (embryogenesis and postnatally)	Inhibits osteoblast terminal differentiation by targeting Satb2.	Wei et al., 2012
5.	miR-31	Bone formation	Inhibits osteoblast differentiation by reversing Osx expression and suppressing the level of the Satb2 protein.	Baglìo et al., 2013; Deng et al., 2013; Xie et al., 2014
6.	miR-322	Bone formation	Enhances BMP-2 response and Osx expression by targeting Tob2.	Gámez et al., 2013
7.	miR-203 and miR-320b	Bone formation	Inhibits BMP-2 stimulates osteoblast differentiation by targeting Dlx5, which inhibits the roles of Runx2 and Osx.	Laxman et al., 2016
8.	miR-27a	Bone formation	Inhibits Osx expression and attenuates Satb2-induced osteoblast differentiation.	Gong et al., 2016
9.	miR-467g	Bone formation	Inhibits osteoblast differentiation by targeting Runx2 and Ihh signaling.	Kureel et al., 2017
10.	miR-376c-3p	Skeletal abnormalities	Inhibits osteoblast proliferation and differentiation through Twist-1 regulation.	Camp et al., 2018
11.	miR-145	Adolescent idiopathic scoliosis	Disrupt osteoblast and osteocyte function through upregulation of β-catenin expression.	Zhang et al., 2018
12.	miR-26b	Osteoporosis and osteoarthritis	Promotes osteoblast differentiation by regulating β-catenin.	Hu et al., 2019; Yang et al., 2022
13.	miR-103	Osteoporosis	Inhibits osteoblast proliferation and differentiation by targeting Satb2.	Lv et al., 2020
14.	miR-92a-3p	Fracture healing	Inhibits IBSP expression and promotes osteoblast differentiation via the PI3K/AKT signaling pathway.	Hu et al., 2021

sFRP2, secreted frizzled related protein 2; PTEN, phosphatase and tensin homolog; IBSP, integrin binding sialoprotein.

(Lekka & Hall, 2018; Li et al., 2020, 2021). Here, we will discuss three ncRNAs that have been hot topics in the development of new therapeutic targets for bone-related diseases: miRNA, lncRNA, and circRNA. Figure 3 depicts the involvement of these ncRNAs in osteoblast differentiation.

MicroRNA

MicroRNAs (miRNAs) are a type of short noncoding RNA that contains 20–22 nucleotides. MiRNAs do not encode proteins, but they do regulate the levels of other proteins, particularly at the post-transcriptional level, by lowering messenger RNA (mRNA) levels or inhibiting translation by binding to the 3'UTR of the target mRNA (Inose et al., 2009; Wang et al., 2020). Interestingly, Davis and Hata (2009) reported that miRNAs regulate approximately one-third of human genes. Evidence of miRNA involvement in regulating osteoblast differentiation and bone formation has been studied continuously over the last two decades. Wnt and BMP are the main signaling pathways in osteoblast differentiation, as previously described, and miRNAs have been shown to target both.

Understanding the role of miRNAs in osteoblastogenesis will provide important therapeutic insights. Previous research has found that miRNAs play a role in the regulation of osteoblast differentiation (Table 3). Several miRNAs, including miR-322, miR-27a, miR-26b, and miRNA-92a-3p, act as positive regulators of osteoblast differentiation. MiR 23a27a24-2, miR-214, miR-34b and -c, miR-31, miR-203, miR-320b, miR-467g, miR-376c-3p, miR-145, and miR-103 are examples of negative regulators.

Long noncoding RNA

Long noncoding (lnc) RNA (lncRNAs) is a diverse class of transcripts that is 200–10,000 nucleotides longer than other types of ncRNAs (Nardocci et al., 2018; Silva et al., 2019). This type of ncRNA is widely transcribed in the nucleus by RNA polymerase II via 5′ capping, 3′ poly-A tail addition, and RNA splicing (Aurilia et al., 2021). LncRNAs are poorly conserved among mammalian species but play critical roles in transcriptional and post-transcriptional regulation, mRNA translation control, and chromatin structure regulation (Nardocci et al., 2018). Furthermore, lncRNAs can act as endogenous RNAs (ceRNAs) for miRNA 'sponges' and influence miRNA expression, thereby reducing the regulatory effect of miRNAs on miRNA targets (Thomson & Dinger, 2016; Xiao et al., 2017).

