Long non-coding RNAs (lncRNAs) as Key Modulators of Osteogenesis in Dental and Periodontal Tissues

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Abstract

A class of non-coding RNA molecules known as long non-coding RNAs (lncRNAs) has become important regulators of gene expression and particular cell functions. Studies on periodontitis and other inflammatory illnesses focused on them because of their significant role in inflammation and bone metabolism. Osteogenesis is compromised in periodontitis, a chronic inflammatory disease that causes gradual loss of alveolar bone. Our goal in this review is to provide an overview of the most recent research on the role of long noncoding RNAs (lncRNAs) in the pathophysiology of periodontal disorders and osteogenesis in dental and periodontal tissues. To identify important lncRNAs implicated in periodontal inflammation and osteogenic processes, a thorough review of recent clinical, in vitro, and in vivo investigations was carried out. According to new research, a number of lncRNAs affect inflammatory signaling pathways, which in turn affects osteoblast and osteoclast activity as well as periodontal tissue degradation. Understanding the molecular mechanisms by which these chemicals interfere can offer new perspectives on the course of disease, as well as the possible use of therapeutic targets and diagnostic biomarkers. Depending on the targeted molecule and signaling pathway, therapeutic approaches may involve either activation or inhibition of certain lncRNAs.

***Keywords**:* lncRNAs, periodontitis, osteogenesis, inflammatory diseases.

1. Introduction

Molecular signaling channels, sequential gene expression patterns, and several intricate physiological processes are all involved in the highly regulated process of tooth development. To create the various components of teeth, such as enamel, dentin, pulp, and cementum, dental epithelial and mesenchymal cells develop into many lineages. (1). By interfering with gene expression, noncoding RNA (ncRNA), which makes up 90% of the human transcriptome, has been shown to be essential to many biological processes (2). Short ncRNAs (less than 200 nucleotides)

and long ncRNAs (more than 200 nucleotides) are the two primary subgroups of ncRNAs. (3). Transcripts longer than 200 nucleotides with little coding potential are known as long non-coding RNAs (lncRNAs), long intergenic RNAs (lincRNAs), antisense RNAs (asRNAs), intronic noncoding RNAs (iRNAs), enhancer RNAs (eRNAs), pseudogenes. (4). There is mounting evidence that lncRNAs are important modulators of a number of physiological and pathological processes, including metabolism, gene regulation, cell development, and tissue formation (5).

Osteogenesis is the process by which preexisting mesenchymal tissue is converted into bone tissue. Intramembranous ossification is the direct transformation of mesenchymal tissue into bone. The cranium's bones are often where this process takes place. In other instances, the mesenchymal cells develop into cartilage, which is subsequently replaced by bone. Endochondral ossification is the process of forming cartilage intermediate and substituting it with bone cells. (6). The normal proliferation, differentiation, and death of bone marrow mesenchymal stem cells may be affected differently by lncRNAs produced to variable degrees during the osteogenic differentiation process. Three ways exist for lncRNAs to regulate osteogenic differentiation: as a precursor of miRNA, lncRNAs take part in the regulation of osteogenic differentiation; as ceRNAs or "miRNA sponges," they regulate osteogenic differentiation by controlling different signal pathways. (7). Numerous studies have been carried out to find lncRNAs (LncRNAs) that show a strong correlation with the tooth creation process. Many lncRNAs involved in tooth germ formation were found by comparing the patterns of mRNAs and lncRNAs expression throughout important developmental stages (8). Alveolar bone, gingival tissue, cementum, and periodontal ligament (PDL) tissue make up the periodontium (9). Numerous cell types, including osteoblasts, cementoblasts, myofibroblasts, nerve cells, endothelial cells, fibroblasts, epithelial cells, and periodontal ligament stem cells (PDLSCs), have been shown to be present in the periodontal ligament. (10). Among these, PDLSCs have demonstrated promise for periodontal regeneration by osteogenic differentiation (9).

