



Babol University  
Of Medical Sciences

IJMCM, Autumn 2025, VOL 14, NO 4

International Journal of Molecular and Cellular Medicine

Journal homepage: [www.ijmcm.org](http://www.ijmcm.org)



## REVIEW ARTICLE

# The Cross Talk of MicroRNAs and SATB2 Signaling Pathway in Osteogenesis in the Context of Dental Implants

Saad Alsaif<sup>1\*</sup> , Mousa Alrashidy<sup>1#</sup> , Saeed Al Dossary<sup>1</sup> 

1. Restorative Department, Prince Abdulrahman Advanced Dental Institute, Riyadh, Saudi Arabia.

### ARTICLE INFO

Received: 2025/05/17

Revised: 2025/06/17

Accepted: 2025/07/21

# These authors contributed equally to this work

#### \*Corresponding:

Saad Alsaif

#### Address:

Restorative Department,  
Prince Abdulrahman  
Advanced Dental Institute,  
Riyadh, Saudi Arabia.

#### E-mail:

saifaboodi@gmail.com

### ABSTRACT

Dental implant integration is dependent on osteogenesis driven by the transcription factor SATB2, which regulates osteogenic genes. MicroRNAs (miRNAs) modulate SATB2 and influence bone formation. This review evaluates miRNA-SATB2 interactions, non-coding RNAs, and biomaterials in dental implant osseointegration.

A critical review of studies from 2015 to 2025 was conducted to elucidate miRNA-SATB2 interactions and their impact on osteogenesis.

Inhibitory miRNAs (e.g., miR-31, miR-140-5p) suppress SATB2 via the Wnt/ $\beta$ -catenin or SIRT1/Smad3 pathways and reduce osteoblast differentiation. Promoter miRNAs (e.g., miR-17-5p, miR-27a-5p) enhance SATB2 through BMP/Smad signaling. Non-coding RNAs (e.g., lncRNA H19, hsa\_circ\_0007292) inhibit miRNAs affecting cancellous bone and promote osteogenesis. Biomaterials such as collagen/nanohydroxyapatite (Col/nHA) scaffolds and comorbidities (e.g., osteoporosis) influence outcomes. Inconsistent miRNA roles and limited in vivo data are key gaps.

miRNA- SATB2 interactions are critical for implant success. Patient-specific miRNA profiling and targeted therapies hold promise, pending clinical validation.

**Keywords:** Non-Coding RNA, MicroRNA, SATB2, Osteogenesis, Dental Implants, Bone Fusion, Wnt Signaling, Biomaterials

**Cite this article:** Alsaif S, et al. The Cross Talk of MicroRNAs and SATB2 Signaling Pathway in Osteogenesis in the Context of Dental Implants. 2025; 14 (4):0 - 0. DOI: 0



© The Author(s).

Publisher: Babol University of Medical Sciences

This work is published as an open access article distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by-nc/4>). Non-commercial uses of the work are permitted, provided the original work is properly cited.

## Introduction

Osteogenesis, the process of bone formation, is essential for the success of dental implants and ensures their mechanical stability and long-term function. Osseointegration, the direct structural and functional connection between bone and implant, requires the proliferation, differentiation, extracellular matrix (ECM) deposition, and mineralization of osteoblasts (1, 2). The transcription factor specific AT-rich sequence-binding protein 2 (SATB2) plays a pivotal role by regulating osteogenic genes, including Runt-related transcription factor 2 (Runx2), Osterix (Osx), Osteocalcin (Ocn), type I collagen alpha 1 (Col1a1), and bone sialoprotein (Bsp) (3). The ability of SATB2 to enhance osteoblast activity makes it a critical target for improving implant outcomes, particularly in patients whose bone quality is compromised, such as those with osteoporosis or diabetes (4, 5).

MicroRNAs (miRNAs), small non-coding RNAs (20–22 nucleotides), regulate gene expression by binding to the 3'-untranslated region (3'-UTR) of target mRNAs and causing translational repression or degradation (6). In osteogenesis, miRNAs modulate SATB2 and influence bone formation. For example, miR-31 inhibits SATB2 and reduces osteogenic markers in osteoporosis, whereas miR-27a-5p increases SATB2 and promotes osteoblast differentiation in hDPSCs (7, 8). Non-coding RNAs, including cyclic RNAs (circRNAs) and long non-coding RNAs (lncRNAs), act as miRNA sponges and further regulate these interactions (9).

The lncRNA sponge TUG1 activates miR-222-3p and increases SATB2 in hBMSCs, while circCDR1a upregulates miR-7 and promotes osteogenesis in periodontal ligament stem cells (PDLSCs) (10-12). Biomaterials, such as collagen/nanohydroxyapatite (Col/nHA) and 3D-printed scaffolds, and systemic conditions such as osteoporosis or hyperlipidemia, affect miRNA-SATB2 dynamics and influence bone integration (7, 13, 14). The interaction of miRNAs, SATB2, and signaling pathways (Wnt/ $\beta$ -catenin, BMP/Smad, SIRT1/Smad3) is complex and directly affects the success of dental implants (15). Recent studies have highlighted miRNA-based therapies, patient-specific profiling, and biomaterial innovations as promising strategies, especially in challenging conditions such as diabetes or aging populations (5, 7, 8). However, conflicting roles of miRNAs (e.g., dual

effects of miR-31), limited in vivo data, small clinical cohorts (e.g., n=15 in osteoporosis studies (16)), and underexplored biomaterial-miRNA synergies create research gaps. This review combines miRNA-SATB2 interactions, their signaling pathways, and applications in dental implant osseointegration, with an emphasis on clinical potential, novel non-coding RNA regulators, and future directions for personalized therapies.

### Role of SATB2 in Osteogenesis and Dental Implants

AT-rich sequence-specific binding protein 2 (SATB2) is a key transcription factor that drives osteoblast differentiation and is critical for dental implant integration (1). SATB2 cooperates with Runx2 and Osterix (Osx) to upregulate osteogenic genes such as osteocalcin (Ocn), type I collagen alpha 1 (Col1a1), and bone sialoprotein (Bsp) (17, 18). In human bone marrow mesenchymal stem cells (hBMSCs), increased expression of SATB2 increases Runx2 and alkaline phosphatase (ALP) activity and enhances matrix mineralization (19). In human dental pulp stem cells (hDPSCs), SATB2 upregulates Ocn expression and supports bone formation at the implant-bone interface (19, 20).