Unlike miRNAs, lncRNAs can be folded into complex secondary and higher-order structures to improve target recognition (Huang et al., 2015). These findings point to their role in the emergence and development of a disease. Several recent studies have found that lncRNAs play a role in osteoblast differentiation and act as ceRNAs targeting downstream miRNAs (Table 4). H19, TUG1, MEG3, and MALAT1 are lncRNAs that act as positive regulators of osteoblast differentiation. H19, ANCR, ODIR1, AK045490, HOTAIR, UCA1, Xist,

Table 4. lncRNAs involved in osteoblast differentiation regulation.

No.	lncRNAs	Roles	ceRNAs	Effects	Therapeutic prospects	References
1.	lncRNA H19	• Positive regulator of osteoblast differentiation by negatively regulates TGF-β1 with miR-675, thus increased Runx2 expression. • H19 is negatively regulated by miR-675-5p via the formation of a feedback loop.	miR-141 and miR-22	Causes target gene depression in conjunction with β-catenin, thereby activating the Wnt/β-catenin pathway and promoting osteoblast differentiation.	Osteoporosis	Huang et al., 2015; Liang et al., 2016
		Negative regulator of osteoblast differentiation.	miR-19b-3p	Reduces the expression of Runx2 and COL1A1, as well as ALP activity	PMOP	Xiaoling et al., 2020
2.	lncRNA ANCR	Negative regulator of osteoblast differentiation.	Not mentioned.	Inhibits both Runx2 expression and osteogenesis by interacting with enhancer of zeste homolog 2 (EZH2).	PMOP	Cai et al., 2019
3.	lncRNA ODIR1	Negative regulator of osteogenic differentiation.	Not mentioned.	Causes a reduction in Osx expression.	Bone formation	He et al., 2019
4.	lncRNA AK045490	Negative regulator of osteoblast differentiation.	Not mentioned.	Inhibits β-catenin nuclear translocation and downregulates the expression of TCF1, LEF1, and Runx2.	Osteoporosis	Li et al., 2019a
5.	lncRNA MEG3	Positive regulator of osteoblast differentiation.	Not mentioned.	Activating the Wnt/β-catenin signaling pathway.	Fracture healing	Li et al., 2019b
6.	lncRNA MALAT1	Positive regulator of osteoblast differentiation	miR-204	Upregulating Smad4, thereby promotes the expression of ALP, OCN, and the formation of mineralized bone matrix.	CAVD	Yi et al., 2019; Xiao et al., 2017
			miR-30	Increases OCN, OPN, and Osx expression through Runx2 mediation.	Bone formation	
7.	lncRNA TUG1	Positive regulator of osteoblast differentiation.	Not mentioned.	Activating the Wnt/β-catenin signaling pathway.	Osteoporosis	Liu et al., 2019
8.	lncRNA HOTAIR	Negative regulator of osteoblast differentiation and bone formation.	Not mentioned.	Suppresses the activity of Wnt/β-catenin signaling pathway.	Osteoporosis	Shen et al., 2019
9.	lncRNA UCA1	Negative regulator of osteoblast differentiation.	Not mentioned.	Suppresses the expression of Runx2, Osx, COL1A1, OPN, osteoprotegerin (OPG), and osteoclasts by inhibiting BMP-2/(Smad1/5/8) signaling pathway.	Osteoporosis	Zhang et al., 2019
10.	lncRNA Xist	Negative regulator of osteoblast differentiation.	miR-19a-3p	Reducing the expression of Runx2 and COL1A1, as well as ALP activity.	Osteoporosis	Chen et al., 2020
11.	lncRNA DANCR	• Negative regulator of osteoblast differentiation. • miR-320a, in conjunction with DANCR, has an additive inhibitory effect.	Not mentioned.	Directly inhibits CTNNB1, the gene encoding β-catenin, lowering TCF-1, Runx2, ALP, OCN, and OPN expression.	Osteoporosis	Wang et al., 2020
12.	lncRNA AK039312 and AK079370	Negative regulator of osteoblast differentiation.	miR-199b-5p	Inhibits the osteogenic transcription factor TCF7/LEF1, which causes an increase in GSK-3, a Wnt/β-catenin pathway inhibitor.	Osteoporosis	Yin et al., 2021

ANCR, anti-differentiation noncoding RNA; ODIR1, osteogenic differentiation inhibitory regulator 1; TUG1, taurine up-regulated gene 1; HOTAIR, HOX transcript antisense RNA; UCA1, urothelial carcinoma associated 1; DANCR, differentiation antagonizing nonprotein coding RNA; PMOP, postmenopausal osteoporosis; CAVD, calcific aortic valve disease.

Table 5. circRNAs involved in osteoblast differentiation regulation.

