Noncoding RNAs in periodontitis: Progress and perspectives (Review)

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Abstract. Periodontitis is the sixth most common chronic non-infectious disease in the world. It mainly leads to the inflammatory destruction of periodontal supporting tissue, which has become the main cause of tooth loss in adults. Periodontitis is also a risk factor for various systemic diseases. Noncoding ribonucleic acids (ncRNAs) are important regulators of normal biological processes and their abnormal expression has been shown to be important to the pathogenesis of inflammatory diseases, including periodontitis. Biologically, they can regulate immune inflammation, bone homeostasis and cell proliferation in periodontitis. Clinically, they are promising diagnostic markers and therapeutic targets. Recent advances in technology have opened up new directions for the study of ncRNAs, including RNA secondary structures, RNA protein interactions, ncRNA-encoded peptides or proteins and single-cell RNA sequencing. Therefore, the present study summarized the function and mechanisms of ncRNAs in periodontitis, as well as their clinical potential for diagnosis and treatment and highlight these exciting areas of research.

Contents

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1. Introduction

Periodontitis is an epidemic disease whose global prevalence increased by 99.0% between 1990 and 2019, reaching 1 billion in the latter year (1,2). Periodontitis reduces patients' quality of life and places an economic burden on society, making exploration of its pathogenesis and achieving a cure urgent (3). As an inflammatory disease, periodontitis is affected by a number of factors such as genomics, epigenetic modification and environmental conditions. Due to the complexity of the disease's etiology and mechanism, conventional treatment for periodontitis cannot completely help regenerate lost periodontal tissue. In recent years, due to the rapid development of sequencing technology, researchers have gained broader and deeper understanding of the transcriptome in periodontitis, which lays a foundation for exploring the disease's pathogenesis and potential targeted therapies (4).

In the past, the linear model of deoxyribonucleic acid (DNA) to ribonucleic acid (RNA) to protein was often regarded as the central dogma of molecular biology, with the greatest attention on coding RNAs (5). However, as sequencing technology matured, researchers found that the number of noncoding RNAs (ncRNAs), previously considered 'dark transcriptomes' or 'genomic dark matter', far exceeds that of coding RNAs (6). Moreover, ncRNAs play important regulatory roles in the occurrence and development of a number of inflammatory diseases (7). At present, there is no unified system of classification for ncRNAs. Commonly, they are divided into those shorter than and those longer than 200 nucleotides (nt) and respectively called short noncoding RNAs (sncRNAs) and long noncoding RNAs (lncRNAs). The former group includes microRNAs (miRNAs), small nucleolar RNAs (snoRNAs), small nuclear RNAs (snRNAs), piwi-interaction RNAs (piRNAs), small interfering RNAs (siRNAs), transfer RNA (tRNAs), tRNA-derived fragments (tRFs) and Y RNA fragments (YRFs). The last can be divided into long intergenic RNAs (lincRNAs), antisense RNAs (asRNAs), intronic noncoding RNAs (iRNAs), enhancer RNAs (eRNAs) and pseudogenes (8). In addition, circular RNAs (circRNAs) have emerged onto researchers' radar and are considered a new class of ncRNAs with regulatory potential (9).

The continuous advancement of high-throughput sequencing technology and computational technology has made significant contributions to the research on ncRNAs (10).

In particular, long-read sequencing has enhanced our understanding of ncRNAs (11). Sequencing analysis involves multiple key steps, starting from sample preparation to high-throughput sequencing. Initially, samples are processed based on the specific type of target ncRNAs (such as small RNA, lncRNA, or circRNA) and the species being studied. Magnetic columns are then used to enrich or remove interfering RNAs. Subsequently, libraries are constructed, which involves connector connection, reverse transcription and PCR amplification. Finally, sequencing is performed using a high-throughput platform, followed by bioinformatics analysis tools (12). These computational tools are essential for revealing the relationship between RNA structure and function (13).