SATB2 integrates Wnt/ $\beta$ -catenin and BMP/Smad signaling to regulate osteogenesis (4). It increases  $\beta$ -catenin activity and cooperates with p-Smad5 to enhance Runx2 and Bsp expression in hDPSCs (4, 19). MicroRNAs (miRNAs) modulate SATB2 and influence implant stability. For example, miR-31 in osteoporosis suppresses SATB2 and reduces bone-implant contact, while miR-17-5p increases SATB2 through SMAD7 and promotes osteogenesis (8, 21). Non-coding RNAs enhance the role of SATB2 in implantology (9, 19). The long non-coding RNA H19 activates miR-140-5p and increases SATB2 in hBMSCs (9).

The circular RNA sponge hsa\_circ\_0007292 activates miR-508-3p and increases Col1 expression for implant applications (19, 21). Biomaterials such as collagen/nanohydroxyapatite (Col/nHA) scaffolds increase SATB2 expression and improve bone-implant contact in vivo (7, 22). Osteoporosis, characterized by increased miR-664-3p expression, suppresses SATB2 and impairs bone fusion (14). However, many studies rely on in vitro models (9, 19) or small-scale animal experiments (e.g., rat (7)), which limit their relevance to humans. The paucity of clinical data and variable effects of miRNAs hinders translation (9, 19).

Regulation of SATB2 by miRNAs, non-coding RNAs, and biomaterials makes it a promising target for enhancing implant outcomes in challenging bone conditions.

### miRNA-SATB2 Interactions in Osteogenesis

miRNAs are key regulators of SATB2 that modulate osteoblast differentiation and bone formation, which are critical for dental implant integration. These small non-coding RNAs exert their effects by targeting the 3'-UTR of SATB2 or its associated signaling molecules, influencing osteogenic gene expression and cellular processes (Table 1).

### Inhibitory miRNAs

Inhibitory miRNAs suppress SATB2 expression, reducing osteoblast differentiation and potentially compromising implant stability: miR-31: This miRNA targets the 3'-UTR of SATB2 in hBMSCs and inhibits the expression of Runx2, Ocn, and BMP through suppression of the Wnt/ $\beta$ -catenin pathway (16).

In patients with osteoporosis, miR-31 was significantly upregulated ( $3.61 \pm 0.54$  vs.  $1.75 \pm 0.27$  in controls,  $P < 0.001$ ), with a strong negative correlation with SATB2 expression ( $r = -0.754$ ,  $P < 0.001$ ). The small sample size of the study ( $n = 81$ ) limits its generalizability and highlights the need for larger clinical cohorts (16). miR-103: miR-103 downregulates SATB2 in hBMSCs, as well as Runx2, bone gamma-carboxyglutamate protein (Bglap), and secreted phosphoprotein 1 (Spp1) (14). Treatment with antagomiR-103 increases ALP activity and matrix mineralization in vitro, but the lack of in vivo validation limits its translational potential (14). miR-140-5p: This miRNA inhibits SATB2 in hBMSCs and reduces ALP activity and the expression of Col1a1, Runx2, and Ocn (20).

The lncRNA H19 acts as a sponge for miR-140-5p and promotes SATB2 expression and bone formation. The in vitro nature of this study emphasizes the need for clinical validation (20). miR-508-3p: miR-508-3p suppresses SATB2 in osteogenesis of posterior longitudinal ligament (OPLL) cells and reduces the expression of Col1, Runx2, and Osteopontin (Opn) (19). The circular RNA hsa\_circ\_0007292 promotes osteogenesis by acting as a sponge for miR-508-3p. Although its relevance to dental implants is indirect, it shows potential applications in implant-associated bone formation (19). miR-29a-5p: This miRNA targets

SATB2 in ligamentum flavum cells and inhibits osteogenesis through deacetylation of SIRT1/Smad3 (23). Its role in the context of dental implants remains unknown, but its effect on SATB2 suggests broader implications (23).

### Promoting miRNAs

Promoting miRNAs increase SATB2 expression and support osteoblast differentiation and bone formation: miR-17-5p: This miRNA upregulates SATB2 by targeting SMAD7 in human bone marrow-derived mesenchymal stem cells (HMSC-bm) and increases the expression of Runx2 and Col1a1 (7, 9, 24). However, in C2C12 cells, miR-17-5p inhibits osteogenesis by targeting Smad5, suggesting context-dependent effects that require clarification in vivo (25).

This dichotomy highlights a critical research gap (7, 9, 24). miR-20a-5p: miR-20a-5p targets BMP and the membrane-bound inhibitor of activin (BAMBI) in hDPSCs and increases the expression of p-Smad5, p-p38, Runx2, and Bsp (25). In vivo studies demonstrate its ability to enhance bone regeneration in cranial defects, suggesting its potential for implant applications (25).

miR-27a-5p: This miRNA downregulates Dickkopf-related protein 3 (DKK3) and sclerostin domain-containing protein 1 (SOSTDC1) in hDPSCs, activates the Wnt/ $\beta$ -catenin and BMP pathways, and increases the expression of Opn, Runx2, and ALP (7, 8). In vivo transplantation of hDPSCs transfected with miR-27a-5p enhances hard tissue formation, highlighting its therapeutic potential (7, 8).

### Challenges in miRNA Research

The study of miRNA-SATB2 interactions faces several challenges, including the predominance of in vitro studies (16), (14), small clinical sample sizes (e.g.,  $n = 81$  (16)), and conflicting roles of miRNAs (e.g., miR-17-5p (7, 9, 24)). In addition, some miRNAs (e.g., miR-508-3p) have indirect associations with dental implants, which require further validation in implant-specific contexts (19).