LncRNAs play a role in tooth development and alveolar resorption through their interactions with chromatin regulators, RNA enhancers, miRNAs, and their modulation of signaling pathways (11). However, little is known about the pathogenic involvement of lncRNAs in skeletal and dental diseases (12). 8925 distinct lncRNAs were found to be expressed differentially in chronic periodontitis tissues as compared to nearby normal tissues, according to microarray analysis of the

lncRNA expression profile. Subgroup analysis revealed 1218 lincRNAs, 238 HOX cluster lncRNAs, and 589 enhancer-like lncRNAs. According to the data, more research is required to understand the role and mechanisms of lncRNAs linked to periodontitis (13).

1.1 lncRNAs in tooth development

The complex process of tooth development begins on the 37th day of pregnancy when primary epithelial bands begin to form in the future upper and lower jaws. The stages of tooth development are called bud, cap, and bell (early and late). These phases of tooth development, which include cellular activity, molecular signaling pathways, and gene expression patterns, are critical in determining the size and shape of the tooth's phenotypic (14). During this procedure, precise temporal and spatial organization is crucial. Long non-coding RNA (lncRNA) functions as an intermediary regulatory factor in tooth formation and proliferation within this intricate regulatory network. Through spatial pattern coordination in the early stages and functional differentiation in the later stages, it contributes to the formation of teeth (15, 16). Previous studies have demonstrated the expression of long non-coding RNAs (lncRNAs) in human dental tissues isolated from the vas differ from dental epithelium (DE) and dental mesenchyme (DM) throughout the late bud, cap, and early bell stages using RNA-seq analysis (17). The dynamic expression of lncRNAs was found to cooperate with neighboring protein-coding genes, a behavior frequently observed in organ development (18). Certain lncRNAs and developmental regulators, Odontogenesis was discovered to be considerably enriched in genes including PANCR, DLX6-AS1, H19, DANCR, and MEG3, which are expressed in the dental epithelium (DE) and dental mesenchyme (DM) (19). By focusing on important signaling pathways such WNT, BMP, FGH, and SHH, they have been found to regulate the development of dental-derived mesenchymal stem cells. (20, 21). LncRNA SNHG1 has been found to supress the wnt/B-catenin pathway via miR-328-3p, therby promoting odontogenic differentiation of human dental pulp stem cells (hDPSCs). Overall, lncRNAs play an important regulatory role in odontogenic differentiation (22).

The PANCR gene, a long, non-coding RNA found close to the PITX2 gene, a crucial transcription factor in tooth development that results in the loss of teeth, the skull, and the face, has been linked to the Axenfeld-Rieger syndrome, which is caused by a significant deletion in both PITX2 and PANCR (23,24). According to a 2025 study, PANCR's high expression in the DE gradually rises during development along with PITX2. When the PANCR gene was experimentally inhibited

using small interfering RNA (siRNA) in human stem cell-derived cells, PITX2c gene expression significantly decreased, indicating that PANCR positively regulates PITX2 transcription (25). DLX6-AS1 was highly expressed in the DM. Functionally, it was shown that certain DLX6-AS1 improved odontoblastic development in dental pulp stem cells and human tooth germ mesenchymal cells (hTGMCs) (26, 27). This further supports its regulatory involvement in mesenchymal cell fate during tooth formation by controlling odontogenic differentiation under BMP9 stimulation via a miR-128-3p/MAPK14 axis (28). Long noncoding RNA Due to its crucial involvement in controlling numerous physiological and/or pathological processes, such as embryogenesis, development, cancer, osteogenesis, and metabolism, H19, one of the earliest lncRNAs encoded by H19, has drawn a lot of attention (29). During embryonic development, H19 is widely expressed, primarily in tissues derived from endoderm and mesoderm. According to findings, H19 may be a stimulatory regulator of odontogenesis since it positively regulates the odontoblastic differentiation of hDPSCs via the miR-140-5p/BMP-2/FGF9 axis (30).