In inflammatory diseases, ncRNAs are abnormally expressed and regulate the occurrence and development of disease (14). The pathogenesis of periodontitis, as a nonspecific inflammatory disease, involves different types of ncRNAs (15). For example, the function of ncRNAs depends on their sequence, secondary and tertiary structures, subcellular localization and interactions with other molecules. Commonly, ncRNAs bind to microRNAs or RNA-binding sites, thereby affecting gene expression. The present review briefly summarized the reports of ncRNAs in periodontal immune inflammation, cell proliferation and bone homeostasis, subsequently moving on to descriptions of new ncRNA research areas. Finally, it addressed the potential of ncRNAs in the diagnosis and treatment of periodontitis, the limitations of this research field at present and its future prospects (Fig. 1). Micro (mi)RNA is a common ncRNA and previous comprehensive articles have summarized the mechanism and function of miRNAs in periodontitis (16). However, there are a number of research reports on lncRNA and circRNA in periodontitis and no systematic review summary has been seen yet. Therefore, this review instead mainly discusses the relevance of newly emerging lncRNAs and circRNAs to the field of periodontitis.

2. LncRNAs in periodontitis

LncRNAs regulate immune inflammation in periodontitis. Periodontitis is a chronic inflammatory disease. Most tissue damage during the progression of periodontitis has been proven to be caused mainly by the host's immune response to infection, rather than from the direct effects of microorganisms. Activation of the inflammatory process is a double-edged sword. On the one hand, a moderate inflammatory response can maintain the health of the body; on the other, activation and continuous stimulation of relevant inflammatory pathways harm the host, resulting in the occurrence or aggravation of rheumatoid arthritis, atherosclerosis (AS), kidney injury, periodontitis and other diseases (17-19). In immunoinflammatory studies, related genes mainly pass through the Janus-associated kinase/signal transducer and activator of transcription/interleukin-6 (IL-6), nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), Toll-like receptor (TLR), B-cell receptor and T-cell receptor signaling pathways to regulate disease progression (20,21). The same is true of lncRNAs involved in periodontitis.

TLR4 is mainly expressed in cells involved in the host defense function. It can conduct signal recognition and transmission by recognizing specific antigenic components of pathogen-related molecular patterns, a capability considered to be closely related to immune inflammation (22). One study on periodontitis demonstrated that the lncRNA papillary thyroid carcinoma susceptibility candidate 3 (*PTCSC3*) can downregulate TLR4 (23), while another found that the lncRNA *MFG-AS1* can upregulate TLR4 (24). The two studies indicated that lncRNAs could affect the progression of periodontitis by regulating TLR4. Conversely, TLR4 could also regulate lncRNAs and thereby affect periodontitis. For example, in macrophages of periodontitic tissues, the response of the lncRNA metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) to TLR4 activation is time dependent and contributes to macrophage polarization (25).

LncRNAs also play an important role in the regulation of periodontitis by acting on interleukin, a common inflammatory factor. Knockdown of the lncRNA nuclear paraspeckle assembly transcript 1 (*NEAT1*) can downregulate IL-6, IL-1β and tumor necrosis factor-α (TNF-α); reduce the ratio of B-cell lymphoma 2 (*Bcl-2*)-like protein 4 (*BAX*) to *Bcl-2* through the microRNA (*miR*)-*200C-3p*/TNF receptor-associated factor 6 (*TRAF6*) axis; and reduce inflammation and apoptosis in periodontal-ligament cells (PDLCs), thereby helping alleviate the progression of chronic periodontitis (26). Lysyl oxidase homolog 1 (*LOXL1*)-*AS1* inhibits IL-1β expression in periodontal ligament stem cells (PDLSCs) to reduce the severity of periodontitis (27). The lncRNA zinc finger Y-chromosomal protein (*ZFY*)-*AS1* inhibits the release of inflammatory factors in periodontitis, such as IL-6 and IL-1B, by regulating the *miRNA-129-5P*/DEAD-box helicase 3 X-linked (*DDX3X*) axis (28). The lncRNA small nucleolar RNA host gene 5 (*SNHG5*) mediates periodontal inflammation by influencing the expression of inflammatory cytokines through the *NF-κB* signaling pathway (29). In lipopolysaccharide (LPS)-induced PDLSCs, *Linc00616* promotes ferroptosis through the *miRNA-370*/transferrin receptor (*TfR*) axis, aggravating the progression of periodontitis (30). *Linc01126* suppressed proliferation while promoting apoptosis and the secretion of inflammatory cytokines IL-1β, IL-6, IL-8 and TNF-α in human PDLCs (hPDLCs) under hypoxia by sponging *miR-518a-5p* (31). A recent study found that *Linc01126* acts a sponge for *miR-655-3p*, inhibiting its binding to *IL-6* mRNA and thereby promoting inflammation progression and *JAK2*/*STAT3* pathway activation in periodontitis (32) (Fig. 2).