### Mechanisms of miRNA-SATB2 Interaction

miRNA-SATB2 interactions form complex regulatory networks, as shown in Figure 1. miR-31 inhibits SATB2 translation at the 3'-UTR (position 2376–2383), as confirmed by luciferase assays. Its inhibitor restores SATB2 in hBMSCs and osteoporotic serum (4,

16). miR-23a and miR-27a downregulate SATB2 and increase *Sost* expression during osteocyte differentiation through TGF- $\beta$  signaling (8, 26). miR-103, miR-140-5p, and miR-508-3p target the 3'-UTR of SATB2 and reduce its expression in hBMSCs and PLL cells, as confirmed by RNA immunoprecipitation (RIP) (14, 19, 20). miR-144-3p targets *Smad4* and indirectly suppresses SATB2 in MSCs (27). miR-24-3p targets *Smad5* and reduces SATB2 activity in hPDLSCs (28). miR-29a-5p modulates SATB2 in TOLF via SIRT1/*Smad3* deacetylation (23).

Promoter miRNAs promote osteogenesis. miR-17-5p targets *SMAD7* and upregulates SATB2 and *Runx2* (21). miR-20a-5p targets *BAMBI* and activates *Smad5/p38* pathways (9). miR-27a-5p targets *DKK3* and *SOSTDC1* and upregulates *Wnt/ $\beta$ -catenin* and *pSMAD1/5* in hDPSCs (7). miR-29a-3p represses *Dvl2* and *Fzd4* and enhances osteogenesis in hyperlipidemia. miR-106b-5p repression restores *Smad5* and SATB2 in hBMSCs (25). miR-21 promotes hBMSC osteogenesis via the *PTEN/PI3K/Akt* pathway but inhibits hPDLSC osteogenesis by targeting *Smad5* (29, 30). Non-coding RNAs regulate these interactions (9, 20). The lncRNA *PWAR6* upregulates miR-106a-5p and increases *BMP2* (31).

The lncRNA *H19* upregulates miR-140-5p and increases SATB2 (20). The circular RNAs *circSIPA1L1* and *hsa\_circ\_0007292* upregulate miR-617 and miR-508-3p, respectively, and increase *Smad3* and SATB2 (19, 32). The lncRNA *TUG1* enhances miR-222-3p and increases SATB2 (11, 12). The circular RNA *circCDR1as*, acting as a sponge for miR-7, enhances *GDF5/Smad* signaling (10). Limited in vivo validation, inconsistent miRNA effects (e.g., dual

roles of miR-21), small clinical cohorts (e.g., n=15 in osteoporosis (16)), and lack of standardized delivery systems pose challenges (9, 16). The impact of comorbidities such as diabetes on miRNA-SATB2 dynamics requires further investigation (5). These mechanisms highlight the central role of SATB2 in bone formation for dental implants.

### Role of Epigenetic Modifications in miRNA-SATB2 Regulation

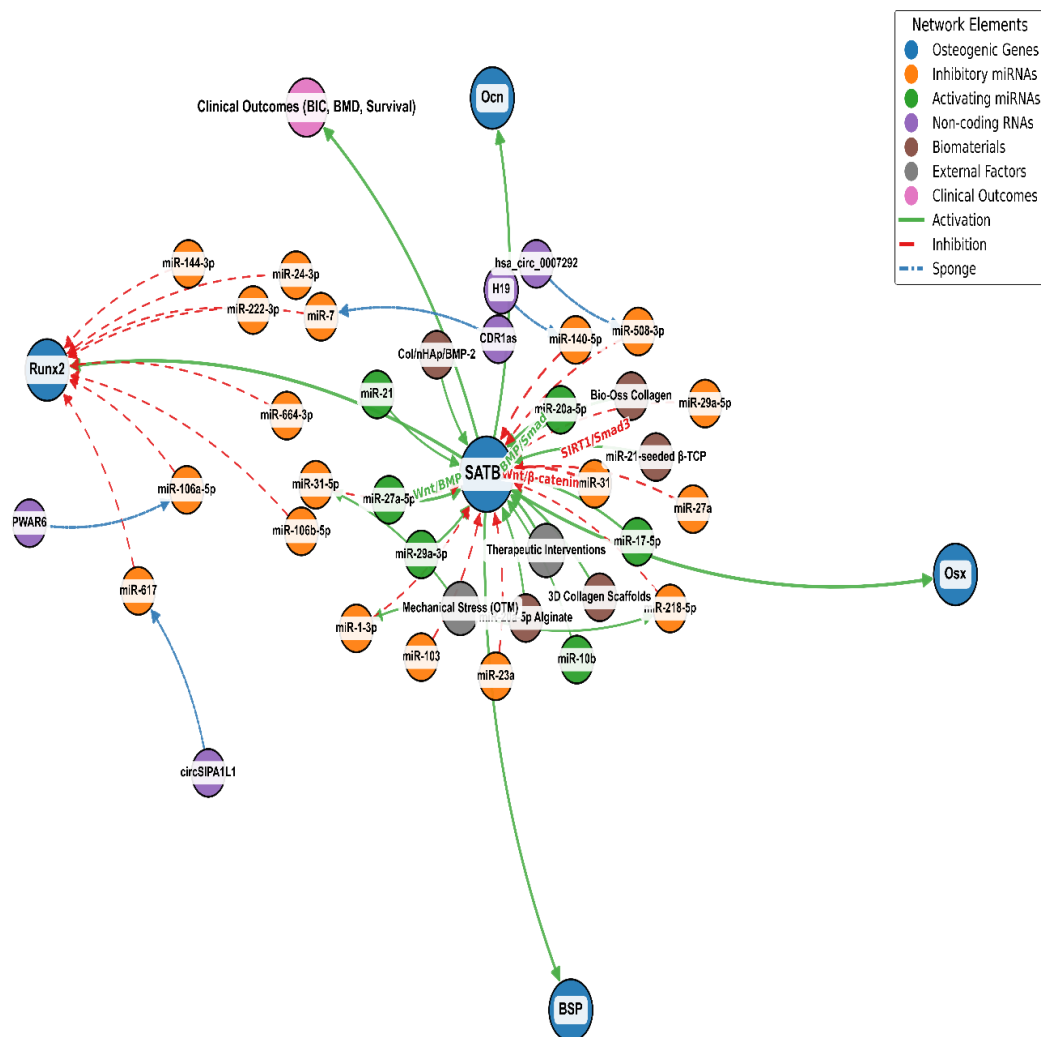
Epigenetic modifications, including DNA methylation and histone acetylation, regulate miRNA-SATB2 interactions and influence bone formation for dental implants. DNA methylation at CpG islands in the miR-31 promoter represses its expression and upregulates SATB2 in hBMSCs and hPDLSCs (4, 16). Conversely, hypomethylation of the miR-140-5p promoter increases its expression and downregulates SATB2 in hBMSCs (20). Histone deacetylase (HDAC) inhibitors, such as trichostatin A, upregulate miR-29a-3p via H3K9 acetylation and enhance SATB2-induced bone formation in hyperlipidemia (13). Hypermethylation of miR-664-3p in osteoporosis patients suppresses *Smad4* and *Osterix* and limits SATB2 activity (33).

