Babol University Of Medical Sciences

IJMCM, Summer 2025, VOL 14, NO 3

International Journal of Molecular and Cellular Medicine

Journal homepage: www.ijmcmed.org

IJMCM

REVIEW ARTICLE

From Bench to Bedside: Translating Research on miR-138 miR-195-5p and Long Non-Coding RNA H19 into Therapeutic Applications of Orthodontic Tooth Movement

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ARTICLE INFO

Received: 2024/11/13
Revised: 2024/12/30
Accepted: 2025/01/05

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ABSTRACT

This research investigates the roles of microRNAs (miR-138, miR-195-5p) and the long non-coding RNA (lncRNA) H19 in orthodontic tooth movement (OTM). A literature review using databases such as PubMed and Scopus identified 148 articles, which were subsequently narrowed down to 61 unique studies after duplicate removal. The findings underscore the significance of mechanical stimulation in bone metabolism and the complex biological mechanisms of OTM, with a focus on the functions of osteoblasts and osteoclasts. The study aimed to elucidate the expression patterns of non-coding RNA and microRNA in response to orthodontic force, potentially revealing new clinical methods to enhance the safety of orthodontic treatment. Additionally, it examines the therapeutic roles of miRNAs in orthodontics, specifically their influence on inflammation and bone regeneration. Notably, recent evidence has suggested miR-138 may inhibit osteogenesis, indicating its potential role in regulating bone remodeling during OTM, as mechanical forces affect both alveolar bone and periodontal tissues. Furthermore, miR-195-5p has been shown to directly interact with crucial osteogenic proteins, such as Wingless/Integrated 3 A (WNT3A), fibroblast growth factor 2 (FGF2), and bone morphogenetic protein receptor type 1A (BMPR1A). By downregulating these proteins, miR-195-5p negatively impacts essential osteogenic pathways related to bone formation and stability. The cyclic strain was found to upregulate lncRNA H19 while downregulating miR-138, promoting osteogenic differentiation of MSCs. This review outlines the complex regulatory networks involving these molecules, contributing to an understanding of OTM in dental and skeletal health, and aims to enhance treatment outcomes for malocclusion.

***Keywords*:** miR-138, miR-195-5p, long non-coding RNA H19, OTM, Therapeutic aspects

Cite this article: Nikeghbal D, et al. From Bench to Bedside: Translating Research on miR-138 miR-195-5p and Long Non-Coding RNA H19 into Therapeutic Applications of Orthodontic Tooth Movement. International Journal of Molecular and Cellular Medicine. 2025; 14 (3): 949-963. DOI: 10.22088/IJMCM.BUMS.14.3.949

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[DOI: 10.22088/IJMCM.BUMS.14.3.949]

Introduction

Orthodontic tooth movement (OTM), which is fundamentally the pivotal process aimed at rectifying malocclusion, is profoundly acknowledged as a complex sequence of intricate biological reactions that encompass bone remodeling alongside the regeneration of periodontal tissues, all of which are instigated by mechanical forces (MF) (1). This multifaceted process is characterized by the initial proliferation and differentiation of osteoblasts (OB), osteoclasts (OC), and their respective precursor cells; research has demonstrated that the compressed and disorganized state of the periodontal ligament (PDL) incites bone resorption, in stark contrast to the observation that the stretching of PDL fibers promotes bone deposition, thus illustrating the duality of response elicited by mechanical stimuli (2, 3).

Numerous studies have consistently validated the assertion that mechanical stimuli are of paramount importance for maintaining bone metabolism and play a regulatory role in osteogenic differentiation, alongside the processes of bone formation. The phenomenon of OTM encompasses a diverse array of mechanical forces in vitro, which are included but are not limited to stretch stress, compressive force, and shear stress induced by fluid flow, each contributing uniquely to the overall biological response (1). Thus, understanding the precise roles and mechanisms by which these forces operate is crucial for advancing the field of orthodontics and enhancing treatment outcomes for patients suffering from malocclusion. As we delve deeper into the intricacies of these mechanical forces, we aimed to elucidate the underlying biological principles that govern OTM, thereby contributing to the broader understanding of orthodontic interventions and their respective impacts on dental and skeletal health (1, 4, 5).

Recent investigations have elucidated that microRNAs (miRNAs) serve as pivotal modulators in the physiology of bone. The aberrant regulation of miRNAs has the potential to influence the modeling of maxillofacial bone by modulating cellular processes such as proliferation, migration, differentiation, and apoptosis. Throughout the remodeling continuum, miRNAs act as sensors for mechanical stimuli, regulators of cellular behavior, and facilitators of intercellular communication (6). Furthermore, contemporary research has unveiled the therapeutic promise inherent to miRNAs. For instance, miRNAs are capable of functioning as biomarkers for the detection of diseases and promoting the acceleration of bone remodeling and dental movement. These revelations significantly enhance our comprehension of the regulatory functions of miRNAs within bone physiology and illuminate potential avenues for their prospective clinical applications (6, 7). The exploration of lncRNA-mediated periodontal regeneration is currently in its nascent stages and offers less comprehensive insights than those provided by miRNAs, attributable to the intricate mechanisms of action associated with lncRNAs and their diverse array of targets. Mechanical tension, compressive force, and PDL tissues derived from orthodontic patients are predominantly employed to examine the differentially expressed lncRNAs in OTM (8).

Recent research has highlighted miR-138 as a possible suppressor of osteogenesis and a key player in the differentiation of stem cells and the formation of tissues. Its established role in these processes positions miR-138 as a potential regulatory factor in maintaining periodontal health and influencing stem cell differentiation in the context of periodontal inflammation. The expression of miR-195-5p was found significantly reduced and exhibited a negative correlation with the process of osteogenic differentiation (9). The overexpression of miR-195-5p markedly impeded the differentiation of periodontal ligament cells (PDLC) under conditions of cyclic tensile strain (CTS), whereas the functional suppression of miR-195-5p produced a contrasting outcome. Subsequent investigations substantiated that WNT3A, FGF2, and bone morphogenetic protein receptor-1A (BMPR1A), which are crucial proteins for osteogenic function and stability, were identified as direct targets of miR-195-5p (10).

Long non-coding RNA H19 is pivotal in orthodontic tooth movement as it affects the processes of bone remodeling. OTM is a multifaceted biological phenomenon that entails the alteration of alveolar bone and periodontal tissues due to mechanical forces. Non-coding RNAs, such as lncRNA H19, play a vital role in the regulation of gene expression throughout these processes. Specifically, H19 has been recognized as a mechano-sensitive lncRNA that reacts to mechanical stimuli, thereby impacting osteogenesis and osteoclastogenesis, both of which are critical for bone remodeling during OTM (8, 11).

