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ORIGINAL RESEARCH

MICRORNAS IN PERIODONTAL AND ALVEOLAR BONE REGENERATION: BRIDGING MOLECULAR BIOLOGY AND CLINICAL DENTISTRY

Vinodhini Priyanka[1], Taniya Mary Martin[2], Meenakshi Sundaram Kishore Kumar[2], Murugesan Krishnan[1]

[1]Department of Oral and maxillofacial surgery, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India

[2]Department of Anatomy, Zebrafish Facility, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India

Corresponding Author: Meenakshi Sundaram Kishore Kumar Department of Anatomy, Zebrafish Facility, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India vinodhini.908@gmail.com

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ABSTRACT

Background: MicroRNAs (miRNAs) are small non-coding RNAs that have emerged as key regulators in the orchestration of bone regeneration, particularly within the dental and periodontal domains. These molecules influence a wide range of cellular processes by modulating gene expression at the post-transcriptional level. In the context of oral health, miRNAs play crucial roles in controlling osteoblast and osteoclast differentiation, inflammatory signaling, angiogenesis and extracellular matrix remodeling-processes essential for successful periodontal repair, guided bone regeneration, and implant osseointegration.

Materials and Methods: Several miRNAs including miR-21, miR-29b, miR-214, and miR-26a, have been identified as critical regulators of osteogenic pathways such as Wnt/β catenin, BMP, TGF-β, and P13K/Akt. These miRNAs either promote or inhibit bone formation, offering novel molecular targets for enhancing regenerative therapies.

Results: The application of miRNAs in dentistry is further advanced by delivery strategies such as exosome-loaded constructs, lipid nanoparticles and gene-activated scaffolds, which ensure localized and sustained release at defect sites. This review provides a comprehensive overview of the role of miRNAs in alveolar bone healing and regeneration, emphasizing their translational potential in clinical dentistry.

Conclusion: Additionally, the integration of miRNA profiling with biomaterial-based therapies may pave the way for personalized regenerative strategies tailored to individual patient needs. Despite existing challenges related to specificity and delivery efficiency, miRNA-based approaches hold significant promise in redefining the future of dental regenerative medicine.

Keywords**:** MicroRNA, bone regeneration, periodontal therapy, guided bone regeneration, dental implants, osteogenesis, regenerative dentistry.

INTRODUCTION

Bone regeneration is an essential biological process that plays a pivotal role in the maintenance of oral and maxillofacial integrity, especially in the context of periodontal disease, tooth loss, implant therapy, and traumatic injuries. In the dental field, achieving predictable and functional bone regeneration is critical for procedures such as guided bone regeneration (GBR), Sinus lift augmentation, alveolar ridge preservation and peri-implant bone remodeling. Despite the development of sophisticated biomaterials and surgical techniques, limitations such as unpredictable healing outcomes, insufficient vascularization and delayed bone maturation continue to hinder clinical success[1]. Recent advances in molecular biology have unveiled the central role of gene regulation in bone remodeling, bringing MicroRNAs(miRNAs) into focus as key post transcriptional regulators of cellular functions involved in osteogenesis, angiogenesis, inflammation resolution and extracellular matrix remodeling (ECM)[2]. microRNAs are a class of small, non-coding RNA molecules, typically 18-25 nucleotide in length, that bind to the 3'untranslated regions (3'-UTRs) of target messenger RNAs (mRNAs), leading to their degradation or translational repression. By modulating gene expression, miRNAs influence a vast array of

physiological and pathological processes, including cellular proliferations, differentiation, apoptosis, immune response and tissue remodeling[3]. In the context of bone regeneration, miRNAs have emerged as fine tuners of osteoblast and osteoclast activity, essential for maintaining the delicate balance between bone formation and resorption. Given that the bone regeneration in the dental and craniofacial region involves a complex interplay of multiple check points[4]. In dental regenerative therapy, particularly in periodontology and implantology, miRNA research is gaining momentum for its potential to modulate critical signaling pathways involved in bone repair. miRNAs such as miR-21, miR-29b, miR-26a, miR-34a, and miR-214 have been shown to regulate transcription factors and signaling molecules such as Runx2, BMPs, SMADs, Wnt/β catenin, and TGF-β pathways that are indispensable in osteogenic differentiation and matrix mineralization. For instance, miR-21 enhances osteogenesis by suppressing PTEN and activating the P13k/Akt pathway, whereas miR-29b facilitates ECM remodeling and collagen deposition. On the contrary, miR-214 and miR-133 have been associated with inhibitory effects on osteoblast function and have been proposed as targets for therapeutic inhibition in bone loss conditions[5].

Periodontal disease remains a major cause of alveolar bone loss, posing challenges to both functional rehabilitation and esthetic restoration. The regenerative approach to periodontal therapy involves not only the restoration of alveolar bone but also the coordinated repair of supporting soft tissues such as the periodontal ligament and cementum[6]. In this milieu, miRNAs such as miR-146a and miR-155 act as negative regulators of inflammation by targeting components of the NF-κb signaling pathway, thereby promoting a microenvironment conducive to healing and regeneration. This immunomodulatory property of miRNAs is of particular significance in chronic inflammatory conditions like periodontitis, where unresolved inflammation hinders regenerative outcomes[7].