In TOLF, overexpression of HDAC3 increases miR-29a-5p and represses SATB2 through SIRT1/*Smad3* deacetylation (14). The lncRNA *H19* recruits histone acetyltransferases to the miR-140-5p promoter, reduces its expression, and relieves SATB2 repression (9). circRNA *hsa\_circ\_0007292* modulates DNA methyltransferases, reduces miR-508-3p promoter methylation, and increases SATB2 in PLL cells (19).

**Table1. hensive summary of key miRNAs, their targets, effects on osteogenesis, signaling pathways, cell types, clinical applications, and references, offering a detailed overview of miRNA-SATB2 interactions (see Figure 1 for signaling pathways).**

miRNA	Target(s)	Effect on Osteogenesis	Signaling Pathway	Cell Type/Context	Clinical Application	References
miR-17-5p	SMAD7, SMAD4	Promotes	TGF- $\beta$ /Smad	MSCs, BMSCs	Enhances BMP-2 scaffolds	(21, 25)
miR-10b	SMAD2	Promotes	TGF- $\beta$	hADSCs	Improves HA/TCP scaffolds	(34)
miR-20a-5p	BAMBI	Promotes	BMP/Smad, p38 MAPK	hDPSCs (calvarial defects)	Alginate scaffolds for defect repair	(9)
miR-27a-5p	DKK3, SOSTDC1, BMP2,	Promotes	Wnt/BMP, BMP/Smad	hDPSCs (cranial defects)	Collagen scaffolds for bone regeneration	(1, 33)

miRNA	Target(s)	Effect on Osteogenesis	Signaling Pathway	Cell Type/Context	Clinical Application	References
	BMPRI1A, SMAD9					
miR-29a-3p	DVL2, FZD4	Promotes	Wnt/BMP	BMSCs (hyperlipidemia models)	Counteracts hyperlipidemia effects	(13)
miR-21	PTEN (BMSCs), SMAD5 (hPDLSCs)	Promotes (BMSCs), Inhibits (hPDLSCs)	PTEN/PI3K/Akt, Smad	BMSCs, hPDLSCs	$\beta$ -TCP scaffolds for mandibular repair	(29, 30)
miR-31	SATB2, Wnt/ $\beta$ -catenin	Inhibits	Wnt/BMP	hMSCs, BMSCs, hPDLSCs (osteoporosis)	Biomarker for osteoporosis	(4, 16, 31)
miR-23a	SATB2, RUNX2	Inhibits	TGF- $\beta$	Osteoblasts, ROBs	Modulates osteocyte differentiation	(8, 26)
miR-27a-5p	SATB2, SOST	Inhibits	TGF- $\beta$	Osteoblasts, ROBs	Regulates osteoblast maturation	(8, 26)
miR-222-3p	SMAD5, RUNX2, SMAD2/7	Inhibits	Smad	hMSCs	Potential target for lncRNA TUG1 therapy	(11, 12)
miR-24-3p	SMAD5	Inhibits	Smad	hPDLSCs	Inhibitor for enhanced osteogenesis	(28)
miR-144-3p	SMAD4	Inhibits	Smad	hMSCs, osteoblasts	Biomarker for stress-induced inhibition	(27)
miR-664-3p	SMAD4	Inhibits	Smad	hMSCs (osteoporosis)	Osteoporosis diagnostic marker	(33)
miR-106b-5p	SMAD5	Inhibits	Smad	hMSCs	Potential target for osteogenic enhancement	(25)
miR-103	SATB2	Inhibits	unknown	hBMSCs	Osteogenic differentiation inhibitor	(14)
miR-140-5p	SATB2	Inhibits	unknown	BMSCs	Potential target for H19-based therapy	(20)
miR-508-3p	SATB2	Inhibits	unknown	PLL cells (OPLL)	Potential target for hsa_circ_0007292 therapy	(19)
miR-29a-3p	SATB2, SIRT1/SMAD3	Inhibits	SIRT1/Smad3 deacetylation	Ligamentum flavum (TOLF)	TOLF therapeutic target	(23)
miR-106a-5p	BMP2	Inhibits	BMP/Smad	hPDLSCs	PWAR6-based osteogenic enhancement	(31)
miR-617	SMAD3	Inhibits	Smad	DPSCs	circSIP1L1 scaffolds for bone repair	(32)
miR-7	GDF5	Inhibits	Smad, p38 MAPK	Osteoblasts	CDR1as-based therapy	(10)
miR-31-5p, miR-218-5p, miR-1-3p	SATB2, others	Inhibits	unknown	Osteoblasts (OTM)	OTM stress management	(35)
miR-4634	unknown	Potential biomarker	unknown	Salivary exosomes (OTM)	OTM biomarker	(36)



**Figure 1. Schematic representation of miRNA-SATB2 interaction in osteogenesis**

Figure 1 shows the miRNA-SATB2 regulatory network in osteogenesis for dental implants. SATB2 (central node) upregulates osteogenic genes (Runx2, Osx, Ocn, Bsp), as indicated by green arrows. Inhibitory miRNAs (miR-31, miR-103, miR-140-5p, miR-508-3p, miR-29a-5p, miR-23a/27a, miR-144-3p, miR-24-3p), shown in red, repress SATB2 or Smad4/Smad5 (dashed lines). Promoter miRNAs (miR-17-5p, miR-20a-5p, miR-27a-5p, miR-29a-3p, miR-10b, miR-106b-5p), targeting SMAD7, BAMBI, or DKK3, activate Wnt/BMP/TGF- $\beta$  pathways (solid arrows). Non-coding RNAs (circSIPA1L1, CDR1as, hsa\_circ\_0007292, PWAR6, H19, TUG1), shown in blue, act as sponges for inhibitory miRNAs. Biomaterials (Col/nHA, alginate, 3D-printed scaffolds) and mechanical stress (OTM) influence the network. A guide clarifies symbols and interactions.