Studies have revealed that the long non-coding RNA DANCR plays a major role in controlling the odontoblast differentiation program. It has been observed that DANCR and miR-216a have an inverse expression relationship, and DANCR possesses a binding site for miR-216a. Specifically, DANCR positively regulates the production of c-Cbl by acting as a molecular sponge for miR-216a. whereas miR-216a binds to the 3′-UTR of c-Cbl and suppresses its expression. DANCR prevents human dental papilla cells (hDPCs) from differentiating into odontoblasts by this mechanism. On the other hand, hDPCs differentiate into dentin-forming cells when DANCR is inhibited (31). Additionally, the long non-coding RNA MEG3 (lncRNA maternally expressed gene 3, MEG3) has been shown to be involved in both regeneration and inflammation in in vitro pulpitis (32). In human pulp cells treated with liposaccharide (LPS), MEG3 inhibition can stop the release of inflammatory cytokines and encourage odontogenic differentiation. By controlling the Wnt/β-catenin signaling pathway, MEG3 knockdown encouraged odontogenic differentiation of hDPCs and indicated that MEG3 had an adverse influence on inflammation and dentin-pulp complex regeneration in pulpitis (33).

1.2 lncRNAs in osteogenic differentiation of periodontal ligament stem cells

Mesenchymal stem cells are mature, undifferentiated cells that have the capacity for multidirectional differentiation and self-replication (34). Because of their high capacity for self-

renewal and ability to differentiate into osteogenic lineages, which are essential for preserving the integrity of periodontal tissues, periodontal ligament stem cells (PDLSCs) are a specialized population of pluripotent mesenchymal stem cells that are perfect for use in bone regeneration research. PDLSCs are therefore regarded as an important cellular source for alveolar and periodontal bone regeneration (35, 36). It has been demonstrated that a variety of long noncoding RNAs (lncRNAs) support osteogenesis by encouraging cell division and inhibiting apoptosis. Its effects on osteoporosis and osteoblast formation in human bone marrow-derived mesenchymal stem cells have been investigated. As a competitive endogenous RNA (ceRNA), it sponges microRNAs, interacts with chromatin-modifying complexes, and controls important osteogenic signaling pathways like TGF-β, MAPK, and Wnt/β-catenin (37). Furthermore, there is strong evidence that certain lncRNAs, such as lncRNA-MEG3, H19, MALAT1, and DANCR, may control stem cell osteogenic differentiation both normally and abnormally. Because H19 regulates BMP9-induced osteogenesis in mesenchymal stem cells through miRNA-dependent control of the Notch signaling pathway (functioning as a competitive endogenous RNA and sponged miR-541-3p), balanced H19 expression is necessary for optimal bone formation. On the other hand, poor bone formation is linked to its abnormal expression (38, 39).

By maintaining the expression of osteogenic genes and sponging the osteogenesis-inhibitory miR-129-5p, MALAT1 functions as a lncRNA. In the end, this coordinated regulation encourages matrix mineralization and osteoblast-like maturation of periodontal ligament stem cells, maintains Runt-related transcription factor2 (RUNX2) activation, and strengthens osteogenic signaling pathways including Wnt/β-catenin. All things considered, lncRNA Malat1 is essential for preserving bone mesenchymal stem cells' capacity to differentiate into osteoblasts (40). Downregulation of lncRNA MEG3 may facilitate osteoblast differentiation and fracture repair, according to vivo studies (41). Interestingly, a distinct mechanistic study revealed that MEG3 functions as a negative regulator in BMSCs by triggering the Wnt/β-catenin signaling pathway, whereas Wnt/β-catenin inhibition prevents MEG3-induced osteogenic differentiation (42). Like this, ANCR (also called DANCR) suppresses RUNX2 and inhibits important osteogenic signaling pathways, such as Wnt/β-catenin and BMP/Smad, to keep mesenchymal stem cells in an undifferentiated state. These results collectively show that MEG3 and ANCR are both inhibitory lncRNAs, and that successful osteoblast development and bone formation depend on their downregulation (43). LncRNAs can interfere with and influence these cellular processes

considering their interaction with the Wnt/β-catenin signaling pathway which has a key regulatory role in controlling cell proliferation, differentiation and apoptosis by activating or suppressing target gene transcription. (44)