LncRNAs regulate bone homeostasis in periodontitis. In healthy periodontal tissue, the rates of bone matrix degradation and bone resorption are balanced by those of matrix mineralization and new-bone deposition, a state known as periodontal-bone homeostasis. When periodontal tissue is infected with pathogens, this balance is disturbed and the rates of matrix degradation and bone resorption exceed those of matrix mineralization and new-bone deposition. This results in periodontal-tissue inflammation, bone absorption and even tooth loosening and loss (33).

Existing studies have shown that lncRNAs play important roles in bone metabolism, regulating the occurrence and development of various bone diseases (34,35). Therefore, studying the mechanisms of ncRNAs in periodontal homeostasis can provide new ideas for exploring the pathogenesis and clinical treatment of periodontitis. Studies on the role of lncRNAs

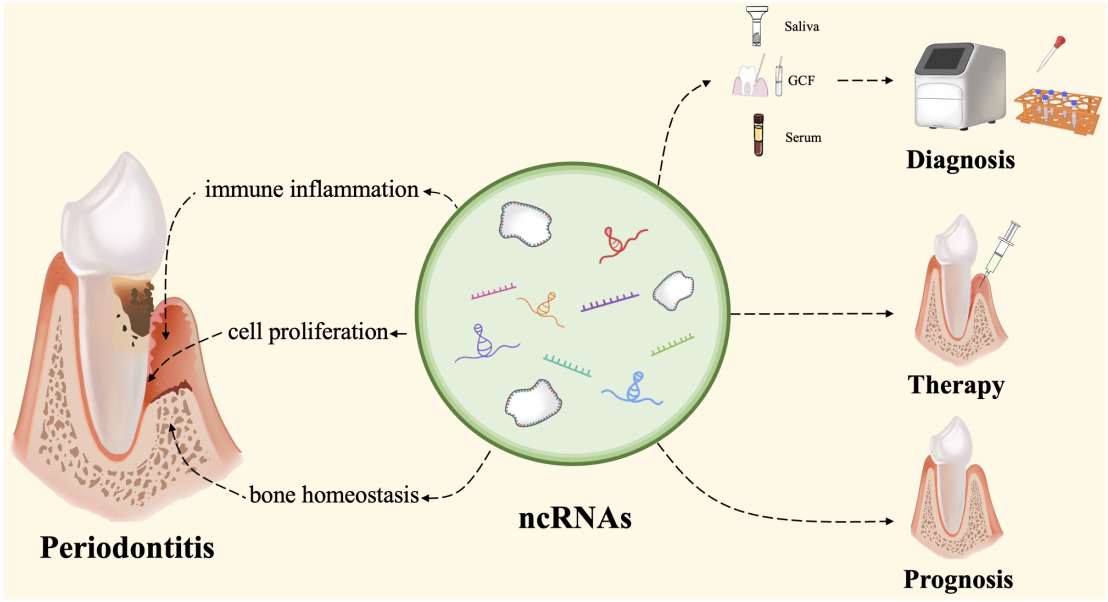

Figure 1. Graphical Abstract. Brief overview of ncRNAs in periodontitis. NcRNAs not only regulate immune inflammation, bone homeostasis and cell proliferation in periodontitis, but also serve as diagnostic marker and nucleic acid drug. nc, noncoding; GCF, gingival crevicular fluid.

