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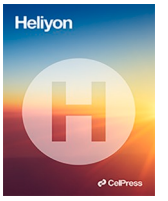

Review article

LncRNAs modulating tooth development and alveolar resorption: Systematic review

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ABSTRACT

Tooth development is an intricate process that encompasses cellular activities, molecular signaling pathways, and gene expression patterns. Disruptions in any of the processes can lead to structural anomalies, impairments in function, and increased vulnerability to oral disorders. Alveolar resorption, which refers to the pathological loss of alveolar bone around teeth, poses a substantial clinical problem in periodontal disorders such as periodontitis. Long non-coding RNAs (LncRNAs) have been implicated in the regulation of these physiological and pathological processes, and they exert their impact on gene expression through both transcriptional and post-transcriptional mechanisms. However, they also interact with certain microRNAs (mi-RNAs), thereby modulating the expression of downstream genes that are involved in tooth development. An exemplar is lncRNA ZFAS1, which has been demonstrated to regulate gene expression and impact these physiological and pathological processes. As a result, lncRNAs contribute to these processes by interacting with chromatin regulators, RNA enhancers, mi-RNAs, and their modulating signaling pathways involved in tooth development and alveolar resorption. Taken together, this review explores and gives a systematic account of the recent research findings that enhance our understanding of the molecular mechanisms that drive these processes and their potential consequences for the remodeling of teeth and bones in the oral cavity.

1. Introduction

Tooth development is a precisely coordinated process involving a sequence of complex cellular events, molecular signaling pathways, and sequential gene expression patterns. The differentiation of dental epithelial and mesenchymal cells into distinct lineages gives rise to the diverse components of teeth, including enamel, dentin, pulp, and cementum [1]. Disruptions at any stage of this developmental process can lead to structural abnormalities, functional deficits, and susceptibility to various oral diseases [2].

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Alveolar resorption, predominantly in the case of periodontal diseases like periodontitis, denotes the pathological loss of alveolar bone surrounding teeth due to inflammatory processes. Such bone loss poses significant clinical challenges, leading to compromised tooth stability, increased tooth mobility, and eventual tooth loss if left unchecked [2]. In this process, there is usually agitation of the balance between bone-forming osteoblasts and bone-resorbing osteoclasts, which is essential for maintaining alveolar bone density [3].

Long noncoding RNAs (lncRNAs) are a class of RNA transcripts made of 200 nucleotides and higher that were initially considered inconsequential in genetics based on their inability to encode proteins [4]. Coming research reveals their involvement in diverse physiological and pathological processes, including tooth development and periodontitis [5], through their interaction with chromatin regulators, functioning as RNA enhancers, engagement with microRNAs (mi-RNAs), and participation in signaling pathways [6].

Here, we followed the 2020 PRISMA guidelines for the systematic literature search process from four different databases: PubMed, Google Scholar, Web of Science, and Elsevier. As a result, we are to provide a systematic review of recent findings elucidating the regulatory roles and mechanisms of lncRNAs in controlling gene expression and signaling pathways during tooth development, as well as their impact on the modulation of alveolar resorption. These insights could contribute to our understanding of the molecular mechanisms underlying the development of functional teeth and the complex process of pathological bone remodeling in the oral cavity.

2. Study methods

2.1. Search strategy

This systematic review adhered to the guidelines outlined in the PRISMA 2020 statement. All studies that looked at the roles of lncRNA on tooth development and alveolar resorption, their mechanisms, and impact on the two processes were found in four databases: PubMed, Google scholar, Web of science, and Elsevier. The articles that were researched for and used were written in English, and they covered the period from January 1st, 2016, to December 31st, 2023. To ensure that no articles had been missed or omitted, every reference to the included articles was carefully examined.

2.2. Search terms

Various terms were adapted to ensure the identification of all studies concerning LncRNAs modulating tooth development and alveolar resorption. The search equations were developed in this manner: “Tooth development and lncRNA” OR “regulatory roles of lncRNA on tooth development and alveolar resorption” OR “mechanism of lncRNA regulation of tooth development and alveolar resorption” OR “role of lncRNA on osteoclast and osteoblast differentiation” OR “lncRNA regulation of tooth development-related genes, proteins, and signaling pathways.” When attempting to solve this problem, it was necessary to divide it into several components.

2.3. Inclusion/exclusion criteria and study selection

The inclusion criteria were as follows: a) studies conducted using cells or human and animal models; b) studies related to the expression or regulation of lncRNAs in tooth development and alveolar resorption; and c) studies that were published in English. The following were the exclusion criteria: editorials, conference abstracts, or evaluations.

Two reviewers separately looked at the titles and abstracts of articles on electronic sheets. Duplicate studies were excluded after looking at titles and abstracts. The entire text of an article was requested and closely examined to see if its abstract lacked enough information to support an inclusion or exclusion determination. The discussion settled any inter-examiner conflict. Cohen’s kappa values helped one evaluate the degree of agreement between the two examiners.

2.4. Data extraction

The authors conducted an independent assessment of all the studies that were identified in the inclusion/exclusion criteria. The data that was extracted included the first author’s name, the year of the study, the title, significant definitions or statements, the methods employed, and the results of each study were all included in the data that was extracted, as shown in Table 1.1.5 Quality Assessment.

The quality assessment of the chosen papers was conducted using a well-known system outlined by Wells and Littell. The quality scoring method consisted of the following eight questions: i) Was the study hypothesis, aim, or objective properly articulated? ii) Did the study provide clear and detailed descriptions of the experimental designs? iii) Did the study provide clear and comprehensive descriptions of the procedures and materials used? iv) Were the temporal intervals for data collection in the study explicitly delineated? v) Were the primary measurements’ results explicitly specified in the study? vi) Was there a thorough comparison between the experimental groups and the control group in the study? vii) Were the findings in the study adequately elucidated? viii) Were the study’s limitations addressed? Each question was assigned a score of 1 for a "yes" response and 0 for a "no" response. The scores for each study were calculated separately, and the maximum achievable score was 8. A study with a score of 7–8 is considered to have exceptional quality, while a score of 5–6 indicates excellent quality. A score of 3–4 indicates poor quality, and a score of 0–2 indicates bad quality.

3. Results

3.1. The illustration of the process of literature search and summary of selected studies

The literature search generated approximately 1000 references, and after excluding duplicate 550 studies and 50 studies for other reasons from PubMed, Google Scholar, Web of Science, and Elsevier, as well as a step-by-step exclusion of research outside the scope of the review, 60 articles were retained for inclusion in this systematic review (Fig. 1). The included articles in this systematic review were published from January 1st, 2016 to December 31st, 2023, and were mostly experimental studies (Table 1).

Fig. 1 displays a flow chart of the research strategy and study selection process. The data presented in Tables 1 and 2 indicate the chosen experimental studies that are related to the roles of lncRNAs on tooth development and alveolar resorption. We used the renowned system of Wells and Littell in the quality assessment of the chosen articles.