1.3 Expression patterns of lncRNAs in periodontal disease

Periodontitis is a long-term immune-related bacterial disease that damages the bone and connective tissues surrounding teeth. Osteogenic differentiation, inflammation, proliferation, apoptosis, and autophagy are just a few of the critical events in periodontal cells that lncRNAs can regulate according to their unique regulatory mechanisms (45). (lncRNAs) have important roles in the development of several diseases, including periodontitis. Numerous investigations have found that gingival tissues or blood samples from patients with periodontitis exhibit dysregulation of lncRNAs, including MALAT, NEAT1, UCA1, ANRIL, FGD5-AS1, and NKILA (46).

Nuclear paraspeckle assembly transcript (NEAT)1 and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) are two lncRNAs believed to be involved in the pathophysiology of periodontitis. It has been shown that NEAT1 promotes apoptosis and inflammation in periodontal tissue samples and in vitro models of periodontitis (47). MALAT1 may play a regulatory function in periodontal inflammation since it increases the production of inflammatory cytokines through the miRNA/Toll-like receptor (TLR)4 axis (48). In (hPDLSCs), there was a negative correlation between the expression of miR-96-5p and urothelial carcinoma associated 1 (UCA1). UCA1 expression rose while miR-96-5p expression fell during the osteogenic differentiation of hPDLSCs. In hPDLSCs, UCA1 knockdown reduced osteogenic differentiation while increasing the expression of miR-96-5p, and vice versa (49). Several research groups have identified the genetic locus for antisense non-coding RNA in the INK4 locus (ANRIL) as a risk locus for periodontitis (50). This lncRNA interacts with the Yin Yang 1 protein to modify the immunological response. Periodontitis susceptibility may be influenced by ANRIL rs1333048, rs1333042, rs2891168, and rs496892 polymorphisms (51). The SOCS6/NF-KB pathway allows the lncRNA FGD5-AS1 to prevent the development of periodontitis. The expression of FGD5-AS1 was significantly lower in patients with periodontitis than in healthy individuals, and both FGD5-AS1 and miR-130a were independent predictors of chronic periodontitis (52). It was demonstrated that the ceRNA FGD5-AS1 lncRNA targets miR-142-3p (53). NF-KappaB In order to decrease NF-κB over-activation, interacting with LncRNA (NKILA) is crucial (54). In the

context of periodontitis, NF-κB contributes to bone loss (55). We anticipated down-regulation of this lncRNA in periodontitis due to the involvement of NKILA in inhibition of NF-κB, but we found the opposite. It has been demonstrated that this lncRNA makes T cells more susceptible to activation-induced cell death (56). Figure (1) illustrates the fundamental function of lncRNA as regulatory molecules, connecting inflammatory stimuli to osteogenic and periodontal consequences.