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[DOI: 10.22088/IJMCM.BUMS.14.3.949]

To elucidate the forefront advancements of long non-coding RNA H19, the miR-138, and miR-195-5pwithin OTM, we present a comprehensive summary of the orthodontic force-mediated specific expression profiles of ncRNA and miRNA alongside their roles in cellular and molecular responses. Clarifying the intricate regulatory mechanisms will yield novel clinical methodologies for the implementation of safe orthodontic interventions. The summary of the mentioned effects is described in figure 1.

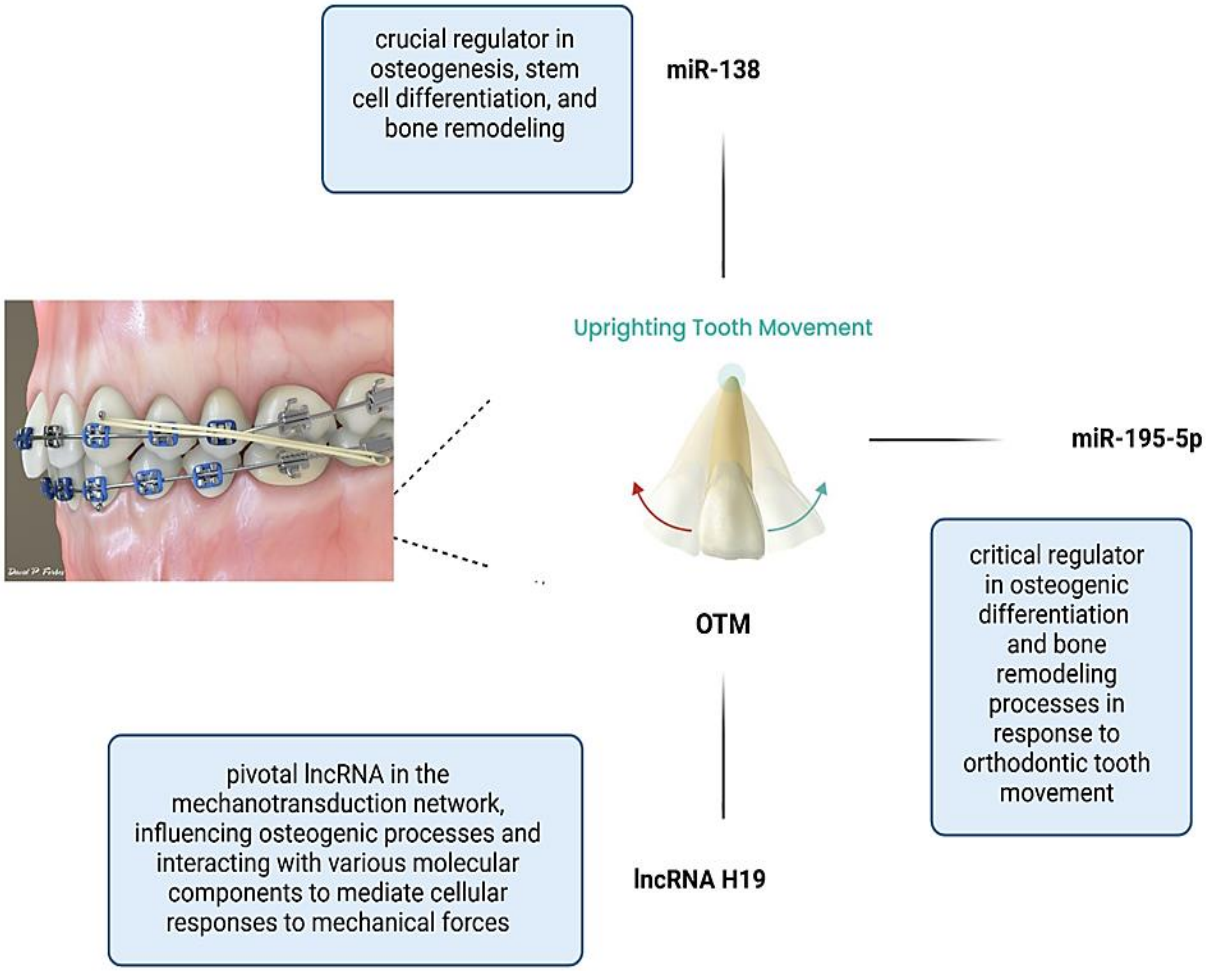

Figure 1. The miR-138, miR-195-5 p, and lncRNA H19 effects on OTM. miR-138 and miR-195-5 p regulate osteogenesis, stem cell differentiation, and bone remodeling and play a role in OTM. Additionally, lncRNA H19 has a vital effect on the mediation of the cellular response in response to mechanical forces.

Literature Search and Selection

A comprehensive narrative review of the extant literature concerning the context of miR-138, miR-195-5p, and lncRNA H19 association effect in orthodontic tooth movement was executed. The criteria for inclusion encompassed scholarly articles that were composed in the English language, accessible in full-text format, exhaustive in nature, and directly pertinent to the subject matter under scrutiny. An extensive search was undertaken within the PubMed and Scopus databases during October 2024, employing keywords associated with OTM, orthodontic tooth movement, miR-138, lncRNA H19, miR-195-5p, lncRNA, and miRNA. From the initial search parameters, 148 articles were procured based on their titles, abstracts, and publication dates. Following the removal of duplicate entries, a total of 59 unique articles remained for consideration.

The full texts of these selected articles were meticulously reviewed, resulting in the identification of a subset of four articles that were relevant to the research inquiry. Subsequently, in November 2024, an additional search was performed utilizing Google Scholar, PubMed, and Scopus, yielding the

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identification and incorporation of two further articles that were directly relevant to the area of interest.

Orthodontic tooth movement

Orthodontic tooth movement involves a complex interplay between the physiological adaptation of alveolar bone to mechanical forces and minor reversible damage to the periodontium. In healthy conditions, this movement is facilitated by a well-coordinated and effective process of bone remodeling, which necessitates the coupling of bone formation with bone resorption. The traditional pressure-tension theory suggests that chemical signals, rather than electrical ones, act as the primary stimuli for cellular differentiation and subsequent tooth movement. According to this theory, when a force is applied, the tooth almost immediately begins to move within the periodontal ligament (PDL) space, resulting in areas of compression and tension in the PDL (1, 2). These chemical mediators have distinct effects on cellular activities in the compressed and tense areas of the PDL, promoting bone resorption on the compression side and bone formation on the tension side. The magnitude of the applied force influences the cellular responses in the compressed area; excessive force can disrupt blood flow, leading to cell death and a condition known as hyalinization (12).