In the domain of dental implants, the role of miRNAs in enhancing Osseointegration is being actively explored. Osseointegration, defined as the direct structural and functional connection between living bone and the surface of a load bearing implant, is influenced by local bone quality, vascularity, and cellular signaling. miRNAs that promote osteoblast differentiation and inhibit osteoclast mediated resorption can potentially enhance early implant stability and long-term success. For example, studies have demonstrated that upregulation of miR-21 and down regulation of miR-138 can enhance osteogenic differentiation of human bone marrow stem cells on titanium surfaces, suggesting a role for miRNA-based modulation in implant surface functionalization[8].

From a tissue engineering perspective, the integration of miRNAs into biomaterial scaffolds represents a promising frontier. Gene-activated scaffolds incorporating miRNA mimics or inhibitors can provide spatial and temporal control over cellular activities, thereby enhancing the regenerative capacity of graft materials[9]. Exosome-based delivery systems and nanoparticle encapsulated miRNAs offer additional avenues for controlled and targeted therapy. Such strategies are particularly relevant in GBR and socket preservation techniques, where local bone formation is required to stabilize implants and maintain ridge volume. Moreover, miRNAs can be harnessed to precondition stem cells used in scaffold seeding, improving their osteogenic potential prior to transplantation.

Despite these promising developments, several challenges remain before miRNA based therapies can be translated into routine dental practice. Delivery barriers, off-target effects, immune responses and limited understanding of miRNA dynamics in human bone physiology are significant hurdles. Additionally, the pleiotropic nature of miRNAs, where a single miRNA can target multiple genes and pathways, raises concern regarding safety and specificity. Advances in bioinformatics, high through put sequencing, and systems biology are being employed to predict miRNA target interactions and optimize therapeutic design, Furthermore, personalized approaches using salivary miRNA profiling hold potential for identifying patients at high risk for bone loss or implant failure, paving the way for precision regenerative dentistry[10].

In summary, miRNAs are emerging as powerful regulators of bone regeneration with vast implication in dental and craniofacial therapies. Their ability to modulate key signaling pathways involved in osteogenesis, inflammation, and vascularization positions them as ideal candidates for enhancing current regenerative strategies. A deeper understanding of miRNA biology in the dental context, coupled with the development of safe and efficient delivery systems, can revolutionize the way we approach bone regeneration in clinical dentistry. As research progresses, the integration of miRNA based diagnostics and therapeutics into routine dental practice may soon

become a reality, offering new hope for patients with compromised bone structures due to disease, trauma or aging[11].

2.1 Biological functions of MicroRNAs in Bone Physiology

miRNAs are crucial regulators of bone physiology, exerting significant control over the cellular and molecular processes that govern skeletal development, maintenance, and regeneration. These small, non-coding RNA molecules modulate gene expression post transcriptionally by binding to the 3'untranslated regions of target miRNAs, leading to translational repression or degradation. In the context of bone biology, miRNAs are central to maintaining bone homeostasis by balancing the dynamic activities of osteoblasts and osteoclasts. This balance is essential for skeletal remodeling, repair and adaptation to mechanical stress –processes that are especially critical in the dental domain where continuous remodeling of alveolar bone occurs in response to mastication, periodontal inflammation and dental procedures such as extractions or implant prosthesis[12]. Numerous miRNAs have been identified as key modulators of osteoblastogenesis, the process by which mesenchymal stem cells differentiate into osteoblasts. For instance, miR-21 promotes osteogenic differentiation by targeting negative regulators such as Sprouty 1 and PTEN, leading to activation of P13K/Akt pathway. Conversely, miR-133 and miR-138 suppress osteoblast differentiation by inhibiting key osteogenic transcription factors like Runx2, a master regulatory of osteoblast lineage commitment. The dual nature of miRNAs capable of both promoting and inhibiting osteogenesis depending on the context-demonstrates their precision in fine tuning bone formation. In parallel, miRNAs also regulate osteoclastogenesis, the differentiation of hematopoietic precursors into osteoclasts responsible for bone resorption. miR-223 and miR-21 are to influence RANKL/RANK signaling, a central axis in osteoclast differentiation. For example, miR-21 promotes osteoclast formation by targeting PDCD4, a pro-apoptotic protein, thereby enhancing osteoclast survival. On the other hand, miR-34a and miR-146a suppress osteoclast activity, offering protective roles against pathological bone resorption seen in diseases like periodontitis and osteoporosis[13] (Figure 1).The regulatory influence of miRNAs extends to their interactions with major signaling pathways essential for bone development. The Wnt/β catenin pathway, crucial for promoting osteogenesis and inhibiting adipogenesis, is modulated by miRNAs such as miR-29b and miR335-5p. These miRNAs enhance Wnt signaling by suppressing inhibitors like DKK1 and SOST, thereby promoting osteoblast proliferation and matrix mineralization. Similarly, the bone morphogenetic protein (BMP) signaling pathway, known for its dual role in both promoting and inhibiting bone formation depending on context, is also under miRNA control, with miR-181a and miR -200 family members fine tuning its effects on proliferation and ECM production[14].

Collectively, these miRNA-mediated regulatory networks ensure precise control over bone remodeling and regeneration. In dental and craniofacial applications, understanding the biological functions of miRNAs offer a molecular basis for developing targeted therapeutics that can enhance bone regeneration, control pathological resorption and improve clinical outcomes in procedures such as implantology and periodontal reconstruction.