3.2. LncRNAs regulate tooth development and alveolar resorption based on their sub-cellular distribution

LncRNAs regulate tooth development and alveolar resorption based on their cellular distribution, where in the nucleus they exert epigenetic control through DNA methylation, histone modification, and chromatin remodeling. They also participate in transcriptional regulation by promoting or inhibiting transcription, as shown in Fig. 2. In the cytoplasm, they carry out post-transcriptional regulation by functioning as precursors of micro-RNA (miRNA) and small interfering RNAs (siRNAs), serving as molecular scaffolds, engaging in alternative splicing, competing with miRNAs, coding micro-peptides, and maintaining mRNA stability and translation (Fig. 2).

Nuclear lncRNAs chiefly impose their influence on chromatin modifiers like Polycomb Repression Complex 2 (PRC2), consequently impacting gene expression at both transcriptional and post-transcriptional levels [7]. Meanwhile, cytoplasmic lncRNAs act as competitive endogenous RNAs (CE-RNAs), forming interactions with specific miRNAs. They essentially act as "sponges" that modulate other miRNAs, subsequently affecting downstream genes associated with bone and tooth formation and related pathways [8]. An illustrative instance is the lncRNA ZFAS1 (Zinc finger anti-sense 1), which has gained much attention for its multifaceted function as a modulator of gene expression by engaging in complex interfaces with various cellular components to influence critical physiological

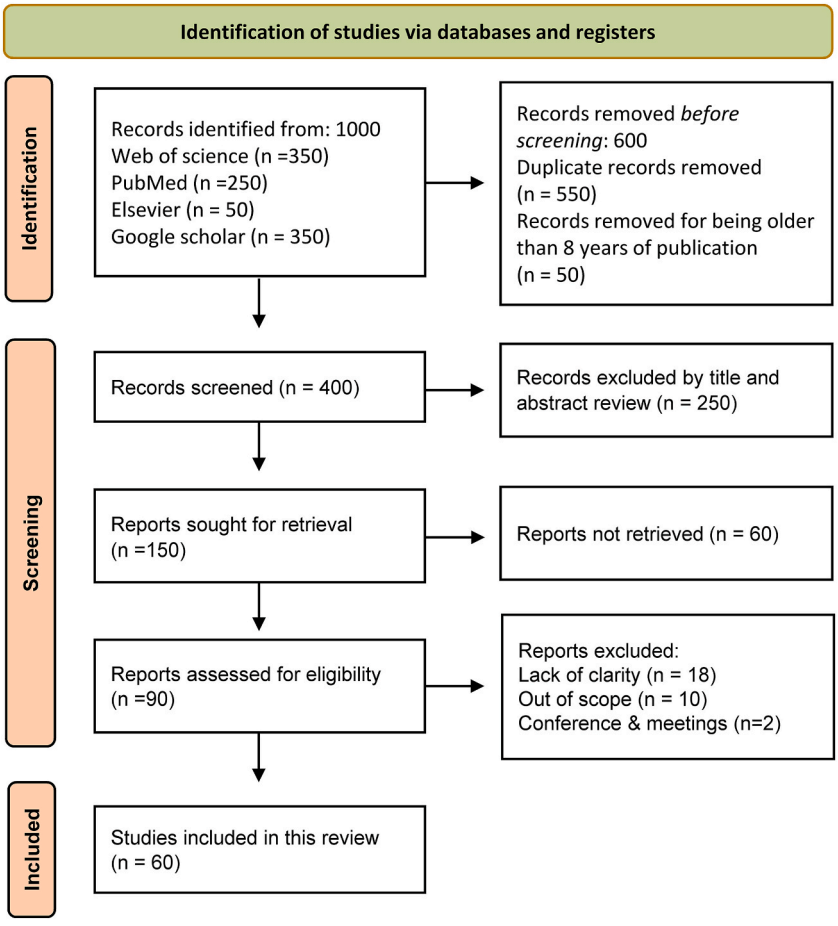

Fig. 1. Flow diagram of the process of systematic literature search in accordance with PRISMA guidelines.

Table 1
Summary of the selected studies included in this review showing related available literature from different Databases.

No.	Author (year)	Literature title	Literature source	Major findings
1	Wang et al. (2022)	*Single cell atlas of developing mouse dental germs reveals populations of CD24^{+} and Plac8+ odontogenic cells*	Journal	The differentiation of dental epithelial and mesenchymal cells into distinct lineages gives rise to the diverse components of teeth, including enamel, dentin, pulp, and cementum
2	Passanezi et al. (2019)	*Role of occlusion in periodontal disease.* Periodontology	Journal	Alveolar resorption, predominantly patent in the situation of periodontal diseases like periodontitis, denotes the pathological loss of alveolar bone surrounding teeth due to inflammatory processes
3	Fernandes et al. (2016)	*Bone cells dynamics during peri-implantitis*	Journal	Agitation of the balance between bone-forming osteoblasts and bone-resorbing osteoclasts, essential for maintaining alveolar bone density
4	Hombach et al. (2020)	*Non-coding RNAs: classification, biology and functioning*	Journal	LncRNAs) are a classes of RNA transcript made of 200 nucleotides and above
5	Zhang et al. (2023)	*Development of ferroptosis-associated ceRNA network in periodontitis.*	Journal	LncRNA involvement in diverse physiological and pathological processes, including tooth development and periodontitis
6	Herman et al. (2022)	*Integrated lncRNA function upon genomic and epigenomic regulation.* Molecular Cell	Journal	LncRNA interaction with chromatin regulators, functioning as RNA enhancers, engagement with microRNAs (mi-RNAs), and participation in signaling pathways
7	Mangiavacchi et al. (2023)	*Behind the scenes: How RNA orchestrates the epigenetic regulation of gene expression.* Frontiers in Cell and Developmental Biology,	Journal	Nuclear lncRNAs chiefly impose their influence on chromatin modifiers like Polycomb Repression Complex 2
8	Herzog et al. (2020)	*Fast Facts: Gene Therapy*. 2020: Karger Medical and Scientific Publishers	Journal	LncRNAs act as "sponges" that modulate other mi-RNAs,
9	Kovacs et al. (2021)	*The role of biomineralization in disorders of skeletal development and tooth formation.*	Journal	lncRNA ZFAS1's multifaceted function as a modulator of gene expression, by engaging in complex interfaces with various cellular components to influence critical physiological and pathological processes
10	Li et al. (2023)	*Transcriptomic Network Regulation of Rat Tooth Germ from Bell Differentiation Stage to Secretory Stage: MAPK Signaling Pathway Is Crucial to Extracellular Matrix Remodeling.*	Journal	Significant number of lncRNAs involved in tooth germ formation were identified
11	Fu et al. (2022)	*lncRNA SNHG1 regulates odontogenic differentiation of human dental pulp stem cells* via *miR-328-3p/Wnt/β-catenin pathway.* Stem cell research & therapy	Journal	LncRNAs exert regulatory control on odontogenesis. The observation indicates that the cells have undergone evolutionary adaptations to suit the specific requirements of each cell type.
12	Yu et al. (2020)	*Molecular and cellular mechanisms of tooth development, homeostasis and repair.* Development.	Journal	LncRNAs exert a substantial influence on the regulation of gene expression associated with the activities of osteoblasts and osteoclasts.
13	Deniz et al. (2017)	*Long noncoding RNA (lincRNA), a new paradigm in gene expression control.* Functional & integrative genomics.	Journal	LncRNA can interact with the promoters and enhancers of genes involved in tooth development, boosting or suppressing their expression
14	Tatello et al. (2021)	*Gene regulation by long non-coding RNAs and its biological functions.* Nature reviews Molecular cell biology.	Journal	The nuclear lncRNAs direct certain chromatin remodeling complexes to specific genomic sites, resulting in alterations in gene transcription
15	Dossin et al. (2022)	*The molecular and nuclear dynamics of X-chromosome inactivation.* Cold Spring Harbor Perspectives in Biology.	Journal	XIST acts by recruiting PRC2 to the female chromosome subsequently leading to cis transcriptional silencing of other chromosomes.
16	Anastasakou et al. (2021)	*Structural, functional and evolutionary characterisaton of the long non-coding RNA MEG3.*	Journal	lncRNA Hotair regulates skeletal development by trans-regulating the expression of the HoxD gene through the recruitment of the PRC2 to the locus of HOXD
17	Shen et al. (2019)	*LncRNA HOTAIR inhibited osteogenic differentiation of BMSCs by regulating Wnt/β-catenin pathway.* European Review for Medical & Pharmacological Sciences.	Journal	HOTAIR enact a regulatory role in the modulation of several lncRNAs by specifically targeting their genomic regions.
18	Puppo et al. (2021)	*Non-coding RNAs in bone remodeling and bone metastasis: Mechanisms of action and translational relevance.*	Journal	LncRNA Msx1-AS negatively impacted the expression of the Msx1 homeodomain protein by down-regulating RUNX2, a key regulator of osteoblast development
19	Sufianov et al. (2022)	*The role of noncoding RNAs in the osteogenic differentiation of human periodontal ligament-derived cells.* Non-coding RNA Research.	Journal	Inhibition of lncRNA ANCR resulted in the enhancement of osteogenic differentiation in periodontal ligament stem cells
20	Zhang et al. (2019)	*lncRNA Rmst acts as an important mediator of BMP9-induced osteogenic differentiation of mesenchymal stem cells (MSCs) by antagonizing Notch-targeting microRNAs.*	Journal	LncRNA Rmst was observed to facilitate the osteo-adipogenic differentiation of iMAD cells caused by BMP9, mediated by a regulatory loop involving Rmst, mi-RNAs, and the Notch signaling pathway