Consequently, osteoclast differentiation is inhibited in the compressed PDL, and instead, delayed recruitment of osteoclasts from the adjacent bone marrow contributing to the "undermining resorption" that removes the lamina dura adjacent to the compressed PDL. Tooth movement occurs only after these processes on the compression side are completed, which typically takes 7 to 14 days following the application of heavy force. Clinically, it is nearly impossible to completely prevent blood vessel occlusion; therefore, hyalinization inevitably occurs to some extent. Consequently, tooth movement results from a combination of undermining and frontal resorption (2, 3, 5). Fluid-induced strain and hypoxia work together to enhance the remodeling of bone and the periodontal ligament (PDL) by triggering an aseptic inflammatory response that is free of bacteria.

When a tooth is subjected to loading, it creates regions of tension and compression within the PDL, affecting its associated nerve endings and blood vessels. The nerve endings in the PDL are closely linked to blood vessels (1). When these nerve endings are disturbed, they release vasoactive neurotransmitters such as substance P and calcitonin gene-related peptide (CGRP), which interact with vascular endothelial cells, leading to vasodilation and increased permeability, resulting in plasma leakage. The activated endothelium then binds and recruits circulating leukocytes, monocytes, and macrophages to the PDL, marking the beginning of acute inflammation. Leukocytes produce cytokines, prostaglandins, growth factors, and colony-stimulating factors that facilitate tissue remodeling. After a few days, the inflammatory response evolves from an acute phase to a chronic and proliferative phase, involving fibroblasts, endothelial cells, osteoblasts, and osteoclasts (13, 14).

The comprehension of the biological mechanisms behind orthodontic tooth movement holds significant clinical relevance. Typically, active orthodontic treatment spans 18 to 24 months, representing a considerable commitment. Consequently, there has been a sustained interest in methods to accelerate tooth movement to reduce treatment duration, a pursuit that dates back to the 1890s (14, 15).

Advances in technology, particularly in customized brackets and wires, have notably enhanced treatment efficiency; however, these innovations cannot perpetually decrease treatment time, as we are ultimately constrained by the biological responses involved in orthodontic tooth movement. Another notable trend in orthodontics is the rising number of adult patients seeking treatment. The 2015 AAO Economics of Orthodontics Survey indicated that, on average, orthodontists treated 125 adult patients in 2014, compared to only 41 in 1989, highlighting a significant increase in recent years.

Adult patients stand to gain, particularly from accelerated orthodontic treatment due to their lack of growth and the slower rates of local tissue metabolism and regeneration compared to younger individuals. Furthermore, adults are at a higher risk for periodontal issues and other time-sensitive complications, such as oral hygiene challenges and root resorption. Thus, expediting treatment for adults presents additional practical advantages. Given that the remodeling of alveolar bone is crucial for orthodontic tooth movement, various techniques, both surgical and nonsurgical, have been developed to hasten tooth movement by targeting the biological pathways that influence the activity of bone cells, including osteoclasts, osteoblasts, and osteocytes (16).

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MicroRNAs

MicroRNAs exhibit an approximate length of 22 nucleotides, serving as post-transcriptional modulators. These miRNAs exert regulatory control over gene expression by binding to their target mRNAs in a sequence-specific fashion. The canonical biogenesis pathway of miRNAs encompasses (i) the transcriptional activity and generation of miRNA precursors within the nucleus and (ii) the transportation and subsequent processing of these precursors in the cytoplasm. miRNA genes are positioned within both intronic and exonic regions of the genomic architecture (17-19). The loci of certain miRNAs are spatially adjacent to one another, exemplified by the miR-17-92 cluster, which is typically co-transcribed and operates synergistically. The transcriptional process of miRNAs is modulated by a plethora of transcription factors (TFs) and is executed by RNA polymerase II, yielding primary miRNAs (pri-miRNAs) characterized by a stem-loop configuration and exceeding 1 kb in length (Ha and Kim, 2014).

Following transcription, extensive pri-miRNAs are subjected to further processing, resulting in the formation of 60-nucleotide hairpin-shaped precursor miRNAs (pre-miRNAs) (20). Within the cytoplasmic milieu, pre-miRNAs undergo additional cleavage by another RNase III-like endonuclease, Dicer, resulting in the generation of mature miRNA duplexes. These duplexes are constituted by the miRNA-5p strands derived from the 5′ end and the miRNA-3p strands originating from the 3′ end of the pre-miRNAs (18, 19, 21).

Differentially expressed miRNAs in orthodontic tooth movement

The variations in miRNA expression profiles can be ascribed to the specific types, magnitudes, and durations of orthodontic forces applied. The expression levels of miR-29 a, b, c, and miR-3198 exhibited an upregulation in response to compressive strain, whereas a downregulation was noted under tensile conditions. Upon the application of the same tensile stimuli, a notable reduction in the expression of miR-29a, b, c, -193, -101, -27a, b, -33a, -337, and -21 was recorded at the 24-hour mark, while a significant decline in miR-1297, -424-5p, -145-5p, -224-5p, and -195-5p expression was documented following 72 hours of stimulation. Gingival crevicular fluid (GCF), obtained from orthodontic patients, offers a more precise representation of the differential miRNA expression profiles (22, 23).

For example, the mechanosensitive miR-195-5p directly targets WNT3A, FGF2, and BMPR1A, thereby influencing the osteogenic differentiation of periodontal ligament cells under mechanical loading conditions. Current efforts are directed toward the integration of RNA sequencing with in vivo investigations to enhance the understanding of the miRNA-mRNA network involved in the OTM process, thereby elucidating the underlying mechanobiological mechanisms (22, 23). miR-138 plays a significant role as a mechanosensitive miRNA in the context of bone metabolism. In bone marrow-derived stem cells (BMSCs) subjected to mechanical stretching, there is an upregulation of FAK expression and tension-induced osteogenesis. This phenomenon is likely attributed to reduced levels of miR-138, which has a specific binding affinity for PTK2, the gene responsible for encoding FAK. On the other hand, miR-195-5p is reduced in human periodontal ligament cells (hPDLCs) subjected to cyclic tensile strain and on the tension side of the orthodontic tooth movement mouse model. This microRNA negatively regulates osteogenesis by directly interacting with Wnt3a and Bmpr1a (23-25).