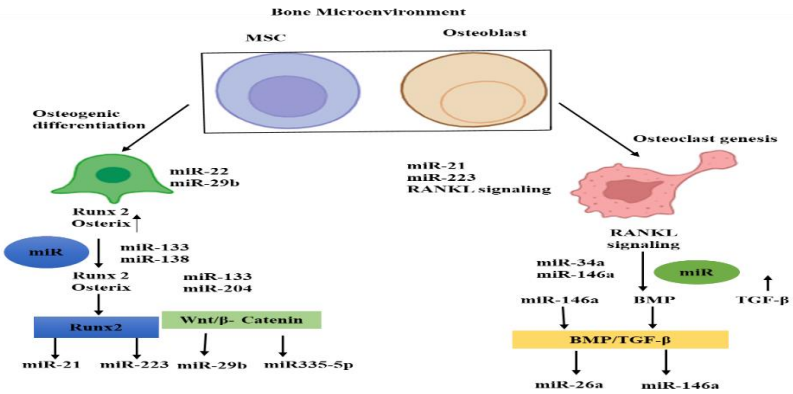

Figure1. MicroRNAs regulate bone physiology by modulating osteoblast and osteoclast activities, thereby maintaining skeletal remodeling, repair, and homeostasis essential for dental and alveolar bone dynamics

2.2 Key MicroRNAs involved in dental bone regeneration

Several MicroRNAs have been extensively studied for their crucial roles in regulating osteogenesis and bone remodeling, making them highly relevant in the context of dental and craniofacial bone regeneration. Among these, miR-21, mir-29b, miR-214.miR-34a, miR-26a and miR-378 represent key molecular regulators that influence the differentiation and activity of osteoblasts and osteoclasts, as well as modulate the signaling pathways critical for bone repair. Their ability to fine tune gene expression in a spatially and temporarily regulated manner offers a powerful tool for enhancing therapeutic outcomes in dental procedures such as guided bone regeneration, implant osteointegration and periodontal defect repair[15].

miR-21 is one of the most widely studied pro-osteogenic miRNAs ,known to promote osteoblast differentiation and bone formation by targeting inhibitors of the P13K/Akt pathway, such as PTEN and Sprouty1.It also suppresses pro apoptotic genes like PDCD4,facilitating osteoblast survival and proliferation, its dual role in promoting osteogenesis and modulating inflammation makes it especially valuable in periodontal regeneration where chronic inflammation often disrupts healing.miR-29b is another potent osteoinductive miRNA that directly targets genes involved in extracellular matrix remodeling, including COLIA1,osteonectin,and MMP2. By enhancing matrix mineralization and suppressing fibrosis, miR-29b contributes to both the early and late stages of bone healing. Its upregulation has been linked to improved outcomes in alveolar ridge preservation and scaffolds-based regenerative techniques[16]. In contrast, miR-214 acts as a negative regulator of bone formation. It suppresses osteoblast differentiation by targeting activating transcription factor 4 (ATF4) AND Osterix, key drivers of osteogenic gene expression.

Elevated levels of miR-214 have been associated with reduced bone density in inflammatory bone diseases and aging, highlighting its potential as a therapeutic target for inhibition in cases of impaired bone regeneration. Similarly, miR-34a is known to inhibit osteoclast differentiation by targeting RANKL and associated signaling molecules, thereby reducing bone resorption. Its upregulation in experimental models has demonstrated a protective effect against pathological bone loss, making it a candidate for therapeutic use in peri-implantitis and periodontitis[17].

miR-26a functions at the intersection of osteogenesis and angiogenesis, targeting SMAD1and components of the BMP signaling cascade. It facilitates endothelial cell migration and tube formation while promoting osteoclast maturation, offering a dual benefit in enhancing vascularized bone regeneration. This particularly relevant in dental implantology and sinus lift procedures where vascular support is essential for graft survival. miR-378 also plays a supportive role in osteoblast differentiation and energy metabolism, contributing to bone tissue homeostasis under mechanical loading –an important aspect in implant stabilization (Table 1).

Table 1. Key miRNAs, Their Targets, Functions and dental applications

miRNA	Target gene/pathways	Functions in osteogensis	Dental relevance
miR-21	PTEN, Sprouty1, PDCD4	Promotes osteoblast differentiation and survival	Enhances periodontal regeneration and implant osseointegration[18]
miR-29b	COLIA1, MMP2, osteonectin	Stimulates ECM remodeling and mineralization	Improves outcomes in GBR and alveolar bone repair[19]
miR-214	ATF4, Osterix	Inhibits osteoblast activity	Potential inhibitor target in aged or inflammed bone[20]
miR-34a	RANKL, TGF-beta, pathway regulators	Inhibits osteoclastogenesis, reduces bone resorption	Useful in managing peri-implantitis and periodontitis[21]
miR-26a	SMAD1, BMP/Runx2	Promotes osteogenesis and angiogenesis	Enhances vascularized bone regeneration in implants/grafts[22]
miR-378	GalNAcT7, IGF1R	Supports osteoblast differentiation and metabolic adaptation	Contributes to bone remodeling and mechanical stress responses[23]

These miRNAs not only serve as therapeutic agents but also hold promise as diagnostic biomarkers. Their expression patterns in gingival crevicular fluid or saliva can provide noninvasive indicators of bone metabolism and healing potential. Integrating these miRNAs into bioactive membranes, hydrogels, or scaffolds materials can potentially revolutionize regenerative dentistry by offering molecular precision to tissue engineering approaches, thus targeting specific miRNAs offers a novel avenue for enhancing bone regeneration and ensuring long term success of dental interventions.