In osteoporosis, hypermethylation of the miR-10b promoter downregulates ALP and Runx2 and limits SATB2-mediated osteogenesis (34). The lncRNA TUG1 modulates H3K27 methylation and increases SATB2 through miR-222-3p spongification in hBMSCs (11, 12). Biomaterials, such as Col/nHA scaffolds, may alter epigenetic landscapes by increasing demethylase regulators and enhancing SATB2 (22). 3D-printed scaffolds with miRNA-containing nanoparticles can target epigenetic regulators and enhance SATB2-induced osteogenesis

(7). Mechanical stress, such as orthodontic tooth movement (OTM), induces HDAC activity, increases miR-31-5p, and represses SATB2 (35). These mechanisms, illustrated in Figure 1, suggest that epigenetic modulators (e.g., HDAC inhibitors) can enhance SATB2-induced osteogenesis, but small sample sizes (e.g.,  $n=12$  in epigenetic studies (28, 34)), lack of diverse clinical cohorts, and limited human trials limit translation (9, 34). The impact of comorbidities such as diabetes on epigenetic profiles remains unknown (5). Future studies should prioritize

epigenetic profiling in patient-derived mesenchymal stem cells and large-scale clinical studies to validate these approaches.

### Impact of Specific Biomaterials on miRNA-SATB2 Signaling Pathways

Biomaterials enhance miRNA-SATB2 signaling for bone integration, as shown in Table 1. Col/nHA scaffolds with BMP-2 increase SATB2 and enhance ALP activity and bone-implant contact in rat tibia (22). miR-17-5p supports BMP-2-induced osteogenesis by downregulating SMAD7 expression, in concert with SATB2 (29). Human adipose-derived stem cells (hADSCs) overexpressing miR-10b on hydroxyapatite scaffolds increase ectopic bone formation (34).  $\beta$ -TCP scaffolds containing miR-21 increase bone mineral density in mandibular defects by 52% and enhance SATB2-induced osteogenesis (30). Human dental pulp stem cells (hDPSCs) treated with miR-20a-5p on alginate scaffolds improve cranial defect regeneration via BAMBI/Smad5/p38 pathways (9).

Human dental pulp stem cells (hDPSCs) transfected with miR-27a-5p on 3D-printed scaffolds increase hard tissue formation by 40% [via Wnt/BMP pathways] (7). Human dental pulp stem cells (hDPSCs) overexpressing circSIPA1L1 on Bio-Oss scaffolds and PLL cells overexpressing hsa\_circ\_0007292 increase bone-like structures by counteracting miR-617 and miR-508-3p (19, 32). Nanoparticles loaded with lncRNA TUG1-miR-222-3p on Col/nHA scaffolds enhance SATB2 in osteoporotic models (11, 12). Inhibitory miRNAs, such as miR-31, miR-103, miR-140-5p, and miR-144-3p, suppress biomaterial-induced osteogenesis (14, 16, 20, 27).

Hyperlipidemia downregulates miR-29a-3p and SATB2, impairing bone fusion; overexpression of miR-29a-3p restores efficacy (13). In vitro studies are predominant, with small animal models (e.g., n=10 rats (22)) and variable performance in comorbid conditions (e.g., diabetes (5)) limiting translation (9, 22). The lack of standardized biomaterial testing protocols and scalability challenges with 3D-printed scaffolds require further investigation (7, 22). Clinical trials with diverse patient populations are essential to validate advanced scaffolds for clinical efficacy.

### Mechanical Stress and miRNA-SATB2 Dynamics

Mechanical stress, such as orthodontic tooth movement (OTM), modulates miRNA-SATB2

interactions, as shown in Figure 1. Compressive forces increase miR-31-5p and miR-21, repress SATB2, and impair bone formation (35). miR-27a, which is increased during OTM, promotes RANKL-mediated osteoblast differentiation (35). miR-34a exhibits a dual role: inhibiting bone formation through CELF3 or enhancing it through Wnt/ $\beta$ -catenin targeting Gsk3 $\beta$  (4, 35). hBMSCs overexpressing SATB2 enhance mandibular bone remodeling under stress, while miR-31 inhibitors restore SATB2 activity (9, 16). miR-140-5p and miR-508-3p repress SATB2, but the circular RNA hsa\_circ\_0007292, acting as a sponge, represses miR-508-3p and restores SATB2 (19). miR-29a-3p, which is downregulated in hyperlipidemia, promotes bone formation and counteracts stress-induced suppression when overexpressed (7, 13, 14). Hyperlipidemic conditions exacerbate miRNA dysregulation and delay bone formation (7, 13, 14). Small-scale OTM studies (e.g., n=8 in mouse models (35)) and limited clinical data limit applicability (9, 35). Targeted miRNA therapies can reduce stress-induced effects, but delivery systems need optimization (9, 19).

### Emerging Therapeutic Strategies

miRNA-based therapies enhance SATB2-driven bone formation for dental implants. miR-20a-5p mimics targeting BAMBI increase bone mineral density (BMD) in rat skull defects via alginate scaffolds by 30% (9). miR-27a-5p mimics targeting DKK3/SOSTDC1 increase bone formation in 3D-printed collagen scaffolds by 40% (7).