Therapeutic implications of miRNAs in orthodontic interventions

The levels of miRNAs in periodontal tissues are amenable to observation during orthodontic interventions due to their responsiveness to mechanical stimuli. Gingival crevicular fluid (GCF), an exudate derived from serum within the gingival sulcus, encompasses various bioactive constituents. Following canine retraction, the concentration of miR-29 in GCF exhibits a rapid increase, persisting for six weeks post-treatment (25).

Conversely, miR-34 levels exhibit a gradual downregulation in GCF from both tension and compression sites, returning to baseline levels after twelve weeks. Moreover, the concentration of miR-155-5p in GCF correlates with the extent of root resorption, with levels in healthy subjects being twice as high as those observed in individuals with severe root resorption, thus indicating its potential as a biomarker for root resorption during orthodontic tooth movement. Several miRNAs, including miR-4291, -1245b-3p, and -1825, have been associated with peri-

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implantitis in patients utilizing miniscrew implants throughout orthodontic treatment. These observations imply that miRNAs may serve as effective indicators for monitoring the risks inherent in orthodontic procedures (26, 27).

Understanding how different miRs influence bone formation and reabsorption can help orthodontists develop better treatment plans that promote healthy tooth movement and minimize complications. Figure 2 illustrates the molecular regulation of bone remodeling during orthodontic tooth movement, showing how mechanical forces on periodontal ligament cells activate either osteoblasts (for bone formation) or osteoclasts (for bone resorption). It highlights the role of microRNAs in these processes (Figure 2). Orthodontic interventions generally extend over 2–3 years. Extended treatment duration may elevate the likelihood of caries, gingival recession, and root resorption.

Various surgical and physical methodologies, such as periodontal accelerated osteogenesis orthodontics (PAOO), vibration, and pulsed electromagnetic fields (PEMFs), have been employed to expedite bone remodeling and tooth mobility (28).

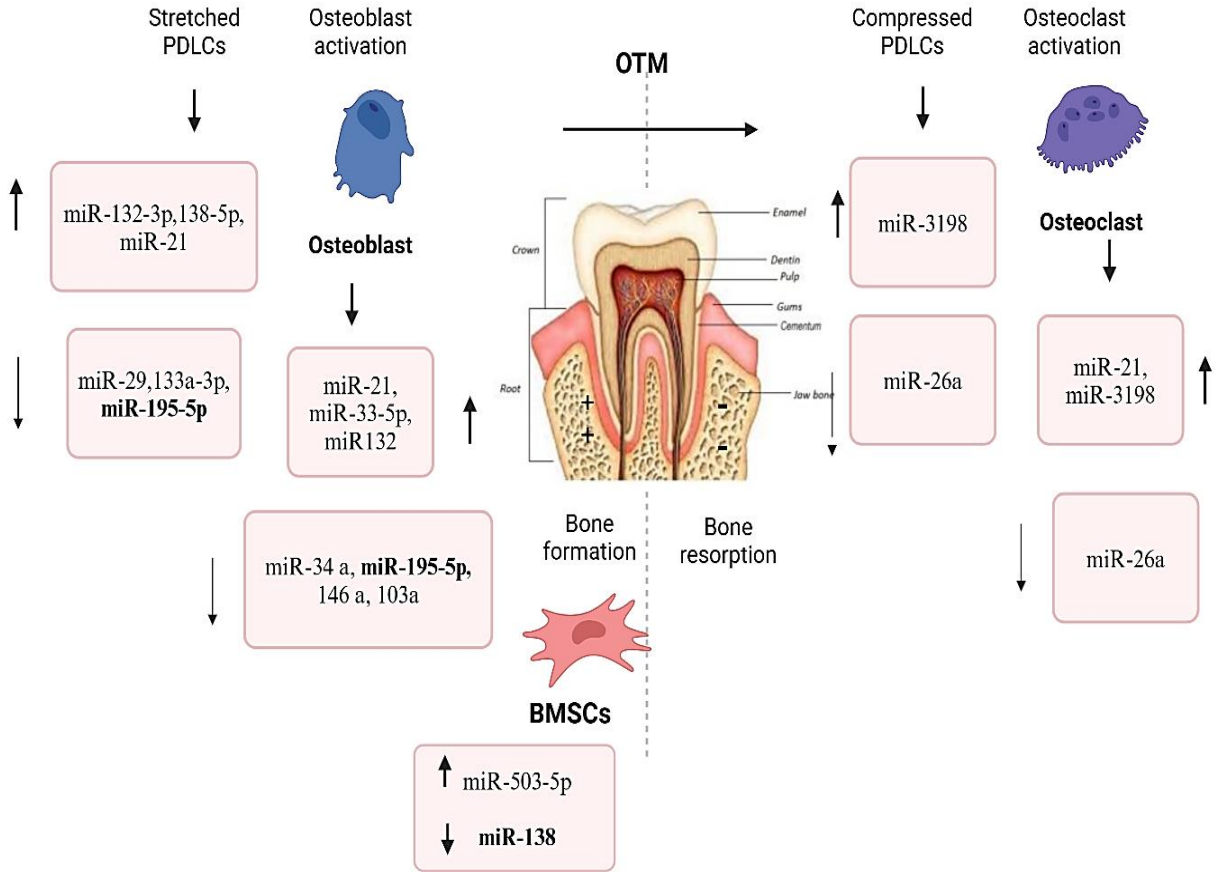

Figure 2. Understanding the impact of MicroRNAs on Dental Bone Formation and Reabsorption. This diagram emphasizes the role of miRNAs as molecular switches in OTM. By targeting key signaling pathways, they regulate osteoblast and osteoclast activities, ensuring a balanced remodeling process. Understanding these mechanisms is crucial for enhancing orthodontic treatments and addressing bone metabolism disorders.

The significant involvement of miR-138 in various human cancers has been documented. Research indicates that miR-138 levels are often reduced in tissues and cells associated with non-small cell lung cancer, and its overexpression has been shown to inhibit cancer cell proliferation both in vitro and in vivo by targeting the zeste homolog 2 enhancer (29-32). More recently, miR-138 has emerged as a potential prognostic marker for overall survival in patients with non-small cell lung cancer, primarily through its regulation of 3-phosphoinositide-dependent protein kinase-1 (33, 34). Additionally, findings by Ye et al.

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revealed that miR-138 suppresses the proliferation of lung cancer cells by inhibiting 3-phosphoinositide-dependent protein kinase-1. In the context of human anaplastic thyroid carcinoma cells, reduced levels of miR-138 were linked to an increase in human telomerase reverse transcriptase protein (32, 34).