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Table 1 (*continued*)

No.	Author (year)	Literature title	Literature source	Major findings
21	Kazimierczyk et al. (2020)	*Human long noncoding RNA interactome: detection, characterization and function.* International journal of molecular sciences.	Journal	LncRNAs control of mRNA stability and translation, pre-mRNA splicing, modulation of protein activities, as well as serving as precursors for miRNAs and siRNAs
22	Li et al. (2019)	*Insights into the Functions of LncRNAs in Drosophila.* International Journal of Molecular Sciences.	Journal	Some lncRNAs possess the ability to encode certain polypeptides and function as miRNA sponges
23	Zhang et al. (2017)	*The long noncoding RNA Malat1: Its physiological and pathophysiological functions.* RNA biology.	Journal	LncRNA MALAT1 regulates alternative splicing (AS) of endogenous pre-mRNAs by controlling the phosphorylation of Serine/arginine splicing factors
24	Wei et al. (2019)	*Long noncoding RNAs in adipogenesis and adipose development of meat animals.* Journal of Animal Science.	Journal	lncRNA-adipoQ-AS translocation to cytoplasm from the nucleus forms a sense/antisense RNA duplex preventing the translation of adiponectin mRNA,
25	Tang et al. (2020)	*Runx1 up-regulates chondrocyte to osteoblast lineage commitment and promotes bone formation by enhancing both chondrogenesis and osteogenesis.*	Journal	LncRNA-00961 has the potential to encode polypeptides, called amino acid response.
26	Li et al. (2020)	*LncRNA, important player in bone development and disease.* Endocrine, Metabolic & Immune Disorders-Drug Targets	Journal	LncRNA MEG3 has direct interaction with the transcription factor SOX2, leading to the initiation of transcription of BMP4.
27	Liao et al. (2017)	*lncRNA H19 mediates BMP9-induced osteogenic differentiation of mesenchymal stem cells (MSCs) through Notch signaling.*	Journal	H19 promotes the development of MSCs into osteoblast by suppressing the TGF-1/Smad3/HDAC signaling pathway
28	Guo et al. (2020)	*Regulation of bone marrow mesenchymal stem cell fate by long non-coding RNA.* Bone.	Journal	Linc-ROR act as a sponge for microRNAs of miR-138 and miR-14 by suppressing their activity and inhibiting the co-target ZEB2 a transcription factor
29	Xia et al. (2017).	*Long non-coding RNA ZFAS1 interacts with miR-150-5p to regulate Sp1 expression and ovarian cancer cell malignancy.* Oncotarget.	Journal	LncRNA ZFAS1, transcribed from the antisense strand of the ZNFX1 gene locus has been identified as a multifunctional lncRNA
30	Wu et al. (2022).	*Long noncoding RNA ZFAS1 suppresses osteogenic differentiation of bone marrow-derived mesenchymal stem cells by upregulating miR-499-EPHA5 axis.* Molecular and Cellular Endocrinology.	Journal	ZFAS1 had a dual effect of alienating the positive effect of adipogenesis, and facilitated differentiation of osteoblast through miR-499 interaction.
31	Dong et al. (2018)	*ZFAS1: a novel tumor-related long non-coding RNA.* Cancer cell international.	Journal	ZFAS1 functions as a ceRNA to upregulate the expression of genes such as ZEB2, BMI1, MMP-16, MMP14 that are associated with proliferation, invasion, and metastasis accomplished by sponging miR-200c, miR-150, or miR-200b in a competitive manner
32	Wang et al. (2020).	*TNF-α and IL-6: the link between immune and bone system.* Current Drug Targets.	Journal	The intricate modulation of osteoclast differentiation encompasses the participation of various cytokines including TNF-α, M-CSF, IL-1, IL-6, and IL-11, and the RANKL-RANK pathway
33	Dou et al. (2016).	*Changing expression profiles of lncRNAs, mRNAs, circRNAs and miRNAs during osteoclastogenesis.* Scientific reports, 2016. **6**(1): p. 21499.	Journal	LncRNAs have a role in the processes of osteoclastogenesis and bone resorption by exhibiting different expression patterns that are specific to different stages of osteoclastogenesis
34	Silva et al. (2019).	*Long noncoding RNAs: a missing link in osteoporosis.* Bone research.	Journal	LncRNA MALAT1 controls the inflammatory responses triggered by LPS by interacting with NF-kB.
35	Feng et al. (2020).	*Denosumab inhibits MCF-7 cell line-induced spontaneous osteoclastogenesis* via *the RANKL/MALAT1/miR-124 axis.* Translational Cancer Research.	Journal	LncRNA MALAT1 regulates the RANK/RANKL/OPG pathway in vitro settings to control osteoclast activity.
36	Cavalla et al. (2018).	*Inflammatory pathways of bone resorption in periodontitis.* Pathogenesis of Periodontal Diseases: Biological Concepts for Clinicians.	Journal	Periodontitis a prevalent chronic oral disease characterized by the inflammatory resorption of alveolar bone that supports teeth.
37	Lin et al. (2023).	*LncRNA XIST regulates osteoclast formation and promotes orthodontically induced inflammatory root resorption through miR-130b-3p/PTEN axis.* Biotechnology and Genetic Engineering Reviews.	Journal	LncRNA XIST overexpression enhanced the secretion of inflammatory factors, and augmented positive osteoclast numbers.
38	Sufianov et al. (2023)	*The role of noncoding RNAs in the osteogenic differentiation of human periodontal ligament-derived cells.* Non-coding RNA Research.	Journal	LncRNA-MIR22HG enhanced osteogenic differentiation of pPDLSCs by Acting as a ceRNA for miR-182 thereby activating FOX01
39	Wang et al. (2022).	*A reduced level of the long non-coding RNA SNHG8 activates the NF-kappaB pathway by releasing functional HIF-1alpha in a hypoxic inflammatory microenvironment.* Stem Cell Research & Therapy.	Journal	LncRNA-POIR functions as a competing endogenous RNA for miR-182, thereby enhancing the expression of FoxO1
40	Zhang et al. (2020).	*LncRNA Nron regulates osteoclastogenesis during orthodontic bone resorption.* International Journal of Oral Science.	Journal	Nron demonstrated effective inhibition of osteoclastogenesis and alveolar bone resorption
41	Bala et al. (2018).	*Exploring the mechanisms behind long noncoding RNAs and cancer.* Non-coding RNA research, 2018.	Journal	LncRNA TUG1 hinders cell proliferation by inducing transforming growths factor-b