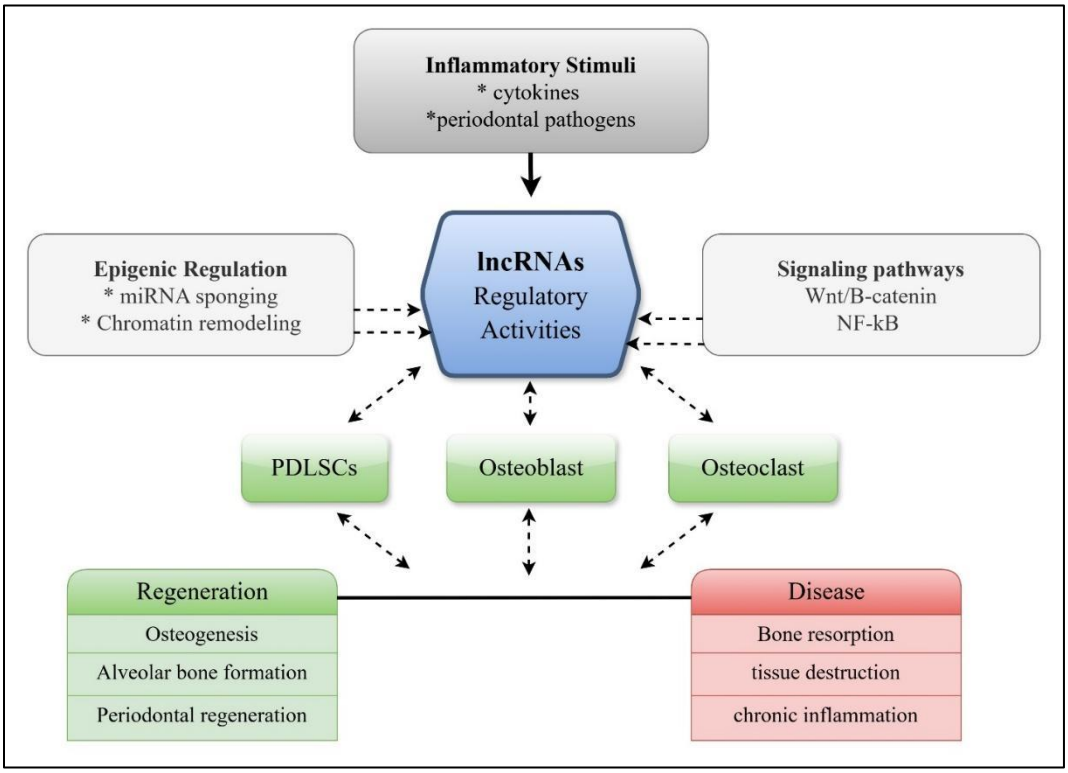

Figure (1): lncRNA-mediated regulation of osteogenesis and periodontal tissue hemostasis. Created using *Draw.io*

1.4 lncRNAs as therapeutic targets for periodontitis

In clinical practice, treatment methods for periodontitis focus primarily on mechanical debridement (non-surgical procedure) and surgical procedures followed by the individuals' commitment to oral hygiene instructions, biofilm control and periodic periodontal maintenance (57). These practices alone do not prevent recurrence of the condition which consequently presses the need for innovative therapeutic approaches that involve the underlying molecular mechanisms of periodontitis. These approaches include non-coding RNA that mediate epigenic regulatory

mechanisms which may improve therapeutic efficacy and accomplish a true tissue regeneration and sustain periodontal health (58). Among the intended non-coding RNA, researchers identified fifty lncRNAs involved in periodontitis with few specific indicating a role in the development of the disease by being differentially expressed in healthy and diseased tissue. It was suggested that some of these upregulated and downregulated lncRNAs can serve as therapeutic targets or biomarkers for treatment or diagnosis considering their involvement in immune and inflammatory pathways. (59). Additionally, it has been shown that the activity of some lncRNAs influences periodontal stem cells and enhances osteogenic differentiation leading to repair and regeneration of alveolar bone. Such repair will prevent tooth loss associated with the chronic inflammatory nature of periodontitis which usually results from the compromised ability of stem cells to differentiate into osteogenic cells due to altering of the microenvironment (60). Beyond their role in regulating bone growth, lncRNAs plays a critical role in modulating immune responses through activation of inflammatory signaling pathways. They become abnormally expressed and affect expression of other genes leading to harmful continuous stimulation of inflammatory pathways thereby causing the occurrence of various diseases including periodontitis (61). This highlights the potential targeting of immune regulatory pathways to modulate the immune microenvironment which may enhance periodontal regeneration through stem cells activation, oral microbiome modulation and improvements in tissue repair. Moreover, emerging anti-inflammatory therapies contribute to the establishment of a balanced local immune microenvironment which also aids in periodontal tissue regeneration (62).

In the following section, inhibition and activation of selected lncRNAs will be addressed.