Moreover, miR-138 has been shown to play a role in the regulation of hepatocellular and colorectal cancers by targeting cyclin D3 and the Twist basic helix-loop-helix transcription factor 2 gene. In head and neck squamous cell carcinoma cell lines, the overexpression of miR-138 led to decreased cell invasion and enhanced cell cycle arrest and apoptosis, while its knockdown resulted in the opposite outcomes. Jiang et al. reported that miR-138 inhibited migration and invasion in tongue squamous cell carcinoma by downregulating RhoC and ROCK2, key components of the Rho GTPase pathway. Furthermore, G protein α inhibiting activity polypeptide 2 was confirmed as a direct target of miR-138 in tongue squamous cell carcinoma. In our current study, we have established that miR-138 directly regulates YAP1 in OSCC cells, demonstrating that its overexpression significantly reduces both mRNA and protein levels in OSCC cells, as well as inhibiting cell proliferation and tumor growth. Conversely, the downregulation of miR-138 produced opposing effects (35).

Osteogenic differentiation and bone formation are intricately controlled by various factors, including microRNAs (miRNAs). Nonetheless, the expression patterns and roles of miRNAs during the osteogenic PDLCs induced by mechanical loading are not well understood. In an experimental study, the expression of miRNA-195-5p in the periodontal tissues of mice subjected to orthodontic mechanical loading, as well as in primary human PDLCs under simulated tension strain, was examined. It was found that miR-195-5p was downregulated and showed a negative correlation with osteogenic differentiation (36).

The overexpression of miR-195-5p significantly hindered PDLC differentiation in response to cyclic tension strain (CTS), while inhibiting miR-195-5p produced the opposite outcome. Additional experiments revealed that WNT family member 3A, fibroblast growth factor 2, and bone morphogenetic protein receptor-1A —key proteins for osteogenic activity and stability—are direct targets of miR-195-5p. Mechanical loading led to an increase in the protein levels of WNT3A, FGF2, and BMPR1A, whereas miR-195-5p suppressed their expression. The signaling pathways involving WNT, FGF, and BMP were found to play a role in the osteogenic differentiation of PDLCs under CTS (36).

The most recent investigation conducted utilizing high-throughput sequencing presents an examination of 47 established miRNAs: 31 exhibited upregulation (associated with mechanical force-induced osteoblastic/cementoblastic differentiation in periodontal ligament cells (PDLCs)) while 16 demonstrated downregulation in the stretched PDLCs when compared to the control group. Moreover, the target genes that were upregulated in PDLCs following force stimulation include Runt-related transcription factor 2 (RUNX2), osterix (OSX), Distal-less homeobox 5 (DLX5), and Special AT-rich sequence-binding protein 2 (SATB2); notably, only RUNX2, Msh homeobox 2 (MSX2), and SATB2 were additionally found to be upregulated in PDLCs subjected to tension force loading (37, 38). In a separate in vitro investigation wherein PDLCs were exposed to cyclic tension for 72 hours, miR-195-5p was likewise identified as downregulated and negatively correlated with osteogenic differentiation. miRNA-21 has been identified as having a role in certain surgical interventions, specifically Periodontally Accelerated Osteogenic Orthodontics (PAOO), which notably decreases the duration of treatment. PAOO is further linked to various clinical benefits, such as a decrease in root resorption, as the miRNA responsible for inhibiting the differentiation of osteoclasts through the targeting of CXCR2 is miRNA-155-5p. Nevertheless, there exists a paucity of research investigating the involvement of miRNA-155-5p in PAOO. Beyond dentin phosphoproteins (DDP), miRNA-155-5p may also serve as a credible biomarker for root resorption, given that its levels in CGF samples exhibit a consistency that is inversely related to those of DDP (39, 40).

Recently, miR-138 has been documented to exert significant influence in various physiological biological processes within distinct bone cell types for instance proliferation, apoptosis, differentiation, and invasion, while also functioning as a pivotal regulator in pathological bone disorders. Prior investigations have indicated that miR-138 negatively modulates osteogenic differentiation and ectopic bone formation (9, 10). In the context of therapeutic implications, these investigations have incorporated mesenchymal stem

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cells (MSCs) that were pretreated with a miR-138-5p inhibitor into immunocompromised murine models. In a study, miR-138-5p exhibited a negative correlation with bone formation in both human and murine subjects, and the administration of a miR-138-5p inhibitor via an osteoblast-targeted delivery system ameliorated the reduction of bone formation in hindlimb-unloaded and aged mice, which are recognized as common models for osteoporosis. These observations advocate for the potential application of miR-138-5p as a therapeutic target and the inhibition of miR-138-5p as a viable pharmacological intervention for osteoporosis (41).

Moreover, comprehensive investigations revealed that the therapeutic benefits associated with the administration of the miR-138-5p inhibitor were found to be superior in efficacy when compared to the effects induced by mechanical loading interventions, such as those experienced during treadmill exercise regimens; however, it is also important to note that the effectiveness of the miR-138-5p inhibitor alone was found to be comparatively less potent than the synergistic impact observed when the miR-138-5p inhibitor was administered in conjunction with mechanical loading techniques.

The investigation into the downstream targets of miR-138-5p culminated in the identification of microtubule actin crosslinking factor 1 (MACF1). The previous findings elucidate that MACF1 positively influences osteoblast differentiation and bone formation through the activation of the Wnt/β-catenin or BMP signaling pathways, which are also presumably implicated in the regulatory effects of miR-138 on osteogenic differentiation. Furthermore, MACF1, functioning as a cytoskeletal crosslinker, has been shown to exhibit a negative correlation with aging and also demonstrates mechanoresponsiveness under varying mechanical conditions. Additionally, we discovered that the transfection of the Macf1 3'UTR repetitive sequence elicited effects analogous to those produced by the miR-138-5p inhibitor. These findings provide a plausible mechanistic insight into the role of miR-138-5p in mechanosensitivity (41, 42).

Non-coding RNAs (ncRNAs)

Non-coding RNAs, which constitute 98% of the total RNA within cells, are categorized into two primary classifications: short ncRNAs (less than 200 nucleotides) and lncRNAs (greater than 200 nucleotides). MicroRNAs are a subset of short ncRNAs, typically measuring approximately 19–22 nucleotides in length, that function to degrade or inhibit mRNAs primarily by binding to the 3′ untranslated region (UTR) of target mRNAs. The synthesis of miRNAs begins with the formation of pri-miRNAs, which are subsequently processed by Drosha into pre-miRNAs and subsequently cleaved by Dicer to yield mature miRNAs (22). LncRNAs exhibit a biogenesis process akin to that of mRNAs and are integral to the transcriptional, post-transcriptional, and epigenetic regulation of gene expression, serving as guides, signals, decoys, or scaffolds. For instance, lncRNAs possess miRNA response elements that function to sequester miRNAs, thereby establishing a ceRNA that modulates the expression of target mRNAs. Non-coding RNAs are recognized as significant modulators of cellular functions, biological mechanisms, and various oral pathologies, including periodontitis, cleft lip and palate, and oral carcinoma (11).