2.3 MicroRNA modulation in periodontal regeneration

Periodontitis is a chronic inflammatory disease characterized by the destruction of the supporting structures of teeth, including the gingiva, periodontal ligament and alveolar bone. The persistent inflammatory environment impairs the natural regenerative processes of periodontal tissues, making effective healing significant clinical challenge. miRNAs have emerged as critical regulators of immune responses, tissue remodeling, and stem cell differentiation in the periodontium, offering novel avenues for enhancing periodontal regeneration[24].

One of the hallmarks of periodontitis is an imbalance between pro –inflammatory and anti-inflammatory mediators. The sustains release of cytokines such as TNF-α. IL-β and IL-6 contributes to osteoclast activation and matrix degradation, ultimately leading to bone loss. miRNAs modulate this inflammatory milieu by targeting signaling pathways that govern immune cell recruitment and cytokine production. miR-146a, for example, is a well –established negative regulator of inflammation, It inhibits key adaptor proteins in NF-κB pathway, such as TRAF6 and IRAKI, thereby dampening the production of pro-inflammatory cytokines. In experimental models of periodontitis, up regulation of miR-146a has been shown to reduce inflammation induced bone loss making it a promising therapeutic target. Similarly, miR-155 plays a dual role in inflammation and immune cell differentiation. While it is often associated with the promotion of inflammation by enhancing the activation of macrophages and T cells, its expression is also involved in feedback regulation during the resolution phase. The timing and magnitude of miR-155 expression are therefore crucial in determining its impact on periodontal outcomes. Targeted modulation of miR-155 could help in transitioning the inflammatory phase to a regenerative one, particularly in chronic periodontitis[25].

Beyond inflammation control, miRNAs also influence the regenerative capacity of periodontal ligament stem cells (PDLSCs) which are essential for the repair and regeneration of periodontal tissues. These cells have multilineage differentiation potential and can form cementum like and bonelike structures under appropriate cues. miR-21, miR-29b and miR-26a have been shown to enhance osteogenic differentiation of PDLSCs by targeting negative regulators of the BMP and Wnt signaling pathways. For instance, miR-29b promotes the expression of extracellular matrix proteins like collagen and osteocalcin, critical for periodontal tissue integrity. Additionally, miR-1405p and miR200c have been implicated in promoting PDLSC migration and adhesion which are key processes in wound healing and scaffolds integration. The therapeutic modulation of miRNAs in periodontal regeneration can be achieved through the use of synthetic mimics or inhibitors delivered locally via hydrogels, scaffolds or nanoparticles. These delivery systems ensure stability and sustained release in the periodontal pocket or defect site, Moreover, the use of exosome-derived miRNAs from mesenchymal stem cells has shown promise in transferring regenerative signals in a paracrine fashion, further enhancing tissue repair. Overall, miRNAs provide a multitargeted approach to periodontal, regeneration by simultaneously suppressing chronic inflammation and promoting stem cell mediated repair[26]. Their dual capacity to regulate both immune homeostasis and osteogenesis positions them as ideal candidates for integrative regenerative therapies in periodontal medicine (Figure 2).

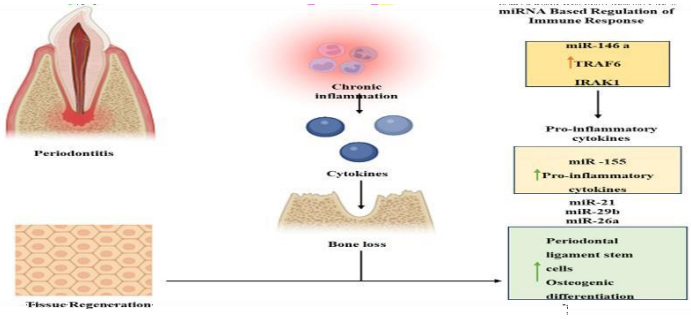

Figure 2. MicroRNAs modulate inflammatory signaling and osteoclast activity, restoring immune balance and promoting periodontal tissue regeneration in periodontitis.

2.4 MicroRNAs in dental implantology and osseointegration

Dental implantology relies on the process of osteointegration, which refers to the direct structural and functional connection between the surface of a dental implant and the surrounding bone tissue. Successful osseointegration is vital for long term implant stability, load bearing capacity and overall prosthetic function. However, impaired healing, poor bone quality or systemic inflammation can compromise this integration. In recent years, miRNAs have gained attention as key molecular regulators capable of enhancing osseointegration by modulating gene expression in osteogenic, inflammatory and angiogenic pathways at the bone implant interface[27].

During the early phase of osseointegration, mesenchymal stem cells (MSCs) migrate to the implant site and differentiate into osteoblasts, initiating new bone formation around the implant surface, miRNAs such as miR-21 and miR29b have been shown to up regulate osteogenic markers including Runx2, ALP and COLIA1, facilitating early matrix deposition and mineralization. Additionally, miR26a supports the coupling of angiogenesis with osteogenesis by enhancing endothelial cell function and bone vascularization-critical factors for implant healing in comprised sites. Conversely, inhibitory miRNAs like miR-133 and miR-214 can suppress osteoblast activity, and their down regulation near implant surfaces has been associated with improved osseointegration in animal models.