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Table 1 (*continued*)

No.	Author (year)	Literature title	Literature source	Major findings
42	Chen et al. (2017).	*Epithelial–mesenchymal transition (EMT): A biological process in the development, stem cell differentiation, and tumorigenesis.* Journal of cellular physiology.	Journal	Cellular differentiation is a complex process wherein undifferentiated cells acquire distinct characteristics and functions.
43	Mohamad et al. (2016).	*A concise review of testosterone and bone health.* Clinical interventions in aging,	Journal	The differentiation of osteoblasts and osteoclasts is intricately linked in maintaining bone health.
44	Kim et al. (2020)	*Osteoblast-osteoclast communication and bone homeostasis.* Cells.	Journal	Osteoblasts secrete factors like RANKL, OPG, and various growth factors that regulate osteoclast differentiation and activity.
45	Lisowska et al. (2018)	*Lights and shadows of NSAIDs in bone healing: the role of prostaglandins in bone metabolism.* Drug design, development and therapy.	Journal	In bone/dental tissue, the differentiation of osteoblasts and osteoclasts plays a crucial role in maintaining bone homeostasis
46	Jiang et al. (2022).	*Comprehensive ceRNA network for MACF1 regulates osteoblast proliferation.* BMC genomics.	Journal	MC3T3-E1 is an extensively researched cell line of pre-osteoblasts that is commonly employed to investigate the process of osteoblastogenesis.
47	Yu et al. (2018).	*LncRNA TUG1 sponges miR-204-5p to promote osteoblast differentiation through upregulating Runx2 in aortic valve calcification.* Cardiovascular research.	Journal	LncRNA TUG1 promotes osteoblast differentiation through up-regulation of Runx2 by sponging miR-204-5p.
48	Yan et al. (2022).	*β-Ecdysterone enhanced bone regeneration through the BMP-2/SMAD/RUNX2/Osterix signaling pathway.* Frontiers in Cell and Developmental Biology.	Journal	Runx2, a master regulator of osteoblast differentiation, initiates the process by activating genes related to bone matrix formation, such as collagen and osteocalcin.
49	Zhang et al. (2019).	*LncRNA MSC-AS1 promotes osteogenic differentiation and alleviates osteoporosis through sponging microRNA-140–5p to upregulate BMP2.* Biochemical and Biophysical Research Communications.	Journal	LncRNA MSC-AS1 activates BMP2 through promotion of osteogenic differentiation and down-regulation of osteoporosis by sponging miR-140-5p
50	Chen et al. (2020).	*The lncRNA MCF2L-AS1 controls osteogenic differentiation by regulating miR-33a.* Cell Cycle.	Journal	MCF2L-AS1 promoted osteogenic differentiation in hBMSCs by increasing the expression of RUNX2 through inhibition of the miRNA-33a.
51	Xiang et al. (2020).	*lncRNA SNHG1 attenuates osteogenic differentiation* via *the miR-101/DKK1 axis in bone marrow mesenchymal stem cells.* Molecular medicine reports.	Journal	lncRNA SNHG1 had the capability to inhibit the process of osteoblast differentiation
52	Li et al. (2018)	*Insights into the roles of lncRNAs in skeletal and dental diseases.* Cell & Bioscience.	Journal	Overexpression of the histone deacetylase SIRT1 significantly repressed HIF1α-AS1 expression
53	Chen et al. (2021).	*SIRT1, a promising regulator of bone homeostasis.* Life Sciences.	Journal	lncRNA DANCR participates in the differentiation of osteoclast through the activation of tumor necrosis factor-alpha and interleukin-6 expression.
54	Amarasekara et al., 2018	*Regulation of osteoclast differentiation by cytokine networks.* Immune network.	Journal	Osteoclast differentiation is also governed by receptor activator of nuclear factor-kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF)
55	Segeletz et al. (2016).	*Proteomic approaches to study osteoclast biology.* Proteomics.	Journal	RAW 264.7 cells differentiate into multinucleated osteoclasts in response to RANKL, undergoing fusion and forming specialized structures for bone resorption called ruffled borders
56	Xiao et al. (2017).	*LncRNA MALAT1 sponges miR-204 to promote osteoblast differentiation of human aortic valve interstitial cells through up-regulating Smad4.*	Journal	LncRNA MALAT1 has also been involved in the regulation of RANK-RANKL-OPG pathway control in an in vitro osteoclast activity
57	Pang et al. (2019).	*AP-1 and Mitf interact with NFATc1 to stimulate cathepsin K promoter activity in osteoclast precursors.* Journal of cellular biochemistry.	Journal	lncRNA TUG1 promotes increased levels of TRAP, NFATc1, and osteoclast-associated receptor (OSCAR) during the process of osteoclast differentiation
58	Ling et al. (2019).	*Long noncoding RNA MIRG induces osteoclastogenesis and bone resorption in osteoporosis through negative regulation of miR-1897.* Eur Rev Med Pharmacol Sci, 2019.	Journal	lncRNA MIRG could enhance the process of osteoclastogenesis and bone resorption by functioning as a molecular sponge for miR-1897.
59	Alazmah et al. (2021).	*Primary teeth stains and discoloration: a review.* Journal of Child Science.	Journal	Tooth development involves formation and eruption of primary teeth essential factor in maintaining a healthy dentition
60	Kwon et al. (2021).	*Current concepts in the management of periodontitis.* International dental journal.	Journal	Any disruption or abnormality in the alveolar bone can affect the normal development and eruption of teeth.

and pathological processes [9].

3.2.1. LncRNA regulates tooth development at multi-levels

The LncRNA regulation of tooth development can be categorized as epigenetic control, transcriptional regulation, and post-transcriptional modulation. Below, we show the different roles of lncRNAs and their impact on tooth development. As summarized in Table 2, we show an overview of lncRNAs and their impact on osteogenesis and oral bone remodeling.