Differentially expressed lncRNAs in orthodontic tooth movement

A total of 90 differentially expressed lncRNAs were identified in static stress-exposed periodontal ligament stem cells, whereas 1339 lncRNAs, comprising 799 that were upregulated and 540 that were downregulated, were identified in response to applied strain. Under tensile conditions, the expression profiles of lncRNA-mRNA in periodontal ligament cells are significantly enriched in the PI3K-Akt pathway, which is critical for osteoblast differentiation (22, 43, 44). Furthermore, the PI3K-Akt signaling pathway has been implicated in lncRNA-mediated OTM based on analyses of data from orthodontic patients. circRNAs are a unique and relatively stable category of lncRNAs characterized by a single-stranded covalent closure. A total of 2678 differentially expressed circRNAs were observed in the stretched PDLSCs, with circRNA3140 proposed to either directly or indirectly influence miRNA-mediated osteogenic differentiation. Specific lncRNAs and circRNAs could act as ceRNAs to facilitate the osteogenic differentiation of PDLSCs in response to mechanical stimuli. Nevertheless, the majority of studies have predominantly conducted PCR analysis following RNA sequencing and bioinformatics assessments, without validating the intricate networks of lncRNA-miRNA-mRNA interactions (22, 43, 44).

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lncRNA H19 mitigated the inhibition of Protein tyrosine kinase 2 (PTK2) by sponging miR-138, which enhanced the sensitivity of mesenchymal stem cells (MSCs) to mechanical tension and promoted osteoblast differentiation. Thus, the role of mechano-sensitive non-coding RNAs is becoming increasingly significant as they connect specific mechanical sensors with extracellular signals during osteogenic tissue maturation. Additionally, cyclic strain increased the expression of lncRNA H19 while reducing the levels of miR-138 in mesenchymal stem cells, which in turn promoted osteogenic differentiation through the FAK-ERK1/2-RUNX2 signaling pathway (45-47).

NcRNA-based clinical implications and prospects

Ongoing research into the role of ncRNAs in orthodontic tooth movement is enhancing the transition from laboratory findings to personalized clinical applications. The benefits of ncRNA-based therapies are twofold. Firstly, ncRNAs are naturally occurring molecules that offer more precise processing and target selection compared to synthetic alternatives. Secondly, they influence genes and signaling pathways at various levels, resulting in a comprehensive and distinctive response during the remodeling of the periodontium. In the realm of OTM, ncRNAs hold promise for optimizing orthodontic forces, enhancing clinical outcomes, and mitigating complications. Additionally, a review of ncRNA therapy carriers is provided, to achieve optimal OTM while minimizing iatrogenic effects (43, 47).

NcRNAs can accelerate OTM by influencing cell proliferation, differentiation, autophagy, and inflammation. However, the speed of OTM is constrained by the biological principles of periodontal tissue reconstruction. Therefore, effective orthodontic treatment should focus on tooth movement in suboptimal alveolar bone conditions, like atrophic bone, dehiscence, fenestration, and other defects. Additionally, conditions such as osteoporosis or periodontitis can impair bone turnover, leading to uncontrolled OTM and significantly prolonging treatment for affected patients (48).

Several ncRNA therapies are currently in phases I to III of clinical trials, including miRNA mimics Research has yet to advance lncRNA-based therapies to clinical trials, although anti-miRNAs are being explored. Notably, the application of exogenous miR-34a for patients with bone metastases and other disorders related to bone resorption has progressed to phase I clinical trials. Evidence suggests that during orthodontic tooth movement, miR-34a enhances osteogenic differentiation and facilitates alveolar bone formation by activating the Wnt/β-catenin signaling pathway (38, 47). Additionally, therapies targeting the inhibition of miR-195 have been shown to promote osteoblast differentiation during OTM by increasing RUNX2 expression. The strategic loading of specific ncRNAs may also expedite the clinical management of patients with compromised alveolar bone conditions. Furthermore, a targeted increase in lncRNA XIST could potentially enhance the safety of orthodontic treatments for patients with periodontitis. Despite the beneficial effects of ncRNAs on impaired alveolar bone, there remains a need for improvement regarding the tissue specificity of ncRNA carriers and the determination of optimal dosing (22).

As previously noted, miR-34a-5p/DANCR and RUNX2/miR-26a collaboratively regulate osteoclast-mediated root resorption through Jagged1. Furthermore, p21 has been shown to inhibit the autophagy of cementoblasts under stress conditions, negatively affecting their functions. The involvement of ncRNAs in osteoclastogenesis presents potential therapeutic avenues for improving OIIRR. For example, the lentiviral suppression of p21 has been found to restore impaired cementoblastic differentiation and significantly reduce OIIRR. Nonetheless, the local administration of lentivirus may result in unintended inhibition of ncRNAs in periodontal ligament resident cells (22, 49).

The potential of ncRNA interventions in orthodontic tooth movement is significant; however, challenges remain regarding the specificity and delivery efficiency of ncRNA-based therapies due to the degradation and inherent instability of unprotected ncRNAs. Research has explored various ncRNA delivery systems, including viral and non-viral vectors, exosomes, and scaffolds (22). Non-viral vectors, which can be categorized into lipid-based and polymer-based types, are considered safer and more adaptable than immunogenic viral vectors. A recent advancement in polymer-based vectors has involved enhancing transfection efficiency by incorporating hydrophobic groups into PEI25K. This modified vector, loaded with miR-34a, significantly facilitated bone formation during OTM. In contrast to other delivery methods, exosomes serve as natural nanocarriers for ncRNAs

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[DOI: 10.22088/IJMCM.BUMS.14.3.949]

(50). When administered systemically, stable exosomes containing ncRNAs tend to migrate back to their site of origin, suggesting that exosomes carrying pro-osteoclastic ncRNAs may specifically target alveolar bone to enhance osteoclast-mediated OTM. Additionally, the use of scaffolds for the encapsulation or immobilization of ncRNAs is gaining traction.