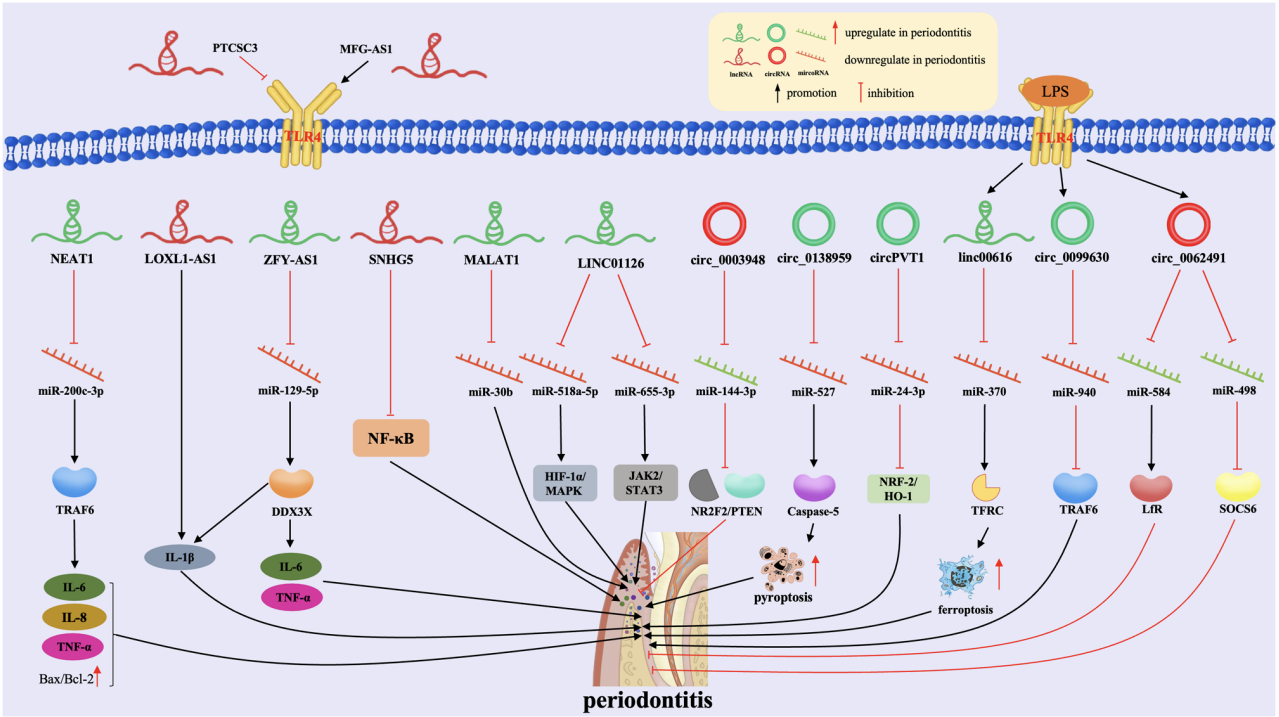

Figure 2. Brief overview of ncRNAs regulate immune inflammation in periodontitis. LncRNA *PTCSC3* can downregulate TLR4 and lncRNA *MFG-AS1* was found to upregulate TLR4. LncRNA *NEAT1*, lncRNA *ZFY-AS1*, lncRNA *MALAT1*, *Linc01126*, *Circ_0138959*, *CircPVT1*, *Linc00616* and *Circ_0099630* are markedly increased in the pathogenesis of periodontitis, which targeting miRNA and upregulating target proteins and then which promoting the occurrence and development of periodontal disease. LncRNA *LOXL1-AS1*, LncRNA *SNHG5*, *Circ_0003948*, *Circ_0062491*, *Circ_0085289* are down-regulated in the pathogenesis of periodontitis and play a protective role in periodontitis. The black arrowheads indicate promotion and the red T indicate inhibition. nc, noncoding; lnc, long noncoding; linc, long intergenic noncoding; circ, circular; mi, micro; TLR4, Toll-like receptor 4; TRAF6, TNF receptor-associated factor 6; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; DDX3X, DEAD-box helicase 3 X-linked; NF-κB, nuclear factor kappa-B; HIF-1α, hypoxia inducible factor 1 alpha; MAPK, mitogen-activated protein kinase; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; NR2F2, nuclear receptor subfamily 2 group F member 2; PTEN, phosphatase and tensin homolog; NRF-2, nuclear factor (erythroid-derived 2)-like 2; HO-1, heme oxygenase-1; TFRC, transferrin receptor; LfR, lactoferrin receptor; SOCS6, suppressor of cytokine signaling 6.