Anti-miR-31 restores SATB2 and Ocn in osteoporotic hPDLSCs and improves bone integration in rat models (16, 22). CircRNAs such as hsa\_circ\_0007292, acting as a sponge for miR-508-3p, upregulate SATB2, while circSIPA1L1, acting as a sponge for miR-617, upregulates Smad3 in Bio-Oss scaffolds (19, 32). The lncRNA H19 upregulates miR-140-5p and enhances SATB2 (20). Nanoparticles containing lncRNA TUG1-miR-222-3p upregulate SATB2 in osteoporosis (11, 12). CRISPR/Cas9 can upregulate miR-17-5p or silence miR-103 and regulate osteogenesis (14, 29).

Exosome-mediated delivery of miR-27a-5p into 3D-printed scaffolds increases osteogenesis in hDPSCs by up to 40% (7). miR-144-3p inhibitors can reverse Smad4 repression and enhance SATB2 (27). These approaches require validation due to variable miRNA

effects (e.g., n=12 in mouse studies (7)), small sample sizes, and lack of standardized delivery systems (7, 9). The lack of large-scale clinical trials and diverse populations (e.g., diabetic patients (5)) limits applicability (5, 9). Incorporating miRNA mimics, antagomirs, and non-coding RNAs with advanced scaffolds holds promise for personalized implant therapies (7, 9).

### Patient-Specific miRNA Profiling

Patient-specific miRNA profiling through next-generation sequencing guides personalized implant therapy. Increased miR-31 expression in osteoporosis is associated with decreased SATB2; anti-miR-31 restores osteogenesis in hPDLSCs (16). Reduced miR-29a-3p expression in hyperlipidemia impairs SATB2, but its overexpression enhances bone inclusion (13). miR-664-3p, increased in osteoporotic patients, serves as a biomarker for bone regeneration and is associated with reduced ALP activity (33). Increased miR-144-3p expression in MSCs suppresses Smad4 and indirectly affects SATB2 (27).

Profiling miRNAs in MSC biopsies predicts implant outcomes. Correlation of miR-10b with ALP and Runx2 in osteoporosis suggests treatment monitoring (34).  $\beta$ -TCP scaffolds containing miR-21 increase bone mineral density in mandibular defects by 52%, which can be modulated by profiling (30). TUG1-miR-222-3p lncRNA profiles could guide SATB2-targeted therapies in osteoporosis (11, 12). Limited clinical cohorts (e.g., n=15 in osteoporosis (16)), lack of diverse populations (e.g., diabetes (5)), and lack of standardized protocols limit generalizability (9, 16). Large-scale clinical validation of miRNA profiling in MSCs and integration with biomaterials is critical for precision medicine (5, 9, 16). Precision medicine exploits miRNA-SATB2 interactions to increase implant success in complex cases (5, 9).

### Challenges to Clinical Translation

Translating miRNA-SATB2 interactions into clinical practice faces several obstacles. Increased expression of miR-31 and decreased expression of SATB2 in osteoporosis suppresses osteogenic markers, complicating miRNA targeting (16). Variable expression of miR-10b requires careful profiling (34). Hyperlipidemia suppresses miR-29a-3p and SATB2, necessitating personalized therapies (13).

Dysregulation of miR-664-3p and miR-144-3p in osteoporosis further challenges therapeutic design (27, 33). Biomaterials such as Col/nHA increase SATB2, but efficacy in diabetes varies (5, 22).  $\beta$ -TCP scaffolds containing miR-21 improve bone mineral density by 47% (30), but scalability and performance in different groups have not been tested. Non-coding RNAs (circSIPA1L1, hsa\_circ\_0007292, TUG1) enhance SATB2 (11, 12, 19, 32), but delivery systems have not yet been developed (9, 19).

In vitro studies predominate (9, 20), with small animal models (e.g., n=10 rats (22)) and limited clinical trials (e.g., n=15 in osteoporosis (16)) limiting human relevance (9, 16). Patient-specific miRNA variability, lack of diverse populations (e.g., diabetes (5)), and lack of standardized protocols complicate translation (5, 9). The lack of standardized miRNA validation protocols and regulatory barriers to biomaterial-based miRNA therapies require further investigation. Clinical trials in diverse patient populations are critical to validate miRNA-SATB2 therapies for robust bone integration (9, 16).

### Crosstalk between miRNAs and SATB2 Signaling in Osteogenesis

As shown in Figure 1, miRNA-SATB2 interaction is essential for osteogenesis. SATB2 increases the expression of Runx2, Osx, and Bsp, but inhibitory miRNAs (miR-31, miR-103, miR-140-5p) repress its expression (8, 14, 20). miR-21 inhibits osteogenesis in hPDLSCs by targeting Smad5, while the lncRNA TUG1, acting as a sponge for miR-222-3p, restores SATB2 (11, 12, 29). Promoter miRNAs (miR-17-5p, miR-20a-5p) upregulate SATB2 by targeting SMAD7 and BAMBI, respectively (9, 24). miR-27a-5p activates Wnt/BMP pathways and upregulates SATB2 (7). The circular RNAs circSIPA1L1 and hsa\_circ\_0007292, acting as sponges, upregulate miR-617 and miR-508-3p, respectively (19, 32).

Biomaterials such as Col/nHA scaffolds and those containing miR-21 upregulate SATB2 (22, 30). Hyperlipidemia suppresses miR-29a-3p, but its overexpression restores SATB2 (13). Promoter miRNAs show stronger therapeutic potential (9, 24).

### Discussion

The miRNA-SATB2 interaction, detailed in Figure 1, is crucial for bone formation. SATB2 directs



osteogenic genes, but inhibitory miRNAs (miR-31, miR-103, miR-144-3p) repress its expression and impair bone formation in osteoporosis and diabetes (4, 5, 14, 16, 27). Promoter miRNAs (miR-17-5p, miR-27a-5p) upregulate SATB2 and promote remodeling through Wnt/BMP pathways (7, 9, 24). Non-coding RNAs (circSIPA1L1, hsa\_circ\_0007292, H19, TUG1), acting as sponges for miRNAs, enhance SATB2, while biomaterials such as Col/nHA and miRNA-containing scaffolds also upregulate SATB2 (7, 9, 19, 22, 30, 32). Challenges include miRNA variability in osteoporosis, hyperlipidemia, and diabetes, requiring personalized therapies (5, 13, 16).