3.2.2. Identification of LncRNAs that contribute to tooth development

Several investigations have been conducted to identify lncRNAs (LncRNAs) that exhibit a significant association with the process of tooth formation. By conducting a comparative analysis of mRNA and lncRNA expression patterns during key developmental stages, a

Table 2
Studies focused on lncRNAs and their role on osteoblastogenesis and osteoclastogenesis during tooth development and alveolar resorption.

lncRNA name	Expression pattern	Target	Impact on osteogenesis and tooth bone remodeling	Mechanism	References
lncRNA ZFAS1	Up	miR-499	Suppresses osteogenic differentiation of BMSCs	up-regulating miR-499 *EPHA*5 axis	[30]
	Down	miR-499	Dual effect of alienating the positive effect of adipogenesis, and facilitated differentiation of osteoblast	interaction with miR-499	[31]
lncRNA XIST	Up	miR-130-3p	Increased osteoclast numbers	Increased secretion of inflammatory factors as a result of sponging miR-130-3p thereby regulating PTEN expression	[15]
lncRNA Hotair	Up	Genomic regions of other lncRNA (Dlk1-Meg3, Igf2-H19, Hoxa)	These loci are known for the regulation of bone development	Regulation of other lncRNAs by targeting their loci	[17]
		RUNX2	Inhibition of osteoblastogenesis	of the Msx1 homeodomain protein by down-regulating RUNX2	[18]
lncRNA Msx1-AS	Up	H3K27me3 on Runx2 gene	Enhances osteoclastogenesis	Recruited by EZH2 to catalyze H3K27me3 on Runx2 gene promoter, ↓Runx2	[36]
lncRNA- ANCR	Up	miR-758, Notch	Suppression of bone formation, Increased osteoclastogenesis	Stimulation of IL-6, TNF-α	[36]
		Canonical WNT signaling pathway	Up-regulation of osteoblastogenesis	Activation of osteogenic marker genes, i.e., ALP, osterix	[34]
lncRNA-DANCR	Down	miR-30 & miR-124	Up-regulation of osteoblast differentiation	Sponging miR-30, miR-124	[35]
lncRNA MALAT1	Up	miR-204	osteoblast proliferation	Sponging miR-204 via activation of Smad4	[37]
		FGF signaling pathway	Odontogenesis	Alternative splicing to form different isoforms FGFR1, FGFR2	[23]
		Mouse adiponectin mRNA	Inhibiting adipogenic differentiation and enhancing osteoblast formation	Sense/antisense RNA duplex preventing the translation of mouse adiponectin mRNA	[24]
lncRNA-adipoQ-AS	Up	mTOR1	Inhibit osteoblast differentiation	Inhibition of activation of mTOR1 pathway	[25]
lincRNA-00961	Up	Transcription factor SOX2	Up-regulation of osteoblastogenesis	Interaction with SOX2 leading to cleavage of SOX2 from the BMP4 promoter, initiating transcription of BMP4	[26]
LncRNA-MEG3	Up	miR-140-5p	Down-regulation of bone loss	Sponging of miR-140-5p leading to activation of BMP2	[26]
		Wnt/β-catenin	Enhance osteogenic differentiation of human dental follicle stem cells	Increase in the presence of H3K27me3 in the promoter region of the Wnt pathway	[26]
	Down	miR-675	Stimulates the differentiation of MSCs into osteoblasts	Interacts with miR-675 by inhibiting the TGF-1/Smad3/HDAC signaling pathway	[27]
lncRNA-H19	Up	miR-138, miR-14, & ZEB2	Increases the process of osteogenesis	Sponging miR-138 & miR-14 & inhibiting activity of ZEB2 leading to activation of Wnt/catenin pathway	[28]
Linc-ROR	Up	PTEN, AKT pathway	Stimulation of osteoclastogenesis	Down-regulation of PTEN thereby stimulating AKT pathway	[38]
LncRNA-MIR22HG	Up	miR-182	enhanced osteogenic differentiation of pPDLSCs	Acts as a ceRNA for miR-182 thereby activating FOX01	[39]
LncRNA-POIR	Up	NF-kB pathway	inhibition of osteoclastogenesis & alveolar bone resorption	Enhance the nuclear transport of NF-κb repressing factor (NKRF), repressing transcription of Nfatc1	[40]
LncRNA -Nron	Up	miR-204-5p	Promotes osteoblast differentiation	Enhances Runx2 gene expression by sponging miR-204-5p	[41]
lncRNA TUG1	Up	miR-140-5p	Promotion of osteogenic differentiation	Activation of BMP2 by sponging miR-140-5p	[42]
lncRNA MCF2L-AS1	Up	miR-101	Inhibit the process of osteoblast differentiation	Sponging of miR-101 & increased expression of DKK1	[43]
LncRNA-SNHG1	Up	HOXD10	Activation of osteoblastogenesis	Inhibited the expression of HOXD10 by interfering with acetylation	[36]
LncRNA HIF1α-AS1	Down	HOXD10	Activation of osteoblastogenesis	Inhibited the expression of HOXD10 by interfering with acetylation	[36]