No.	circRNAs	Roles	ceRNAs	Effects	Therapeutic prospects	References
1.	circRNA AFF4	Positive regulator of osteoblast differentiation.	miR-7223-5p	Activating the PI3K-AKT signaling pathway.	Fracture healing	Mi et al., 2019
2.	hsa_circ_0074834	Positive regulator of osteoblast differentiation.	miR-942-5p	Promotes osteoblast differentiation and repair of bone defects.	Bone nonunion	Ouyang et al., 2019
3.	circSIPA1L1	Positive regulator of osteoblast differentiation.	miR-617	Promotes osteogenesis by targeting Smad3.	Bone defect	Ge et al., 2020
4.	hsa_circ_0076690	Positive regulator of osteoblast differentiation.	miR-152	Enhances osteoblast differentiation by targeting Runx2.	Osteoporosis	Han et al., 2020
5.	circ_0024097	Positive regulator of osteoblast differentiation.	miR-376b-3p	Activating the Wnt/β-catenin signaling pathway by targeting YAP1	Osteoporosis	Huang et al., 2020
6.	circRNA124534	Positive regulator of osteoblast differentiation.	miR-496	Modulates osteoblast differentiation by engaging the Wnt/β-catenin signaling pathway.	Bone formation	Ji et al., 2020
7.	circ_0076906	Positive regulator of osteoblast differentiation.	miR-1305	Promotes osteoblast differentiation by competing with OGN, resulting in increased Runx2 and OCN expression.	Osteoporosis	Wen et al., 2020
8.	circRNA_25487	Negative regulator of osteoblast differentiation.	miR-134-3p	Inhibits bone repair by upregulating p21 expression.	TIONFH	Zhang et al., 2020
9.	circRNA TGFBR2	Negative regulator of osteoblast differentiation.	miR-25-3p	Positively regulates Twist1, which inhibits the formation of calcified nodules, ALP activity, as well as Runx2 and OPN expression.	CAVD	Yu et al., 2021
10.	circRNA-vgll3	Positive regulator of osteoblast differentiation.	miR-326-5p	Promotes osteoblast differentiation of ADSCs via Itga5.	Nonhealing bone defects	Zhang et al., 2021
11.	circ_0000020	Positive regulator of osteoblast differentiation.	miR-142-5p	Regulates BMP2 expression, thereby increasing the expression of Runx2, Osx, OCN, OPN, ALP activity, and mineral accumulation.	Osteoporosis	Zhou et al., 2021
12.	circStag1	Positive regulator of osteoblast differentiation.	Not mentioned.	Regulated HuR-mediated Wnt signaling.	PMOP	Chen et al., 2022
13.	circ_0019693	• Positive regulator of osteoblast differentiation. • Circ_0019693 overexpression increases ALP activity, RUNX2, OPN and OCN expression, and promotes angiogenesis.	miR-942-5p	Regulates PCP4.	Osteoporosis	He et al., 2022
14.	circ_0003204	Negative regulator of osteoblast differentiation.	miR-370-3p	Inhibits osteoblast differentiation by promoting HDAC4 expression.	Bone defect	Yu et al., 2022

YAP1, yes-associated protein 1; OGN, osteoglycin; TONFH, trauma-induced osteonecrosis of femoral head; PMOP, postmenopausal osteoporosis; CAVD, calcific aortic valve disease; TGFBR, transforming growth factor beta receptor 2; Itga5, integrin 5; HuR, human antigen R; PCP4, purkinje cell protein 4.

DANCR, AK039312, and AK079370 are examples of negative regulators.

Circular RNA

Circular RNAs (circRNAs) are a type of ncRNA that is being studied extensively as therapeutic targets and biomarkers. CircRNA has a covalently closed ring structure and is an endogenous biomolecule that lacks a 5′ end cap or 3′ poly(A) tail, making it highly stable and resistant to RNase R and other exonucleases, with a mean half-life of more than 48 hours (Barrett & Salzman, 2016; Chen et al., 2021). CircRNAs are found exclusively in the cytoplasm, but some can also be found in the nucleus, particularly circRNAs containing introns. Like lncRNA, circRNA also acts as a miRNA sponge.

Furthermore, circRNA regulates gene transcription and translation, modifies alternative splicing, and can interact with regulatory RNA-binding protein (RBP) (Chen et al., 2021; Patil et al., 2020). Recent research has revealed that circRNAs play an important role in bone disease by regulating osteoblast differentiation. Table 5 shows some examples of circRNA's role in osteogenic regulation. CircRNAs that promote osteoblast differentiation include AFF4, has_circ_0074834, circSIPA1L1, has_circ_0076690, circ_0024097, circRNA124534, circ_0076906, circRNA-vgll3, circ_0000020, circStag1, and circ_0019693. CircRNA 25487, circRNA TGFBR2, and circ_0003204, on the other hand, inhibited osteoblast differentiation.