Small in vitro studies and trials (e.g., n=15 (16)) limit translation (9, 16). Lack of standardized profiling protocols, regulatory barriers for biomaterial-miRNA therapies, and limited diverse clinical populations (e.g., diabetic patients (5)) hinder progress (5, 9). Future trials combining miRNA-SATB2 targeting, patient-specific profiling, and advanced biomaterials such as 3D-printed scaffolds will optimize implant success and transform patient-centered dentistry (7, 9). The scarcity of large-scale clinical trials evaluating miRNA-based therapies for bone regeneration, particularly in dental implant applications, underscores the need for robust human studies to validate preclinical findings (37). Recent research has highlighted the critical role of Wnt/ $\beta$ -catenin signaling in mediating miRNA-SATB2 interactions, offering a potential target for improving osseointegration in dental implants (38, 39).

Emerging evidence indicates that circular RNAs, such as circSIPA1L1, regulate miRNA-SATB2 networks, presenting a novel therapeutic avenue for personalized bone regeneration strategies in implant dentistry (3, 40). Altered miRNA profiles in diabetic patients significantly impair SATB2-mediated bone remodeling, emphasizing the necessity for tailored implant approaches in patients with comorbidities (41, 42). The integration of miRNA-containing nanoparticles into 3D-printed scaffolds represents a promising strategy for personalized bone regeneration and enhances SATB2 activity in dental implant applications (43, 44).

## References

1. Dong W, Zhang P, Fu Y, et al. Roles of SATB2 in site-specific stemness, autophagy and senescence

of bone marrow mesenchymal stem cells. *J Cell Physiol.* 2015;230(3):680-90.

2. Oelerich O, Kleinheinz J, Bohner L, et al. Dental Implants in People with Osteogenesis Imperfecta: A Systematic Review. *Int J Environ Res Public Health.* 2022;19.(7)
3. Gong Y, Lu J, Yu X, et al. Expression of Sp7 in Satb2-induced osteogenic differentiation of mouse bone marrow stromal cells is regulated by microRNA-27a. *Mol Cell Biochem.* 2016;417(1):7-16.
4. McCully M, Conde J, P VB, et al. Nanoparticle-antagomiR based targeting of miR-31 to induce osterix and osteocalcin expression in mesenchymal stem cells. *PloS one.* 2018;13(2):e0192562.
5. Rafiee M, Sadeghi F, Mirzapour A, et al. Association of MicroRNA-103 expression with Type 2 Diabetes Mellitus. *Casp J Internal Med.* 2025;16(1):106-13.
6. Gong Y, Xu F, Zhang L, et al. MicroRNA expression signature for Satb2-induced osteogenic differentiation in bone marrow stromal cells. *Mol Cell Biochem.* 2014;387(1-2):227-39.
7. Yu Z, Kawashima N, Sunada-Nara K, et al. MicroRNA-27a transfected dental pulp stem cells undergo odonto/osteogenic differentiation via targeting DKK3 and SOSTDC1 in Wnt/BMP signaling in vitro and enhance bone formation in vivo. *J Transl Med.* 2025;23(1):025-06208.
8. Zeng H-C, Bae Y, Dawson BC, et al. MicroRNA miR-23a cluster promotes osteocyte differentiation by regulating TGF- $\beta$  signalling in osteoblasts. *Nat Commun.* 2017;8(1):15000.
9. Cen X, Pan X, Zhang B, et al. miR-20a-5p contributes to osteogenic differentiation of human dental pulp stem cells by regulating BAMBI and activating the phosphorylation of Smad5 and p38. *Stem Cell Res Ther.* 2021;12(1):021-02501.
10. Li X, Zheng Y, Huang Y, et al. Circular RNA CDR1as regulates osteoblastic differentiation of periodontal ligament stem cells via the miR-7/GDF5/SMAD and p38 MAPK signaling pathway. *Stem Cell Res Ther.* 2018;9(1):018-0976.
11. Wu D, Yin L, Sun D, et al. Long noncoding RNA TUG1 promotes osteogenic differentiation of human periodontal ligament stem cell through sponging microRNA-222-3p to negatively regulate Smad2/7. *Arch Oral Biol.* 2020;117:104814.