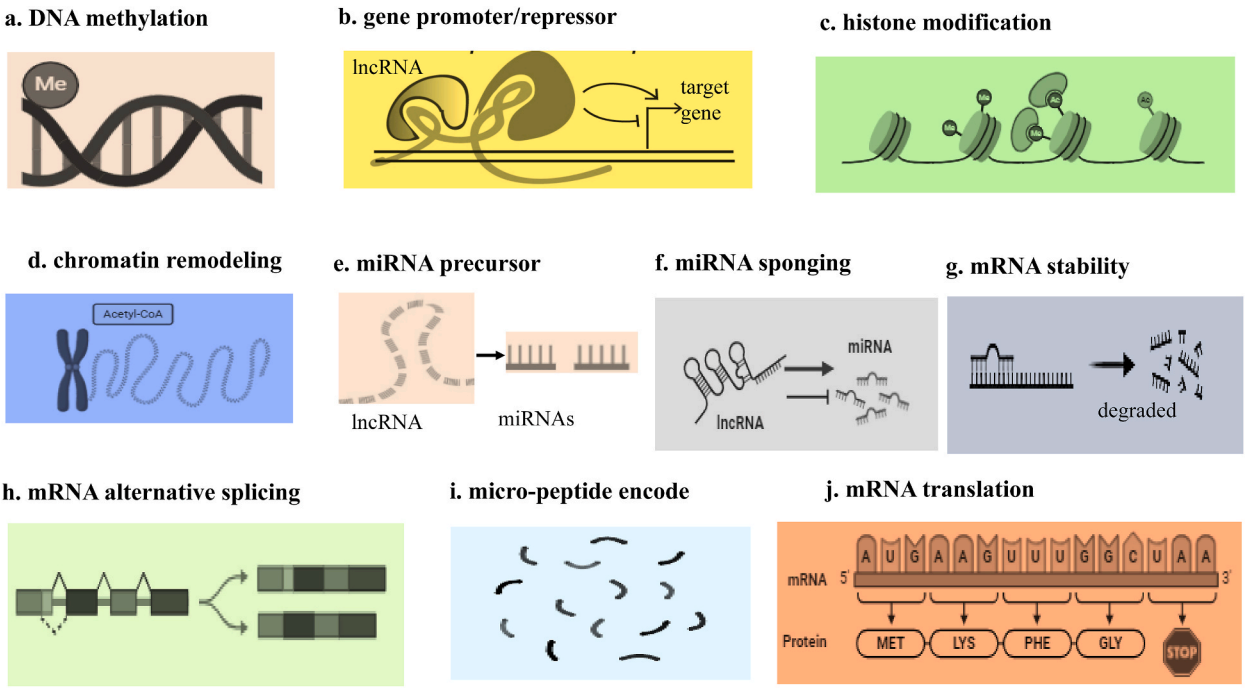

Fig. 2. Mechanism of nuclear and cytoplasmic lncRNAs regulation of tooth development and alveolar resorption: They regulate tooth development related genes, proteins and signaling pathways through: a) DNA methylation b); Act as gene promoters or repressors c) Histone modification, either by methylation or acetylation; d) Chromatin remodeling e) Act as precursors for miRNAs; f); sponging miRNA as competitive endogenous RNAs; g) mRNA stability and degradation; h) participate in alternative splicing; i) some encode small peptides; j) participate in mRNA translation.

significant number of lncRNAs involved in tooth germ formation were identified [10]. Moreover, there is substantial evidence implicating that lncRNAs exert regulatory control over odontogenesis [11]. Fu et al. stated that these cells have expression patterns that are distinct to cell types involved in tooth development. This observation indicates that the cells have undergone evolutionary adaptations to suit the specific requirements of each cell type, hence improving the precision of tooth creation [11].

3.2.3. LncRNA regulates tooth development-related genes

Tooth development requires the coordinated expression of multiple genes and signaling networks. Recent research indicates lncRNAs exert a substantial influence on the regulation of gene expression associated with the activities of osteoblasts and osteoclasts, such as apoptosis, differentiation, proliferation, and activity [12].

(1) LncRNAs regulate gene expression and function as molecular scaffolds by binding to both DNA and proteins, including transcription factors. They can interact with the promoters and enhancers of genes involved in tooth development, boosting or suppressing their expression [13]. Based on their localization, different lncRNAs perform different functions and impact cellular activities and processes. The nuclear lncRNAs direct certain chromatin remodeling complexes to specific genomic sites, resulting in alterations in gene transcription [14]. A prime example is the long intergenic (lincRNA) X inactive-specific transcript (XIST) transcribed on the X chromosome in female mammals [15]. XIST acts by recruiting PRC2 to the female chromosome, subsequently leading to cis-transcriptional silencing of other chromosomes. Furthermore, lncRNA Hotair plays an important role in regulating skeletal development by trans-regulating the expression of the HoxD gene through the recruitment of the PRC2 to the HOXD locus [16]. Notably, HOTAIR has been observed to enact a regulatory role in the modulation of several lncRNAs by specifically targeting their genomic regions [17], which are known to be associated with bone growth. LncRNA Msx1-AS was found to negatively impact the expression of the Msx1 homeodomain protein by down-regulating RUNX2, a key regulator of osteoblast development [18]. Inhibition of lncRNA ANCR resulted in increased osteogenic differentiation in periodontal ligament stem cells (PDLSCs), up-regulating genes associated with osteogenic differentiation [19]. Additionally, lncRNA ANCR is recruited by EZH2 to catalyze H3K27me3 on the Runx2 gene promoter, leading to the suppression of Runx2 expression and subsequently the repression of osteoblastogenesis. Furthermore, Lee et al. discovered that LncRNA Jak3 upregulates cathepsin K (CTSK) expression via Jak3-mediated activation of T-cells 1 (NFATC1), indicating that Jak3 is involved in osteoclast differentiation through the Jak3/NFATC1/CTSK pathway.

(2) LncRNAs have also been observed to form associations with many different chromatin regulators. One instance of lineage-specific imprinting is facilitated by the lncRNA Kcnq1ot1, which is a nuclear transcript originating from the paternal chromosome and exhibiting intermediate stability. Kcnq1ot1 not only engages in interactions with constituents of the PRC2 complex

but also serves as a platform for the recruitment of chromatin regulators, such as G9a methyltransferase. Additionally, lncRNA Rmst was observed to facilitate the osteo-adipogenic differentiation of iMAD cells caused by BMP9, mediated by a regulatory loop involving Rmst, miRNAs, and the Notch signaling pathway [20].

In summary, lncRNAs exert epigenetic control over the various genes associated with tooth development by functioning as molecular scaffolds via their binding to DNA and proteins, interaction with gene promoters and enhancers that are involved in tooth development, and subsequently either repressing or activating their expression.

3.2.4. LncRNA regulates tooth development-related mRNA and protein modification

LncRNAs have been involved in diverse cellular activities, including the control of mRNA stability and translation, pre-mRNA splicing, modulation of protein activities, and serving as precursors for miRNAs and siRNAs [21]. It is worth noting that they possess the ability to encode certain polypeptides and function as miRNA sponges, exhibiting both sequence-dependent and sequence-independent mechanisms [22]. LncRNA MALAT1 is found to be involved in regulating alternative splicing (AS) of endogenous pre-mRNAs by controlling the phosphorylation of serine/arginine splicing factors and influencing the localization of serine/arginine-rich (SR) proteins within nuclear speckle domains, which play a crucial role during the modification of certain tooth development-related proteins and in the cellular expression of specific protein isoforms that control cell proliferation and differentiation during odontogenesis [23]. The lncRNA-adipoQ-AS translocation from the nucleus to the cytoplasm formed a sense/antisense RNA duplex, preventing the translation of adiponectin mRNA, thus inhibiting adipogenic differentiation and enhancing osteoblast formation [24]. LncRNA-00961 has the potential to encode polypeptides called amino acid response (SPAR) in the late endosome or lysosome that interact with the lysosomal vacuolar ATPase to inhibit the activation of mTORC1, subsequently facilitating osteoblast differentiation from pre-osteoblast [25].

3.2.5. LncRNA regulates tooth development-related signal pathways

LncRNAs can modulate the tooth development process by interacting with components of several downstream pathways. Researchers have found that the maternally expressed gene 3 (MEG3) directly interacts with the transcription factor SOX2, which in turn triggers the transcription of BMP4. As a result, mesenchymal stem cells (MSCs) undergo transformation into osteoblasts (OBs). LncRNA MEG3 had a direct interaction with the promoters of SOX2 and BMP4, resulting in an increase in the expression levels of osteogenesis-associated genes. The simultaneous absence of both BMP-2 and BMP-4 will lead to significant hindrance in the process of osteogenesis [26]. LncRNA MEG3 also enhances the osteogenic differentiation capacity of MSCs by acting on microRNA-140–5p, leading to the activation of BMP2 and therefore mitigating bone loss. In a similar vein, the process of down-regulating lncRNA MEG3 led to an increase in the Wnt pathway in the presence of H3K27me3 in the promoter region. Activation of the Wnt/β-catenin signaling pathway enhances the osteogenic differentiation of human dental follicle stem cells [26]. H19, in conjunction with miR-657, promotes the development of MSCs into osteoblasts by suppressing the TGF-1/Smad3/HDAC signaling pathway [26] and serves as a mediator in the process of osteogenic differentiation of MSCs. The specific miRNAs reported to be involved in this modulation include miR-449b, miR-107, miR-27b, miR-34a, miR-106b, miR-449a, miR-125a, and miR-17 [27]. Linc-ROR was found to act as a sponge for microRNAs miR-138 and miR-14, thereby suppressing their activity and inhibiting the co-target ZEB2, a transcription factor known to enhance β-catenin. This inhibition subsequently led to the activation of Wnt/β-catenin [28].