To harness these biological effects, implant surface modifications using miRNA functionalized coatings have been explored as a next generation strategy. Titanium, the gold standard in dental implants, can be chemically or physically modified to incorporate bioactive molecules, including miRNAs. One common method involves immobilizing miRNA mimics or inhibitors on titanium surfaces using carriers such as chitosan, polythyleneimine (PEI), or hydroxyapatite nanoparticles. These coatings allow for localized, sustained release of miRNAs at the implant bone interface, promoting targeted cellular responses without systemic exposure.

Experimental studies have demonstrated that titanium surfaces coated with osteoinductive miRNAs can significantly enhance early bone implant contact and new bone volume. For instance, titanium implants coated with miR-29b mimics increased collagen synthesis and calcium deposits in vitro, while vivo models showed improved bone volume density and mechanical stability. Another study using miR-21 functionalized titanium disks reported enhanced ALP activity, mineralization and reduced inflammatory cytokine expression in human MSC cultures. These findings suggest that surface bound miRNAs not only promote osteogenesis but may also create a pro-regenerative, anti-inflammatory micro environment around the implant. The synergistic effect of titanium's favorable mechanical and biocompatible properties with miRNA mediated molecular signaling represents a promising avenue in implantology. Furthermore, the integration of smart delivery systems, such as stimuli responsive coatings or exosome loaded implants is under investigation to achieve dynamic and controlled miRNA release based on the healing stage or local pH changes. This biofunctionalization approach has the potential to improve implant success in patients with risk factors such as diabetes, osteoporosis or smoking related bone deficits. In conclusion, miRNAs play a multifaceted role in enhancing osseointegration through the regulation of osteogenesis, angiogenesis and inflammation. Their application in functionalizing implant surfaces offers a novel and clinically relevant strategy to improve implant integration, particularly in challenging or compromised bone environments[28].

2.5 MicroRNAs in guided bone regeneration (GBR) and socket preservation

Guided bone regeneration and socket preservation are well established techniques in dental and implantology practices to maintain or restore alveolar ridge dimensions following tooth extractions or bone loss. These approaches rely on the use of barrier membranes and scaffolds to create a protected environment that facilitates new bone growth by excluding soft tissue invasion. However, the biological outcomes of GBR remain variable and are often limited by insufficient vascularization, delayed osteogenic maturations, and local inflammation. In this context, MicroRNAs have emerged as potent biological tools that can be incorporated into scaffold systems to enhance regenerative outcomes through precise control of osteogenesis, angiogenesis and immune modulation[29].

MiRNAs modulate cellular behavior by targeting key genes involved in bone matrix deposition, vascular remodeling and progenitor cell recruitment. Their integration into biomaterials such as hydrogels, bioceramics and membranes enables localized and sustained release at the defect site, promoting a favorable microenvironment for bone regeneration. For instance, miR-29b is known to promote the expression of collagen type 1 and osteonectin while downregulating matrix degrading enzymes like MMP-2, thus facilitating extracellular matrix formation and mineralization. When incorporated into collagen based or hydroxyapatite (HA) reinforced scaffolds, miR-29b significantly enhances osteogenic potential in both in vitro and vivo models of alveolar bone regeneration (Figure 3).

Similarly, miR-26a has been shown to stimulate both osteogenesis and angiogenesis, a dual effect essential for the long-term success of GBR procedures. It targets GSK-3beta and activates the Wnt/beta catenin signaling pathways, leading to up regulation of osteogenic markers such as Run x2 and ALP. Additionally, miR26a promotes endothelial cell migration and tube formation, enhancing vascularization within the grafted site. This makes it particularly valuable in cases where compromised blood supply limits bone healing, such as in large defects or in medically compromised patients[30].

MiRNA delivery platforms are evolving to meet the demands of clinical GBR applications. Natural polymers like chitosan, alginate and gelatin have been used to develop injectable hydrogels that encapsulate miRNA mimics or inhibitors. These hydrogels offer biocompatibility, injectability and tunable degradation rates, making them ideal carriers for localized miRNA release. Electrospun nanofibres and multilayered barrier membranes have also been functionalized with osteoinductive miRNAs to enhance bone fill in extraction sockets. Moreover, the combination of miRNAs with calcium phosphate bioceramics such as beta-TCP or bioactive glass supports both structural integrity and bioactivity.

Recent advancements include the use of exosome mimetic vesicles or nanoparticles-based delivery systems to enhance miRNA stability and cellular uptake. These smart delivery systems respond to local environmental cues such as pH or enzymatic activity, ensuring targeted and stage specific release of mi RNA s at the healing site. Such technologies are promising for socket preservation strategies where bone loss is imminent following extraction and where rapid interventions is needed to maintain ridge volume. In conclusion, miRNA functionalized scaffolds represent a significant leap forward in enhancing the biological efficacy of GBR and socket preservation techniques. By directing osteogenic differentiation, promoting angiogenesis and modulating inflammation, miRNAs provide multifaceted approach to optimizing bone regeneration outcomes in modern dental practice[31].