Scaffolds allow for a three-dimensional distribution and controlled release of ncRNAs within periodontal tissues, aligning with the kinetics of transgene expression necessary for tissue regeneration. One study highlighted an activated scaffold integrating miR-21 and bio-oss particles, which effectively supported stable and sustained alveolar bone regeneration. Although data remained limited, the development of optimized functionalized carriers is anticipated to refine ncRNA applications for the precise remodeling of the periodontium through mechanical, chemical, and biological innovations (51).

ncRNAs collectively offer innovative approaches for investigating optimal forces in orthodontics, enhancing clinical results, and mitigating root resorption. It is essential to further investigate specific delivery systems for ncRNAs to consolidate knowledge regarding target genes and their associated pathways, aiming for effective tooth movement while minimizing adverse effects. Numerous ncRNAs facilitate the differentiation and functionality of osteoblasts in response to mechanical forces by influencing osteogenic factors at the post-transcriptional stage. For instance, miR-33-5p and miR-20a specifically target Hmga2 and SMAD6, respectively, to enhance osteoblast differentiation induced by tension. Additionally, cyclic strain leads to the upregulation of lncRNA H19 and the downregulation of miR-138 in mesenchymal stem cells, thereby promoting osteogenic differentiation through the FAK-ERK1/2-RUNX2 signaling pathway. Furthermore, miR-21 interacts with several genes, including HIF-1, PLAP-1, and Activin A Receptor Type 2B (ACVR2B), to support osteogenic differentiation during orthodontic tooth movement (52). In rat models of OTM and hypoxic PDLCs, miR-21 enhances HIF-1 expression, thereby facilitating osteogenic differentiation, while the suppression of miR-21 hinders this process (53).

Non-coding RNAs have the potential to enhance orthodontic tooth movement by influencing processes such as cell proliferation, differentiation, autophagy, and inflammatory response. However, the overall acceleration of the OTM process is limited due to the inherent biological principles governing periodontal tissue reconstruction. Consequently, effective orthodontic treatment should prioritize tooth movement in less-than-ideal alveolar bone conditions, including atrophic bone, dehiscence, fenestration, and other defects. Additionally, conditions like osteoporosis or periodontitis can disrupt bone turnover, leading to uncontrolled OTM and significantly extending the treatment duration for affected individuals (48).

Notably, certain lncRNAs like Protein Kinase C zeta (Prkcz2), Hexokinase 3 (Hklos), Tumor protein P53 pathway corepressor 1 (Trp53cor1), Ganglioside-induced differentiation-associated-protein 10 (Gdap10), and Ak312-PS have been found to significantly inhibit cementoblastic activity when subjected to stress. In patients undergoing orthodontic treatment, miR-155-5p has been shown to suppress osteoclast differentiation and correlate with the severity of OIIRR (54). LncRNA H19 mitigates the suppression of PTK2, thereby increasing the sensitivity of mesenchymal stem cells to mechanical stress and facilitating osteoblast differentiation during OTM.

This process enhances biomechanical responses and aids in the remodeling of the periodontium. Additionally, lncRNA H19 is found to be upregulated in human bone marrow stem cells under strain during OTM, underscoring its significant role in osteoblast differentiation and its potential as a key regulator in the bone remodeling processes linked to OTM. H19 has been recognized as a mechano-sensitive lncRNA that reacts to mechanical stimuli during orthodontic tooth movement, thereby affecting both osteogenesis and osteoclastogenesis. This lncRNA engages with several signaling pathways, notably the PI3K-Akt pathway, which is essential for cellular responses to orthodontic forces (52).Altering the expression of lncRNAs may provide innovative therapeutic options to improve tooth movement and support periodontal tissue regeneration. However, despite the significant role of lncRNA H19 in OTM, the intricate nature of gene interactions and the impact of other noncoding RNAs indicate that a comprehensive approach is essential for a complete understanding of the biological mechanisms that govern orthodontic tooth movement.

Under conditions of mechanical tension, the long non-coding RNA known as H19 has been observed to

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experience an elevation in its expression levels, acting as a molecular sponge for the microRNA miR-138, which subsequently leads to the liberation of PTK2, a gene responsible for coding focal adhesion kinase (FAK); this cascade of events has been shown to facilitate the process of osteogenesis in hBMMSC through the activation of the FAK-ERK1/2-Runx2 signaling pathway, as reported by Wu et al. in their 2018 study (52). Moreover, H19 plays a significant role in the regulation of the fate of MSCs, particularly in how these cells respond to the nanotopographical cues present in their microenvironment, which is characterized by the orientation of fiber structures; this regulatory mechanism operates through the bone morphogenetic protein (BMP) signaling pathway, as elucidated in the research conducted by Izadpanahi et al. in 2018 (55).

Conversely, during periods of mechanical unloading, alterations in the expression of H19 may be attributed to an observed increase in the levels of DNA methyltransferase 1 (DNMT1), which is a crucial enzyme involved in DNA methylation processes. Specifically, a duration of three to four weeks characterized by stimulated unloading conditions has been documented to result in an anomalous increase in the expression profile of DNMT1, as well as a heightened nucleic-to-cytoplasmic localization ratio of this enzyme, which in turn leads to an enrichment of 5-methylcytosine at specific cytosine-phosphate-guanine (CpG) sites located within the promoter region of H19. The hypermethylation of the H19 promoter region consequently results in diminished levels of H19 expression, which is followed by a subsequent reduction in the phosphorylation and activation of extracellular signal-regulated kinase (ERK) and influences on critical signaling pathways such as TGF-β, WNT, and Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathways.

Ultimately, these molecular alterations culminate in the phenomenon of microgravity (MG)-induced bone loss, demonstrating the intricate interplay between mechanical forces, gene expression, and cellular behavior in the context of bone health and maintenance (56). Based on a published study by Jingyi Cai et al, in 2022, H19 has been shown to respond to mechanical tension. Under such conditions, its expression is elevated, which allows it to act as a competing endogenous RNA by sponging miR-138. This collaboration indicates the release of PTK2, which encodes Focal Adhesion Kinase, thus inducing osteogenesis in human bone marrow mesenchymal stem cells through the FAK-ERK1/2-Runx2 signaling pathway. The study highlights H19's central role in the force-responsive network. It integrates with other components, such as CFS-miRNA and FS mRNA, suggesting that H19 is a critical factor in mechanobiology. This integration provides insights into how H19 may influence cellular responses to mechanical stimuli. H19 is involved in a complex relation with transcription factors (TFs) and other lncRNAs, which indicates its potential monitoring character in the system.

The study suggests that H19 may participate in a crosstalk loop with FS mRNA and TFs, demonstrating its involvement in transcriptional regulation. The research indicates that H19's activity is linked to various signaling pathways, including TGF-β, WNT, and JAK-STAT pathways. The hypermethylation of H19's promoter can lead to its downregulation, which subsequently affects these pathways and contributes to conditions like microgravity-induced bone loss. The study's findings regarding H19's role were supported by literature, confirming its significance as a mechanoresponsive factor. H19's interaction with various signaling pathways, including TGF-β, WNT, and JAK-STAT, suggests that it may have broader implications in regulating cellular responses beyond just osteogenesis (57).