3.2.6. LncRNA ZFAS1 regulates bone development

LncRNA ZFAS1 (Zinc Finger Antisense 1), which is transcribed from the antisense strand of the ZNFX1 gene locus, has been identified as a multifunctional lncRNA involved in various biological processes and diseases [29]. 2By up-regulating the miRNA-499 EPHA5 axis, LncRNA ZFAS1 down-regulated the osteogenic differentiation of BMSCs. This down-regulation of ZFAS1 not only alienated the positive effect of adipogenesis but also facilitated osteoblast differentiation through the miR-499 interaction, acting as a major regulator [30]. ZFAS1 functions as a competitive RNA (ceRNA) that upregulates the expression of genes associated with proliferation, invasion, and metastasis, such as ZEB2, BMI1, MMP-16, and MMP14, by sponging miR-200c, miR-150, or miR-200b [31]. Hence, ZFAS1 is a complex long non-coding RNA (lncRNA) that exerts its influence on cellular behavior through competitive binding interactions with miRNAs, thereby regulating the process of osteogenesis. These regulatory mechanisms collectively contribute to the modulation of bone growth. Understanding the complex mechanisms that govern cellular differentiation and proliferation in bone tissues is of utmost importance, given its relevance to disease and bone development. However, the exact role and mechanism of ZFAS1 in regulating tooth development and alveolar resorption are not yet very clear.

3.3. LncRNAs regulates alveolar resorption

Alveolar resorption is a tightly controlled process that is modulated by the interactions of various key players, including, among others, lncRNAs.

3.3.1. LncRNAs that contribute to alveolar resorption process

The initiation of osteoclast activation is an essential requirement for the process of alveolar bone resorption. The intricate modulation of osteoclast differentiation entails the involvement of various cytokines, including TNF-α, M-CSF, IL-1, IL-6, and IL-11, as well as the RANKL-RANK pathway [32]. LncRNAs play a role in osteoclastogenesis and bone resorption by exhibiting different expression patterns that are specific to different stages of osteoclastogenesis [33]. LncRNA DANCR is involved in osteoclast development

progression, whereby it stimulates TNF-α and IL-6 expression [34]. LncRNA MALAT1 has also been implicated in the regulation of the RANK/RANKL/OPG pathway in vitro settings to control osteoclast activity [35]. LncRNA MALAT1 controls the inflammatory responses triggered by LPS by interacting with NF-kB, which is responsible for RANKL-induced osteoclastogenesis and the destruction of alveolar bone in periodontitis [34].

3.3.2. *LncRNAs facilitates periodontitis leading to alveolar bone resorption*

Periodontitis, a common chronic oral disease, is characterized by the inflammatory resorption of alveolar bone that supports teeth and the presence of aggressive osteoclast activity as a result of the host's uncontrolled response to a periodontal infection [44]. In recent years, lncRNAs have demonstrated significant potential for regulating cellular and tissue homeostasis. However, they are now recognized as significant contributors to the pathogenesis of periodontitis, functioning as regulators of gene expression, mediators of inflammatory responses, maintaining tissue homeostasis, and impacting alveolar bone resorption [44]. In periodontitis, the dysregulation of inflammatory pathways can lead to the destruction of periodontal tissues, including alveolar bone resorption. LncRNAs can influence the expression of pro-inflammatory cytokines and chemokines, exacerbating inflammation and tissue damage. Weilong et al. demonstrated that lncRNA XIST overexpression improved inflammatory factor secretion and increased positive osteoclast numbers. However, it suppressed osteoclast differentiation by acting as a sponge for miR-130b-3p and up-regulating PTEN expression [45]. Overexpression of MIR22HG in human BMSCs increased osteogenic differentiation, whereas silencing MIR22HG inhibited osteogenic differentiation both in vitro and in vivo. MIR22HG also facilitated osteogenic differentiation by suppressing phosphatase and tensin homolog (PTEN), which activated AKT signaling. Furthermore, studies have also discovered that overexpression of MIR22HG stimulates osteoclastogenesis in RAW264.7 cells, suggesting that it may serve as a therapeutic target for osteoporosis and other bone-related disorders and plays a significant role in bone metabolism. Additionally, lncRNAs play a role in maintaining normal cell and tissue homeostasis. LncRNA dysregulation can disrupt the balance in periodontal tissues, causing pathological changes such as alveolar bone resorption [5]. Moreover, Wang and colleagues have recently investigated the function of lncRNA-POIR in the process of periodontitis, where they showed that the expression of lncRNA-POIR was lower in PDLSCs from periodontitis patients (pPDLSCs) compared to hPDLSCs from healthy individuals. As a result, lncRNA-POIR upregulation enhanced osteogenic differentiation in pPDLSCs. In addition, in their subsequent investigation, they demonstrated that lncRNA-POIR functions as a competing endogenous RNA (ceRNA) for miR-182, thereby enhancing FoxO1 expression [39]. LncRNAs can also modulate the expression of genes involved in tissue remodeling and inflammation. Altered gene expression patterns can contribute to the breakdown of alveolar bone and connective tissues in periodontitis [46]. A recent discovery reveals a negative correlation between the lncRNA Nron and alveolar bone resorption in a model of periodontitis. Nron demonstrated effective inhibition of osteoclastogenesis and alveolar bone resorption. Nron was also found to mechanistically enhance the nuclear transport of NF-κb repressing factor (NKRF). Moreover, the presence of NKRF in the nucleus led to significant repression of Nfatc1 transcription, a crucial molecule involved in NF-κB signaling [40]. In the same Nfac1, lncRNA TUG1 inhibits cell proliferation by inducing transforming growth factor-b, which plays a role in the interaction between fibroblasts and epithelial cells in periodontitis [41].

3.3.3. *LncRNAs causes unbalanced osteoblast and osteoclast interaction leading to alveolar bone resorption*

Cellular differentiation is a complex process wherein undifferentiated cells acquire distinct characteristics and functions [47]. The differentiation of osteoblasts and osteoclasts is intricately linked to maintaining bone health [48]. Osteoblasts secrete factors like RANKL, OPG, and various growth factors that regulate osteoclast differentiation and activity [49]. This coupling between bone-forming osteoblasts and bone-resorbing osteoclasts contributes to bone remodeling, ensuring structural integrity and calcium homeostasis [49]. Therefore, in bone and dental tissue, the differentiation of osteoblasts and osteoclasts plays a crucial role in maintaining bone homeostasis [50]. However, LncRNAs are of considerable importance in maintaining the complex balance between osteoblasts and osteoclasts, which subsequently contributes to the resorption of alveolar bone. Meanwhile, lncRNA, several key molecular regulators have been studied that orchestrate osteoblastogenesis and osteoclastogenesis.