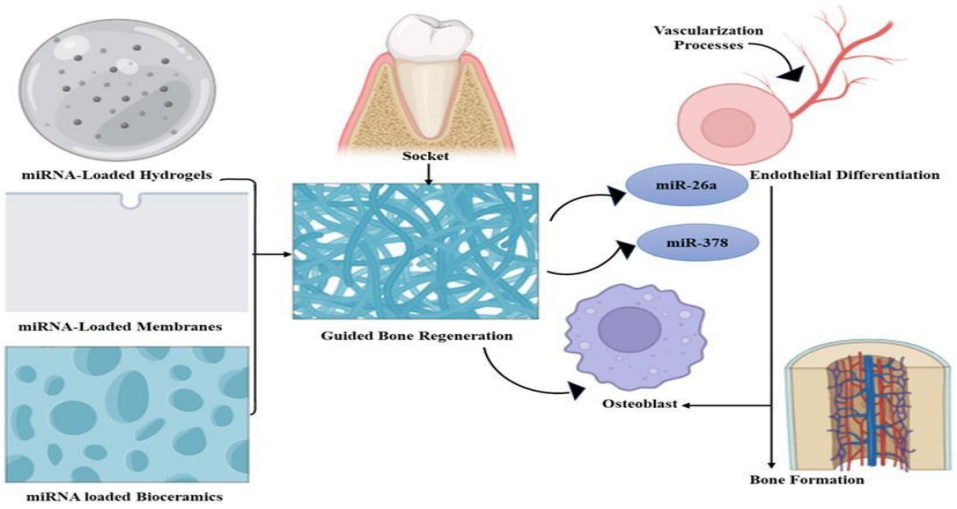

Figure 3. MicroRNAs integrated into scaffolds enhance guided bone regeneration and socket preservation by promoting osteogenesis, angiogenesis, and immune modulation

2.6 Delivery platforms for microRNA -based dental therapies

The therapeutic application of micro RNAs in dentistry requires a robust delivery platform that can ensure stability, biocompatibility and efficient targeting to the desired tissue or cell type. Given the vulnerability of naked miRNAs to enzymatic degradation and their limited ability to cross cellular membranes, advanced carriers have been developed facilitate their controlled and localised release in oral regenerative therapies. Among these, lipid nanoparticles, polymer- based carriers, extracellular vesicles, and gene activated scaffolds represent the most promising tools for effective miRNA delivery in dental contexts.

Lipid nanoparticles (LNPS) are among the most established and clinically validated systems for nucleic acid delivery. They offer high encapsulation efficiency, protection against nuclease degradation, and the capacity for endosomal escape after cellular uptake. LNPs can be engineered with targeting moieties such as peptides or antibodies to home in on periodontal ligament stem cells, osteoblasts or immune cells within the oral cavity. Their injectable format

makes them well suited for minimally invasive administration into periodontal pockets, extraction sockets or preimplant regions. In preclinical studies, LNPs loaded with miR-21 and miR-26a have shown significant enhancement of osteogenesis and angiogenesis in alveolar bone defects[32].

Polymeric carriers, particularly biodegradable materials like chitosan and poly lactic-co-glycolic acid (PLGA) offer another effective approach for localized miRNA delivery. These materials are widely used in dental scaffolding due to their tunable degradation rates, mechanical strength and compatibility with tissue engineering constructs. Chitosan miRNA complexes have demonstrated good muco adhesiveness and transinfection efficiency, making them suitable for periodontal applications. PLGA microspheres and nanoparticles can be incorporated into guided bone regeneration membranes or injectable hydrogels to deliver miRNA mimics over sustained periods, supporting long term tissue remodeling. The ability to fine tune polymer composition allows researchers to control the release kinetics of miRNAs and match them to the specific stages of healing.

Exosomes and extracellular vehicles (EVs)offer a biologically derived, cell free platform for miRNA delivery. These vesicles are naturally secreted by cells and are inherently loaded with signaling molecules, including miRNAs. When derived from mesenchymal stem cells or periodontal ligament stem cells, exosomes contain regenerative and anti-inflammatory miRNAs that can be isolated, purified and readministered to target tissues. Their lipid bilayer structure protects miRNAs during systemic or local delivery, and their intrinsic membrane proteins facilitate cellular uptake. Studies have demonstrated that exosome delivered miRNAs such as miR29b and miR26a enhance bone regeneration and immune modulation in periodontal defects and peri implant bone loss[33].

Gene activated scaffolds represent an advanced platform where miRNA mimics or inhibitors are embedded directly within bio material matrices. These scaffolds, typically made of collagen, hydroxy apatite or synthetic polymers are designed to release genetic cargo in a spatially and temporarily controlled manner. When implanted into bone defects or extraction sites, they provide structural support while directing cellular behavior through miRNA signaling. For example. MiRNA functionalized collagen membranes have been shown to stimulate Runx2 and BMP2 expression in surrounding cells, accelerating new bone formation.

In summary, the integration of smart miRNA delivery systems into regenerative dental therapies offers a precise and multifaceted approach to enhancing tissue healing, with the potential to revolutionize periodontal, implant and bone graft procedures.