1.4.1 Inhibition of lncRNAs in therapy

RNA-based therapy involving the knock down or inhibition of disease-active lncRNAs can be achieved through local delivery of antisense oligonucleotides (ASO). Local administration limits the possible off-target side effects in addition to the site-specific inhibitory action for such novel strategic therapy of diseases (63). Inhibition of targeted lncRNAs can also be achieved through other gene editing techniques including anti-microRNAs (anti-miRNAs), small interfering RNAs (siRNAs), ASO therapeutic circular RNAs (circ-RNAs), miRNA mimics, miRNA sponges, short hairpin RNAs (shRNAs) and CRISPR-Cas9 (64). LINC01126 has been proven to promote periodontitis pathogenesis via miR-518a-5p/HIF-1α/MAPK pathway, providing a possible clue

for LINC01126-based periodontal therapeutic approaches, as well as its potential to serve as a diagnostic biomarker. (65)

1.4.2 lncRNA activation/restoration therapy

An in vitro study was conducted to demonstrate that ANRIL positively regulates osteogenic differentiation of PDLCs by acting as a sponge for miR-7 and modulating the NF-kB signaling pathway. The latter pathway is involved in reduced mineralization and impaired osteogenesis, and it is activated when ANRIL is downregulated. Such findings present ANRIL as a key regulator in periodontal osteogenesis and serve as a potential target for periodontal regeneration (66). Knockout of lncR-ADPC, an ANRIL ortholog in mouse model, also led to increased alveolar bone loss and reduced osteogenic differentiation of bone marrow stem cells suggesting the regulatory role of this lncRNA in bone hemostasis in periodontitis and promising a therapeutic role in the disease (67). A more recent clinical study using gingival sulcus fluid studied the role of EPB41L4A-AS1 in chronic periodontitis where its expression was downregulated to a degree that patients could be distinguished from control subjects with high sensitivity. They concluded that overexpression of this lncRNA enhanced osteogenic differentiation through its role as competing endogenous RNA for miR-214-3P, thereby modulating the expression of the key regulator of cell proliferation and osteogenesis, YAP1 (68). The clinical use of lncRNA-based therapies shows many obstacles regarding off-target effects, delivery systems and safety concerns. These challenges can be overcome by applying chemical modifications and developing delivery methods that are site-specific (69).

1.4.3 Delivery systems for lncRNA-based therapy

Nucleic acids have been widely used in therapeutic biomedical applications such as the use of non-coding RNA molecules in regulation of gene expression at the post-transcriptional level. Delivery of these molecules can be done using non-viral nanoparticles, chemical modification, ligand conjugation and locally injectable hydrogels where RNA molecules are maintained in a water-swollen network and their biological activity is retained (70). To use non-coding RNAs in transducing osteogenic differentiation signals, they must be safely delivered to the target site and avoid nuclease degradation. To do so, liposomes, exosomes, microspheres and nanofibers have been used as vectors to achieve cellular targeting and high biocompatibility (71).

2. Conclusion

LncRNAs have been proven by accumulating evidence to be associated with the pathogenesis of periodontitis and take a pivotal role in regulating osteogenesis. They also maintain alveolar bone hemostasis through their ability to modulate gene expression, epigenic regulation and inflammatory signaling pathways. Dysregulation of specific lncRNAs has been shown to impair osteoblast activity and enhance osteoclast ultimately leading to periodontal inflammation and alveolar bone loss. Their dual association with bone formation and immune regulation positions them as promising biomarkers for early diagnosis and disease monitoring as well as therapeutic targets for bone destruction resulting from periodontitis. Emerging lncRNA based therapeutic strategies have been extensively studied offering novel avenues for promoting osteogenesis and controlled periodontitis, however, significant clinical challenges remain particularly regarding specificity, safety, stability as well as delivery to the target site. Future studies should focus on elucidating the precise molecular mechanism of lncRNA in immune reactions and bone remodeling to validate their clinical relevance and develop efficient delivery methods. Improvements in lncRNA delivery systems, particularly site-specific delivery, should be prioritized to reduce off-target effects and to establish long-term safety profiles in addition to optimized chemical modifications to ensure effective clinical application. Advancing understanding in this field may ultimately lead to innovative personalized regenerative therapies that improve periodontal regeneration and bone healing and prevent reoccurrence of the disease.

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Conflict of Interest

No conflict of interest is associated with this work.

Authors' Contributions

All authors contributed to this work equally.

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