MC3T3-E1 is an extensively researched cell line of pre-osteoblasts that is commonly employed to investigate the process of osteoblastogenesis [51]. The differentiation of MC3T3-E1 cells into mature osteoblasts involves several stages. Multiple studies have elucidated the role of lncRNAs in controlling osteoblastogenesis and osteoblast differentiation. One study by Yu, C. et al., showed that lncRNA TUG1 promotes osteoblast differentiation through up-regulation of Runx2 by sponging miR-204-5p [52]. Runx2, a master regulator of osteoblast differentiation, initiates the process by activating genes related to bone matrix formation, such as collagen and osteocalcin [53]. As osteoblasts mature, they deposit a mineralized extracellular matrix, crucial for bone strength. A recent study by Zhang et al. found that lncRNA MSC-AS1 activates BMP2 through osteogenic differentiation promotion and osteoporosis down-regulation by sponging miR-140-5p [42]. In addition, Chen et al. investigated the involvement of lncRNA MCF2L-AS1 in the osteogenic differentiation of BMSCs and the associated molecular mechanisms. The results of their study of hBMSCs transfected with miR-33a mimic or silenced for MCF2L-AS1 indicated that the aforementioned lncRNA promoted osteogenic differentiation in hBMSCs by increasing the expression of RUNX2 through inhibition of miRNA-33a. These findings suggest that the lncRNA MCF2L-AS1 acts as a facilitator of osteogenic differentiation [54]. Furthermore, Xiang et al. evaluated the involvement of the lncRNA small nucleolar RNA host gene 1 (SNHG1) in the osteogenesis process. The researchers successfully determined that lncRNA SNHG1 had the capability to inhibit the process of osteoblast differentiation. This is achieved through its function as a molecular sponge for miR-101, as well as by promoting an increase in DKK1 expression levels [43]. Another study also revealed that, by acting as a reservoir for miR-30 and miR-124, LncMALAT1 promotes osteoblast differentiation. Still, MALAT1 suppresses miR-204 activity, resulting in an increase in Smad4 levels and ultimately promoting optimal osteoblast functionality. Moreover, the role of the lncRNA HIF1α-AS1 in osteoblastogenesis has only recently been discovered. The overexpression of the histone deacetylase SIRT1, a key regulator of osteoblast

differentiation, significantly repressed HIF1α-AS1 expression. Lower levels of SIRT1 led to increased HIF1α-AS1 expression in human bone marrow stem cells (BMSCs). Furthermore, HIF1-AS1 knockout inhibited HOXD10 expression by interfering with acetylation, suggesting a potential role of HIF1-AS1 in activating osteoblastogenesis [36]. Besides protein-coding genes, various lncRNAs have also been implicated in the process of osteoclastogenesis. Among these, lncRNA DANCR participates in osteoclast differentiation by activating tumor necrosis factor-alpha and interleukin-6 expression [55]. It also promotes osteoblast differentiation by downregulating EZH2 and upregulating Runx2 expression [53]. Osteoclast differentiation is also governed by receptor activator of nuclear factor-kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) [55]. Osteoclast differentiation is also governed by receptor activator of nuclear factor-kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) [56]. RAW 264.7 cells differentiate into multinucleated osteoclasts in response to RANKL, undergoing fusion and forming specialized structures for bone resorption called ruffled borders [57]. Another lncRNA, MALAT1, has also been involved in in vitro osteoclast activity regulation of RANK-RANKL-OPG pathway control [37]. Osteoclast differentiation also involves activation of transcription factors like NFATc1 and c-Fos, which regulate genes essential for bone resorption, including cathepsin K and tartrate-resistant acid phosphatase (TRAP) [58]. For example, lncRNA TUG1 up-regulation promotes increased levels of TRAP, NFATc1, and osteoclast-associated receptor (OSCAR) during osteoclast differentiation. Simultaneously, it also enhances the expression of the V-maf muscular neurofibrosarcoma homolog B (Mafb) protein, thereby exerting a beneficial influence on the process of osteoclast differentiation. A similar effect on NFATc1 expression is also exhibited by Lnc-AK077216, which can eventually lead to enhancement or inhibition of osteoclast development, bone resorption, and the expression of associated genes, respectively. Furthermore, Ling et al.'s study examined the expression levels and impact of lncRNA MIRG on the development of osteoclasts derived from bone marrow macrophages (BMMs) isolated from mice's femurs. Their findings revealed that lncRNA MIRG could enhance the processes of osteoclastogenesis and bone resorption by functioning as a molecular sponge for miR-1897 [38].

3.3.4. Alveolar resorption a vital process during tooth development

Physiological alveolar resorption is one of the vital aspects of tooth development that occurs in the oral cavity. Furthermore, tooth development entails the formation and eruption of primary teeth, followed by the eruption of permanent teeth, which is critical for maintaining a healthy dentition [59]. As a result, tooth development and eruption are dependent on the presence of healthy alveolar bone. The tooth buds need a proper environment and support from the alveolar bone to develop and erupt into the oral cavity. However, any disruption or abnormality in the alveolar bone with respect to periodontitis (a pathological process) can affect the normal development and eruption of teeth. This, in turn, can lead to improper eruption, impaction, and malocclusion, or the misalignment of teeth [60]. Likewise, poor tooth development, such as enamel defects or malocclusion, makes oral hygiene more challenging, thus increasing the risk of periodontal diseases like periodontitis. Therefore, maintaining excellent oral hygiene practices, regular dental check-ups, and early intervention for periodontitis can help mitigate its impact on tooth development.

4. Conclusion

Several studies conducted over the course of the past decade have firmly demonstrated the significant involvement of lncRNAs in a wide range of physiological and pathological processes, including tooth development and alveolar resorption. In this review, we discuss the regulatory role of lncRNAs and their new involvement in tooth development and alveolar resorption. We also explored the different mechanisms by which they regulate these physiological and pathological processes by digging into their involvement and modulation of the molecular pathways and processes that various lncRNAs use to contribute to these critical aspects of oral health. Moreover, they exercise their regulatory roles based on their sub-cellar distribution as well as at multiple levels. Nuclear lncRNAs control tooth development-related genes acting as histone modifiers, DNA methylators, chromatin remodelers, transcription promoters, and repressors. On the other hand, cytoplasmic lncRNAs act as precursors of miRNAs and siRNAs, participate in alternative splicing, sponge miRNAs, mRNA translation, stability, and some encode micro-peptides. They also regulate these processes at different levels, such as the epigenic level, protein level, signaling pathway levels, and the differentiation and activity of osteoclasts and osteoblast cells. Together, these insights contribute to our understanding of the molecular mechanisms underlying these physiological and pathological processes, as well as their potential implications for the development of functional teeth and the complex process of bone remodeling in the oral cavity.

CRediT authorship contribution statement

Lilliane Aol: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Xinhong Zhou:** Writing – review & editing, Writing – original draft, Methodology. **Hong Hao:** Writing – review & editing, Funding acquisition. **Jiaqi Nie:** Visualization. **Wanjun Zhang:** Writing – review & editing. **Dunjie Yao:** Writing – review & editing. **Li Su:** Writing – review & editing, Supervision, Conceptualization. **Wanlin Xue:** Supervision, Funding acquisition, Conceptualization.

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Data availability statement

All data generated or analyzed during this study are included in this published article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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