Table2. Delivery platforms for miRNA-based dental regeneration

Delivery platform	Material type	Advantages	Application in dental regeneration
Lipid nanoparticles	Synthetic lipid-based carriers	High encapsulation efficiency, endosomal escape, targetable, injectable	Local delivery into periodontal defects, enhanced osseointegration[34]
Chitosan	Natural polysaccharide polymer	Biocompatible, mucoadhesive, good transfection efficiency	Periodontal therapy, scaffold functionalization[35]
PLGA (poly lactic-co-glycolic acid)	Biodegradable synthetic polymer	Tunable degradation sustained release, FDA approved	GBR membranes, injectable systems for miRNAs mimic delivery[36]
Exosomes/extracellular vesicles	Cell derived vesicles eg: MSCs	Natural, immune tolerant, high targeting efficiency	Stem cell free therapy, delivery of miRNAs like miR-29b, miR-146a[37]
Gene activated scaffolds	Collagen hydroxyapatite, composite biomaterials	Dual role structural support and biological instruction via miRNA signaling	GBR, socket preservation, bone graft enhancement[38]

2.7 Clinical and translational challenges of miRNA based dental therapies

Despite the promising therapeutic potential of micro-RNA based strategies in dental regenerative medicine, several clinical and translational challenges remain that hinder their widespread application. These include concerns regarding off target effects, delivery specificity, in vivo stability, immune modulation, as well as broader regulatory and ethical barriers specific to the dental field One of the foremost challenges in miRNA therapeutics is the potential for off targets effects. Each miRNA has the capacity to bind multiple messenger RNA (MicroRNA) targets due to partial complementarity, which may result in the unintended modulation of genes unrelated to bone or periodontal regeneration. This lack of specificity can lead to unpredictable cellular responses, including altered cell cycle regulation, apoptosis or immune activation. In a complex tissue like the oral cavity, where different cell types coexist in close proximity, these off target effects pose a particular risk. Therefore, the careful selection and validation of miRNA candidates, along with advanced bioinformatics tools to predict and minimize unintended interactions, is essential for clinical safety[39].

Another critical issue lies in achieving targeted and efficient delivery of miRNAs to specific cells or tissues. The oral cavity presents a unique environment characterized by high enzymatic activity, microbial presence, and frequent mechanical disruption, all of which can degrade naked miRNAs and reduce therapeutic efficacy. Although delivery platforms such as lipid nanoparticles, hydrogels and scaffold systems have improved miRNA stability and release achieving site specific and cell type specific delivery remains a work in progress. Strategies such as ligand targeted nanoparticles or responsive delivery systems that release miRNAs under specific conditions (eg: inflammation, pH changes) are being explored to address this barrier.In vivo stability is further complicated by immune recognition. Exogenous miRNAs or their carriers may trigger innate immune responses, particularly via toll like receptors (TLRs), leading to inflammation or systemic toxicity. While natural delivery systems such as exosomes are less immunogenic, synthetic carriers may still activate immune cells. Additionally, miRNAs themselves can regulate immune genes, creating a dual effect that must be carefully balanced to avoid immunosuppression or unintended inflammatory responses in periodontal or peri-implant tissues.Regulatory and ethical considerations also play a major role in the translational gap. Unlike traditional biomaterials or pharmaceuticals, miRNA-based products fall under gene therapy or advanced biologic categories in most regulatory frameworks, requiring stringent safety, efficacy and manufacturing controls. In the context of dentistry, where the majority of interventions are localized and elective, patient and practioner acceptance of gene-based therapies is still evolving. Long term safety data, cost effectiveness and clear clinical guidelines are required before these therapies can be adopted into mainstream dental practice. Moreover, ethical concerns regarding the use of gene-modified scaffolds or stem cells, particularly in younger or vulnerable populations must be addressed through transparent risk benefit analyses and informed consent procedures. In conclusion while the integration of miRNA-based approaches holds transformative potential for dental regenerative therapies, overcoming these technical and regulatory challenges is critical to ensure their safety and effective translation into patient care. Continued interdisciplinary research, robust clinical trials, and regulatory alignment will be essential for realizing the full promise of miRNAs in dentistry[40].

DISCUSSION

The regeneration of alveolar and periodontal bone remains a central challenge in restorative and regenerative dentistry, particularly in the context of chronic periodontitis, traumatic extractions and implant associated bone loss. While conventional techniques such as guided bone regeneration (GBR), autologous bone grafting, and biomaterial-based scaffolding have provided clinical benefits, the biological complexity of the bone healing demands more precise, bio molecular interventions. MicroRNAs, with their ability to fine tune multiple gene networks simultaneously, offer a novel approach to orchestrating complex regenerative responses in the oral environment.

MicroRNAs regulate critical aspects of bone biology by modulating the transcriptional landscape of osteogenesis, osteoclastogenesis, inflammation and angiogenesis. In particular, miRNAs such as miR21, miR-29b and miR-26a have been shown to promote osteoblast differentiation by targeting key negative regulators of bone morphogenetic protein (BMP) and Wnt/βcatenin signaling pathways. These miRNAs also enhance extracellular matrix deposition and mineralization which are foundational processes in alveolar bone regeneration. On the other hand,

inhibitory miRNAs like miR-133 and miR-214 serves as osteogenic suppression and thus represent potential targets for therapeutic inhibition in conditions characterized by poor bone formation.

In periodontitis, a disease typified by chronic inflammation and bone loss, miRNAs offer dual functionality, immunomodulation and tissue repair. miR-146a,for instance down regulates inflammatory signaling through inhibition of the NF-κB pathway, while simultaneously enabling a regenerative milieu by limiting cytokine mediated tissue breakdown. This dual function is particularly relevant given that unresolved inflammation is a key barrier to periodontal regeneration. miRNAs such as miR-155 and miR-125b also influence immune cell differentiation and cytokine production, further demonstrating the integrative role of these molecules in both destructive and reparative processes within the periodontium.