in periodontal homeostasis are mainly limited to their effects on osteogenic differentiation; in terms of mechanism of action (36,37), the present review mainly focused on the competitive binding of lncRNAs to miRNAs, which affects the expression of target genes and promotes osteogenesis. The bone morphogenetic protein/Smad, Wingless/Integrated

(*Wnt*)/β-catenin, *Notch*, *Hedgehog*, mitogen-activated protein kinase (*MAPK*) and fibroblast growth factor (*FGF*) signaling pathways are the most critical ones in the process of osteogenic differentiation. Our research group previously constructed the competing endogenous RNA (ceRNA) regulatory network of PDLSCs osteogenic differentiation, preliminarily verified that *Loc1001302640*/*miR-1469* and *miR-1469*/*Smad6* may play important roles in the process of osteogenic differentiation, predicted their possible binding sites and screened out that the MAPK and transforming growth factor-β (TGF-β) pathways play important roles in the process of osteogenic differentiation (38). In addition, studies have shown that the lncRNAs maternally expressed gene 3 (*MEG3*) (39), AS ncRNA in the Inhibitor of cyclin-dependent kinase 4 (CDK4; INK4) locus (*ANRIL*) (40), JmjC domain-containing histone demethylation protein 1D (*JHDM1D*)-*AS1* (41), *Linc01126* (31), dendrocyte-expressed seven-transmembrane protein (DCSTAMP) domain-containing protein 1 (*DCST1*)-AS1 (42), *MALAT1* (43), *Linc00707* (44), *LncRNA00638* (45), distal-less homeobox 2 (*DLX2*)-*AS1* (46) and Opa interacting protein 5 (*OIP5*)-*AS1* (47) and *Linc01133* (36) regulate the osteogenic differentiation of PDLSCs by adsorbing miRNAs as ceRNAs. In addition to the key pathways, *MEG3* was found to regulate different miRNAs to affect osteogenic differentiation of PDLSCs through the phosphoinositide 3-kinase (*PI3K*)/protein kinase B (*Akt*) or *Akt*/inhibitor of NF-κB kinase (*IKK*) pathways (37,39).

Some researchers have focused on another aspect of lncRNA regulation of periodontal homeostasis: Bone resorption. Activation of osteoprotegerin (*OPG*)/receptor activator of nuclear factor κ-β ligand (*RANKL*)/TNF receptor superfamily member 11a (*TNFRSF11A*, or *RANK*), a key bone resorption pathway, promotes osteoclastic differentiation and disrupts the balance between bone degradation and bone formation, leading to fracture and related functional loss (48). *NEAT1* in myeloid-derived suppressor cells (MDSCs) activates the classic nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 3 (*NLRP3*) inflammasome activation pathway, leading to the exacerbation of bone destruction in periodontitis (49). In a rat orthodontic tooth movement (OTM) model, the lncRNA differentiation antagonizing non-protein coding RNA (*DANCR*) could disturb the balance of periodontal-bone metabolism by upregulating Jagged1 to increase stress-induced osteoclast formation and root absorption (50). *SNHG5* affects the secretion of *RANKL* and inhibits differentiation of osteoclasts during OTM by combining with CCAAT-enhancer-binding protein-β (C/EBP-β), a regulator of osteoclasts (51). The lncRNA noncoding repressor of nuclear factor of activated T cells (*NRON*) can effectively promote nuclear transport of NF-κB inhibitor, inhibit osteoclastic- and alveolar-bone resorption and correct the imbalance of bone metabolism in periodontitis (52) (Fig. 3). Much study remains to be done on lncRNAs in bone metabolism in periodontitis compared with other diseases, especially in osteoclasts.