Figure 3 illustrates the differentiation of mesenchymal stem cells into osteoblasts (bone-forming cells) and the regulatory roles of various molecular factors, including miRNAs and transcription factors. This process is activated by the Wnt/β-Catenin and BMP/TGF-β signaling pathways, with RUNX2 serving as the central regulator of osteogenic differentiation, positively influenced by these pathways. Progenitor osteoblasts further mature into mature osteoblasts under RUNX2's direct influence. However, RUNX2 activity is inhibited by both the Wnt/β-Catenin and BMP/TGF-β pathways, which can slow down osteogenic differentiation. Moreover, miR-103a and miR-138 directly suppress RUNX2, hindering the progression from progenitor osteoblasts to osteoblasts, while lncRNA H19 indirectly impedes osteogenesis by inhibiting RUNX2. The Wnt/β-Catenin and BMP/TGF-β pathways promote osteogenic differentiation by activating RUNX2 (Figure 3).

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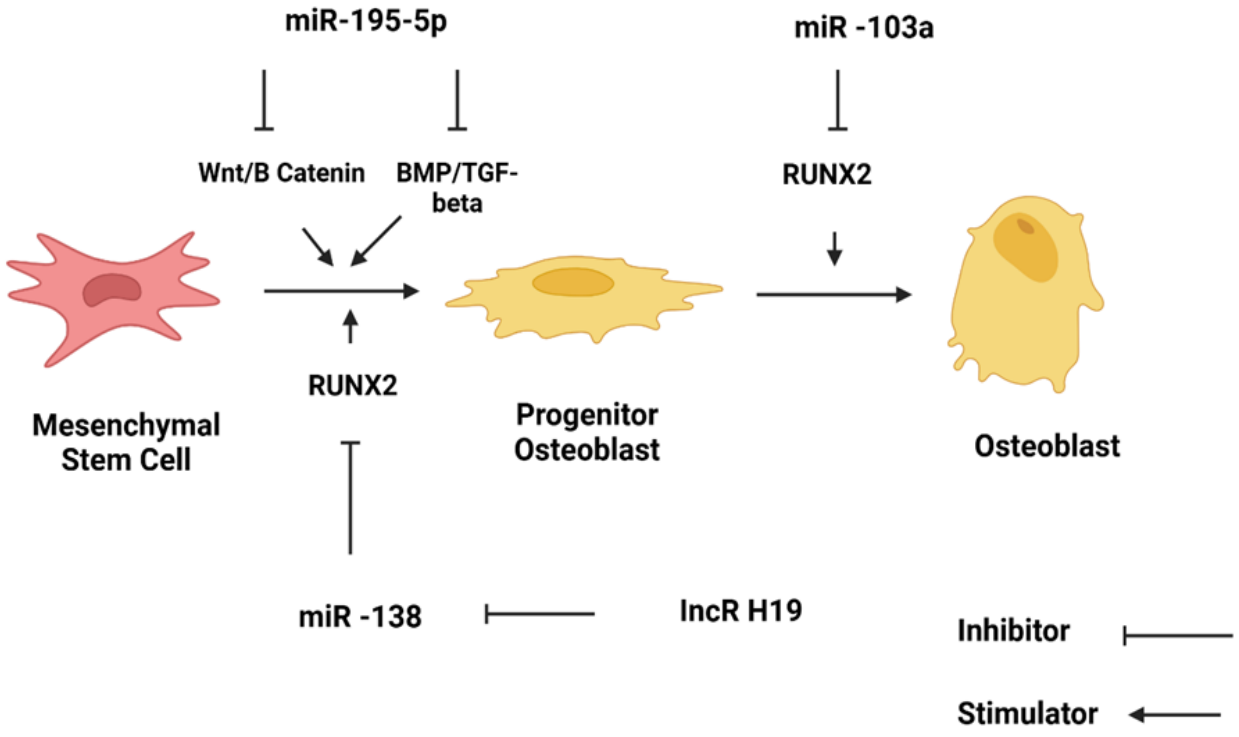

Figure 3. The inhibitory and stimulatory effects of miR-195-5 p, miR -138, and LncR H 19 on pathways related to osteoblasts.miR-195-5p, miR-103a, and miR-138 act as inhibitors of osteogenesis at various stages by targeting RUNX2 or its upstream pathways. The balance of stimulatory signals (e.g., Wnt/β-Catenin, BMP/TGF-β) and inhibitory signals (miRNAs and lncRNAs) determines the progression from MSCs to mature osteoblasts. This diagram underscores the complexity of the regulatory networks in bone formation and highlights potential therapeutic targets for bone-related diseases.

Discussion

In summary, miR-138 plays a vital role in osteogenesis, stem cell differentiation, and bone remodeling, with important implications for orthodontic treatments and broader therapeutic uses. On the other hand, miR-195-5p also regulates osteogenic differentiation and bone remodeling, especially in response to mechanical forces during orthodontic tooth movement. Its ability to target key osteogenic proteins and its sensitivity to mechanics make it a significant area for further research and potential therapies. Overexpression of miR-195-5p has been associated with reduced expression of osteogenic markers essential for stem cell differentiation into bone-forming cells, highlighting its role as a negative regulator in osteogenesis. Additionally, lncRNA H19 is mechano-sensitive, responding to mechanical forces during orthodontic treatment. H19's response is connected to various signaling pathways, notably the PI3K-Akt pathway, which is crucial for cellular responses to orthodontic forces, indicating that H19 not only reacts to mechanical stimuli but also integrates into broader signaling networks regulating bone remodeling. So, the review article emphasizes the role of miR-138 and miR-195-5p as molecular switches in OTM. By targeting key signaling pathways, they regulate osteoblast and osteoclast activities, ensuring a balanced remodeling process. Understanding these mechanisms is crucial for enhancing orthodontic treatments and addressing bone metabolism disorders.

Future directions

Mechanical tension increases H19 expression, allowing it to function as a competing endogenous RNA by sponging miR-138, which is essential for osteogenic differentiation. By mediating mechanical effects on MSCs and influencing osteogenic processes, lncRNA H19 is vital for bone remodeling during orthodontic treatments, highlighting its role in

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modulating gene expression in response to mechanical tension. So, understanding these mechanisms is crucial to enhance orthodontic treatments shortly and addressing bone metabolism disorders.

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