The periodontal ligament stem cells (PDLSCs) are critical cell source in the regeneration of periodontal tissues. These cells under the regulatory influence of osteoinductive miRNAs, can differentiate into osteoblast-like cells, contributing to new cementum and bone formation. miRNAs like miR-29b and miR-378 have been shown to guide PDLSC fate, influencing their migration, adhesion and differentiation potential. Moreover, salivary miRNA profiling offers a non-invasive diagnostic platform for identifying patients at risk of periodontal disease or compromised bone healing, making miRNAs promising tools not only for therapy but also for precision diagnostics.

In dental implantology, miRNAs enhance osseointegration through both direct and indirect mechanisms. Titanium implant surfaces functionalized with miRNA mimics particularly miR21 and miR29b have been shown to increase osteoblast adhesion, ALP activity and mineral deposition, these functional coatings create a bioactive interface that promotes rapid and stable integration between bone and implant surfaces. In vivo studies have demonstrated improved bone to implant contact ratios and mechanical fixation in implants treated with osteoinductive miRNAs. Furthermore, miRNAs like miR34a also play an antiresorptive role by inhibiting RANKL mediated osteoclastogenesis, offering protection against peri implant bone loss

In guided bone regeneration and socket preservation, miRNA loaded scaffolds have shown significant potential in enhancing both vascularization and mineralization. These scaffolds, designed using biocompatible polymers such as chitosan, collagen or PLGA, provide not only structural support but also microenvironment rich in regenerative signals. The inclusion of miRNAs like miR-26a and miR29b in such scaffolds facilitates endothelial cell recruitment and bone matrix synthesis, accelerating the regenerative timeline. Injectables hydrogels, nanofiber membranes and exosome-mimetic vesicles are also being engineered to deliver miRNAs with high spatiotemporal precision, adapting the release to local environmental cues such as PH or enzymatic activity.

However, several clinical and translational challenges need to be addressed before miRNA-based therapies can be routinely implemented in dental practice. The issue of off target effects is particularly concerning due to the promiscuous nature of miRNA-m RNA interactions. A single miRNA may target hundreds of genes, raising concerns over unintended modulation of non - osteogenic pathways. Additionally, the oral cavity presents a hostile environment with high microbial load, proteolytic enzymes and constant mechanical disturbances that could compromise the stability and function of miRNA therapeutics [39-40].

To overcome these barriers, delivery systems have evolved significantly. Lipid nanoparticles provide high encapsulation efficiency and can be functionalized for cell specific targeting. Biodegradable polymers like PLGA and chitosan offer tunable release kinetics and compatibility with existing GBR materials. More biologically relevant systems such as extracellular vehicles(EVs)and exosomes are being explored for their natural targeting capacity,low immunogenicity and potential to deliver multiple miRNA s in a physiologically relevant context. These platforms also facilitate the transition of miRNA-based interventions from the lab bench to clinical settings by enhancing the therapeutic index and reducing systemic toxicity.The regulatory landscape surrounding miRNA therapeutics remain complex. Since miRNAs can be categorized as gene therapy agents, their clinical translation requires compliance with rigorous safety and efficacy guidelines. The need for large scale, GMP grade synthesis of miRNAs along with standardized delivery systems, further adds to the development costs and timeline. Moreover, patient and practioner acceptance of gene-based therapeutics

in dentistry is still limited, underscoring the importance of clinical education, transparent communication, and evidence based guidelines[40].

Ethical consideration, particularly involving gene modified biomaterial or stem cells are also relevant especially in younger patients or those with systemic comorbidities. Questions about long term integration, mutagenicity and heritability of effects must be answered through rigorous preclinical and clinical evaluations. Despite these concerns, the clinical demand for more biologically precise regenerative therapies continues to grow, especially in populations with impaired healing such as diabetics, smokers, or elderly patients[41].

The future of miRNA based dental therapies lies in their integration with precision medicine and digital diagnostics. Salivary miRNA profiling may allow for personalized treatment plans based on individual molecular signatures. Artificial intelligence and machine learning tools are already being developed to predict miRNA –m RNA interactions and therapeutic outcomes, enabling the rational design of miRNA cocktails tailored to specific clinical needs. Combined with advances in biomaterial engineering and 3D printing this precision guided approach may redefine the standard of care in dental regeneration[42].

In addition to clinical use, miRNAs also offer significant value in research and drug discovery. HIGH throughput miRNA screening platforms can help identify novel targets for periodontal and bone related diseases. Moreover, understanding miRNA expression patterns in response to various graft materials or environmental conditions may help optimize scaffold design and biomaterial selection.

CONCLUSION

MicroRNAs have emerged as powerful molecular regulators with multifaceted roles in bone regeneration, offering therapeutic potential in periodontal repair, dental implantology and guided bone regeneration. By modulating key signaling pathways and cellular processes. miRNAs enable targeted and biologically driven healing. While translational challenges remain, advancements in delivery platforms, diagnostics and biomaterial integration are steadily bridging the gap between experimental promise and clinical reality. With continued interdisciplinary research and careful clinical validations, miRNA-based therapies may soon become integral tools in the next generations of precision dental regenerative medicine.

DECLARATION

Competing interest

The authors declare that there are no competing interest.

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Ethical Approval

Not applicable

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