12. Yan J, Guo D, Yang S, et al. Inhibition of miR-222-3p activity promoted osteogenic differentiation of hBMSCs by regulating Smad5-RUNX2 signal axis. *Biochem Biophys Res Commun.* 2016;470(3):498-503.
13. Liu F, Wang Z, Liu F, et al. MicroRNA-29a-3p enhances dental implant osseointegration of hyperlipidemic rats via suppressing dishevelled 2 and frizzled 4. *Cell Biosci.* 2018;8:1-12.
14. Lv H, Yang H, Wang Y. Effects of miR-103 by negatively regulating SATB2 on proliferation and osteogenic differentiation of human bone marrow mesenchymal stem cells. *PloS one.* 2020;15.(<sup>o</sup>)
15. Ghafouri-Fard S, Abak A, Tavakkoli Avval S, et al. Contribution of miRNAs and lncRNAs in osteogenesis and related disorders. *Biomed Pharmacother.* 2021;142:111942.
16. Ouyang X, Li S, Ding Y, et al. Mechanism of miRNA-31 Regulating Wnt/ $\beta$ -catenin Signaling Pathway by Targeting Satb2 in the Osteogenic Differentiation of Human Bone Marrow-Derived Mesenchymal Stem Cells. *J Musculoskelet Neuronal Interact.* 2023;23(3):346-54.
17. Feng L, Xia B, Tian BF, et al. MiR-152 influences osteoporosis through regulation of osteoblast differentiation by targeting RICTOR. *Pharm Biol.* 2019;57(1):586-94.
18. Hojo H. Emerging RUNX2-Mediated Gene Regulatory Mechanisms Consisting of Multi-Layered Regulatory Networks in Skeletal Development. *Int J Mol Sci.* 2023;24.(<sup>r</sup>)
19. Jiang A, Wang N, Yan X, et al. Hsa-circ-0007292 promotes the osteogenic differentiation of posterior longitudinal ligament cells via regulating SATB2 by sponging miR-508-3p. *Aging.* 2021;13(16):20192-217.
20. Bi HU, Wang D, Liu X, et al. Long non-coding RNA H19 promotes osteogenic differentiation of human bone marrow-derived mesenchymal stem cells by regulating microRNA-140-5p/SATB2 axis. *J Biosci.* 2020;45:56.
21. Wei B, Wei W, Zhao B, et al. Long non-coding RNA HOTAIR inhibits miR-17-5p to regulate osteogenic differentiation and proliferation in non-traumatic osteonecrosis of femoral head. *PloS one.* 2017;12(2):e0169097.
22. Pang K, Seo YK, Lee JH. Effects of the combination of bone morphogenetic protein-2 and nano-hydroxyapatite on the osseointegration of dental implants. *J Korean Assoc Oral Maxillofac Surg.* 2021;47(6):454-64.
23. Feng F, Qiu H, Zhu D, et al. miR-29a-5p targets SATB2 and regulates the SIRT1/Smad3 deacetylation pathway to inhibit thoracic ligamentum flavum cell osteogenesis. *Spine.* 2020;45(17):E1057-E65.
24. Jia J, Feng X, Xu W, et al. MiR-17-5p modulates osteoblastic differentiation and cell proliferation by targeting SMAD7 in non-traumatic osteonecrosis. *Exp Mol Med.* 2014;46(7):43.
25. Fang T, Wu Q, Zhou L, et al. miR-106b-5p and miR-17-5p suppress osteogenic differentiation by targeting Smad5 and inhibit bone formation. *Exp Cell Res.* 2016;347(1):74-82.
26. Zheng L, Tu Q, Meng S, et al. Runx2/DICER/miRNA Pathway in Regulating Osteogenesis. *J Cell Physiol.* 2017;232(1):182-91.
27. Huang C, Geng J, Wei X, et al. MiR-144-3p regulates osteogenic differentiation and proliferation of murine mesenchymal stem cells by specifically targeting Smad4. *FEBS letters.* 2016;590(6):795-807.
28. Li Z, Sun Y, Cao S, et al. Downregulation of miR-24-3p promotes osteogenic differentiation of human periodontal ligament stem cells by targeting SMAD family member 5. *J Cell Physiol.* 2019;234(5):7411-9.
29. Wei F, Yang S, Guo Q, et al. MicroRNA-21 regulates Osteogenic Differentiation of Periodontal Ligament Stem Cells by targeting Smad5. *Sci Rep.* 2017;7(1):1660.<sup>^</sup>
30. Yang C, Liu X, Zhao K, et al. miRNA-21 promotes osteogenesis via the PTEN/PI3K/Akt/HIF-1 $\alpha$  pathway and enhances bone regeneration in critical size defects. *Stem Cell Res Ther.* 2019;10(1):65.
31. Xiang J, Bian Y. PWAR6 interacts with miR-106a-5p to regulate the osteogenic differentiation of human periodontal ligament stem cells. *Mol Med Rep.* 2021;23(4):268.
32. Ge X, Li Z, Zhou Z, et al. Circular RNA SIPA1L1 promotes osteogenesis via regulating the miR-617/Smad3 axis in dental pulp stem cells. *Stem Cell Res Ther.* 2020;11(1):020-01877.
33. Xu Y, Jin Y, Hong F, et al. MiR-664-3p suppresses osteoblast differentiation and impairs bone formation via targeting Smad4 and Osterix. *Journal of Cellular and Molecular Medicine.* 2021;25(11):5025-37.

34. Li H, Fan J, Fan L, et al. MiRNA-10b Reciprocally Stimulates Osteogenesis and Inhibits Adipogenesis Partly through the TGF- $\beta$ /SMAD2 Signaling Pathway. *Aging Dis.* 2018;9(6):1058-73.
35. Cultrera G, Lo Giudice A, Santonocito S, et al. MicroRNA Modulation during Orthodontic Tooth Movement: A Promising Strategy for Novel Diagnostic and Personalized Therapeutic Interventions. *Int J Mol Sci.* 2022;23.( $\nu$   $\xi$ )
36. Kazanopoulos N, Sideris CD, Xu Y, et al. Identification of Salivary Exosome-Derived miRNAs as Potential Biomarkers of Bone Remodeling During Orthodontic Tooth Movement. *Int J Mol Sci.* 2025;26.( $\nu$ )
37. Leng Q, Chen L, Lv Y. RNA-based scaffolds for bone regeneration: application and mechanisms of mRNA, miRNA and siRNA. *Theranostics.* 2020;10(7):3190-205.
38. Loh HY, Norman BP, Lai KS, et al. Post-Transcriptional Regulatory Crosstalk between MicroRNAs and Canonical TGF- $\beta$ /BMP Signalling Cascades on Osteoblast Lineage: A Comprehensive Review. *Int J Mol Sci.* 2023;24.( $\nu$ )
39. Long H, Sun B, Cheng L, et al. miR-139-5p Represses BMSC Osteogenesis via Targeting Wnt/ $\beta$ -Catenin Signaling Pathway. *DNA Cell Biol.* 2017;36(8):715-24.
40. Wang J, Liu S, Li J, et al. Roles for miRNAs in osteogenic differentiation of bone marrow mesenchymal stem cells. *Stem Cell Res Ther.* 2019;10(1):197.
41. Yan W, Lin X, Ying Y, et al. Specific RNA m6A modification sites in bone marrow mesenchymal stem cells from the jawbone marrow of type 2 diabetes patients with dental implant failure. *Int J Oral Sci.* 2023;15(1):6.
42. Conte A, Ghiraldini B, Casarin RC, et al. Impact of type 2 diabetes on the gene expression of bone-related factors at sites receiving dental implants. *Int J Oral Maxillofac Surg.* 2015;44(10):1302-8.
43. Pan T, Song W, Xin H, et al. MicroRNA-activated hydrogel scaffold generated by 3D printing accelerates bone regeneration. *Bioact Mater.* 2022;10:1-14.
44. Limlawan P, Insin N, Marger L, et al. 3D-printed TCP-HA scaffolds delivering MicroRNA-302a-3p improve bone regeneration in a mouse calvarial model. *BDJ Open.* 2023;9(1):50.