Prospect for the future

Rapid technological advances have created a plethora of new therapeutic targets for bone-related diseases. In recent years, studies on the involvement of ncRNAs in osteoblast differentiation among the classical mechanisms were reported to influence the activity of transcription factors in regulating physiological and pathological processes. According to this evidence, there is a growing interest in ncRNA-based therapies for bone diseases. Various exogenous ncRNA delivery systems to target sites have also been investigated. Several base scaffolds and carriers are being developed for delivery of ncRNAs, including liposomes, hydrogels, exosomes, synthetic and natural nanoparticles, nanofibers, and microspheres (Balagangadharan et al., 2018; Guan et al., 2022; Li et al., 2021). These findings suggest a new challenge in the discovery and development of therapeutic strategies for bone-related diseases, as well as a promising opportunity in controlling bone regeneration. Notably, it was discovered that microchannel porous hydroxyapatite scaffolds interfere with miRNA expression (Jiajun et al., 2020). More intriguingly, the combination of ncRNAs and specific scaffold biomaterials, such as hydroxyapatite, is expected to not only improve the osteogenic performance of the scaffolds but also act as drugs for bone-related diseases (Damiati & El-Messeiry, 2021; Khotib et al., 2021; Pan et al., 2021). Unfortunately, studies on the potential role of ncRNAs in the mechanism of osteoblast differentiation have not yet covered all bone-related diseases. The research available is limited to common cases like osteoporosis, fractures, and osteoarthritis. Meanwhile, it has not been widely investigated in other cases, such as Paget's disease of bone (PDB), periodontitis, osteogenic imperfecta, osteosarcoma, etc.

As an example, consider PDB. It is a bone regeneration disorder characterized by excessive osteoclastic bone resorption followed by an increase in osteoblastic activity to compensate for bone remodeling (Nebot Valenzuela & Pietschmann, 2017). Despite the fact that PDB is the second most common bone disease after osteoporosis, recent reports indicate a global decline in prevalence and severity, which may be due to changes in environmental and lifestyle factors. Finally, these conditions lead to a decrease in PDB diagnoses (Michou & Orcel, 2019; Gennari et al., 2019). Current research on PDB therapeutic targets has focused on osteoclast-related pathways, such as the receptor activator of nuclear factor-B ligand (RANKL). Surprisingly, Marshall et al. (2009) and Yavropoulou et al. (2012) described the role of osteoblasts in PDB. SOST and DKK-1 levels of antagonists of the Wnt signaling pathway were found to be higher in PDB patients than in healthy controls. By contrast, Idolazzi et al. (2017) and Werner de Castro et al. (2019) reported that serum levels of SOST and DKK-1 in PDB patients were comparable to healthy subjects. On the other hand, the role of the Wnt/β-catenin signaling system in the pathogenesis of PDB cannot be denied.

Likewise, periodontitis is a chronic bacterial (*Porphyromonas gingivalis*)-related inflammation of the soft tissues that support tooth structure. The significant proportion of the variation in periodontitis severity is thought to be due to genetic factors (Sayad et al., 2020). In this case, osteoblasts are functionally important cells that, along with periodontal ligament stem cells (PDLSCs), contribute to the physiological function of periodontal tissues and participate in periodontal regeneration (Yu et al., 2017). Several recent studies have reported the role of ncRNAs in the regulation of osteogenic differentiation gene expression in human PDLSCs (Cuevas-González et al., 2021; Santonocito et al., 2021; Sayad et al., 2020). Anyway, more detailed reports on the various roles of ncRNAs in osteoblast differentiation and their potential effects in this area are still lacking.

Overall, further exploration into the roles of major signaling pathways, essential transcription factors, and ncRNAs in the molecular mechanisms of osteoblast differentiation is urgently needed in order to develop better therapeutic strategies for bone-related diseases.

Conclusion

Studies into the molecular mechanisms of osteoblast differentiation have greatly evolved. Previously, classical mechanisms thought that essential transcription factors were present to control MSC differentiation and commitment to osteogenesis. Surprisingly, in recent years, the use of high-throughput sequencing technology in conjunction with bioinformatics analysis has successfully identified the involvement of ncRNAs in bone regeneration, gaining insights in

the orthopaedic and endodontic fields. This review described advances in the understanding of molecular mechanisms of osteoblast differentiation involving the roles of essential transcription factors and ncRNAs. Both interactions form a regulatory complex that controls gene expression. These findings provide exciting and valuable information in the identification of novel molecular players, paving the way for the future development of therapeutic agents as well as biomarkers for diagnostic and beneficial follow-up procedures in the treatment of bone-related diseases.

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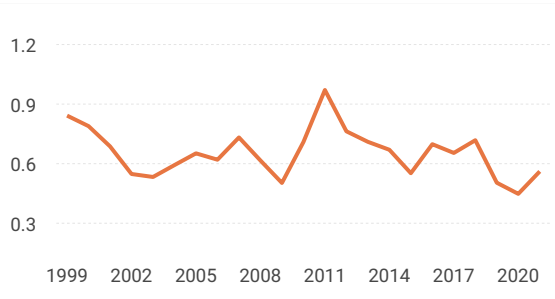

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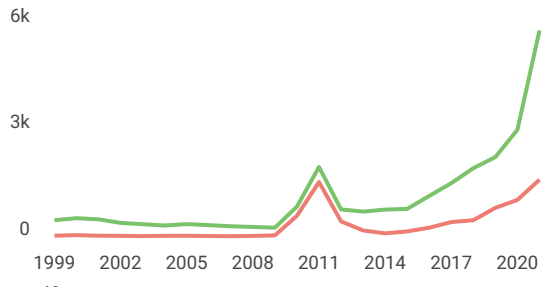

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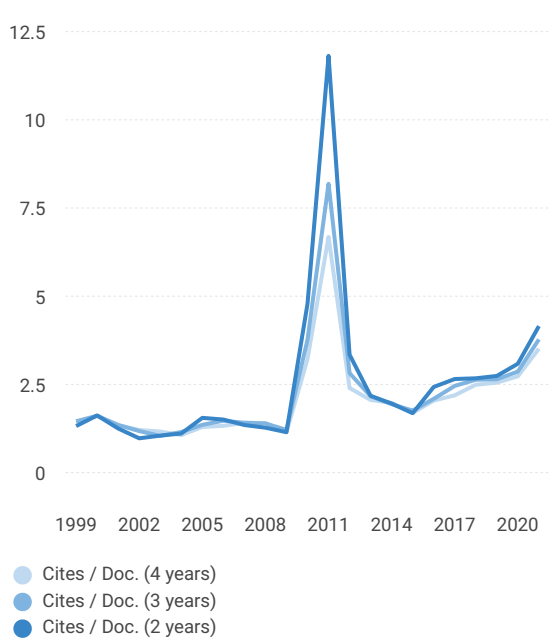

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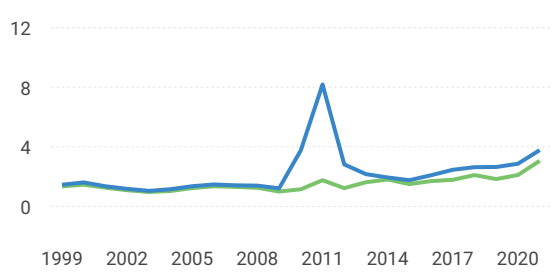

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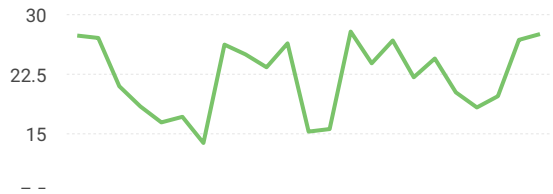

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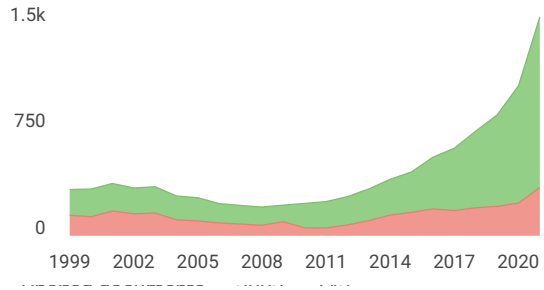

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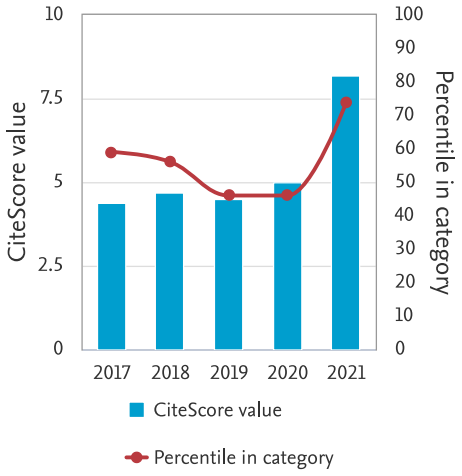

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