LncRNAs regulate the proliferation of PDLSCs/PDLCs. Excessive proliferation of PDLSCs is an abnormal phenotype in periodontitis that is considered to be related to the disease's pathogenesis. It is generally considered that abnormal proliferation of PDLSCs in periodontitis can disrupt the balance between proliferation and apoptosis, leading to aggravation of periodontal inflammation. Various lncRNAs participate in the regulation of PDLSC proliferation and affect disease progression by acting on different targets. The lncRNA erythrocyte membrane protein band 4.1-like 4A (*EPB41L4A*)-*AS1* directly targets the expression of *miR-214-3p*, resulting in changes in Yamaguchi sarcoma virus oncogene (*Yes1*)-associated transcriptional regulatory factor (*YAP1*) levels and ultimately enhancing the proliferation and osteogenic differentiation of hPDLCs (53). *MALAT1* promotes proliferation of PDLSCs in periodontitis as well as disease progression by upregulating *FGF2* (54). The lncRNA mortal obligate RNA transcript (*MORT*) inhibits PDLSC proliferation and reduces recurrence of periodontitis (55). LncRNA activator of myogenesis (*linc-RAM*) was found to be the downstream regulatory factor of *FGF2*; *FGF2* can promote proliferation of PDLSCs by inhibiting expression of *linc-RAM* in periodontitic pathogenesis (56). The lncRNA *DCST1-AS1* upregulates periodontal-ligament-associated protein-1 (*PLAP-1*) by combining with *miR-21* precursor to reduce expression of *CDK4*, *CDK6* and cyclin D1 (*CCND-1*) and inhibit PDLC proliferation, thereby alleviating the inflammatory response in periodontal tissues (40). Similarly, *LOXL1-AS1* might inhibit the proliferation of periodontitic PDLSCs and downregulate *IL-1β* to improve periodontitis (27). The lncRNA taurine upregulated 1 (*TUG1*) mediates LPS-induced proliferative inhibition of hPDLCs by sponging *miR-132* (57) (Fig. 4). However, few studies have been conducted on the exact mechanism of lncRNAs in regulating cell proliferation and apoptosis in periodontitis and further exploration is still needed.

3. CircRNAs as emerging players in periodontitis

CircRNAs regulate immune inflammation in periodontitis. In periodontitis, research into circRNAs in immune inflammation is mainly focused on regulation of downstream target genes by sponging miRNA. Researchers collected gingival tissues from healthy and periodontitic patients for high-throughput sequencing and constructed a circRNA-miRNA-mRNA regulatory network through bioinformatics (58). Similarly, another researcher collected inflamed gingiva and sequenced them to construct a circRNA-miRNA interaction network (59). The key circRNAs in the pathological process of periodontitis were screened out of the interaction network, including *Circ_0095812*, *Circ_0120299*, *Circ_0125699*, *Circ_0062491* and *Circ_0043115*. *Circ_0062491* sponges *miR-584* in THP-1 cells treated with *P. gingivalis*, which enhances the anti-inflammatory effect of lactoferrin receptor. This suggests that circRNAs play a regulatory role in the pathological process of periodontitis. A recent study found that in LPS-induced human PDLCs, *Circ_0062491* targeted *miR-498*/*SOCS6* to alleviate periodontitis (60). These two studies showed that the same circRNA can sponge different miRNAs to function as a ceRNA in different periodontal cells. CircRNA plasmacytoma variant translocation 1 (*circPVT1*) promotes periodontitic progression by modulating the nuclear factor (erythroid-derived 2)-like 2 (*Nrf-2*)/heme oxygenase-1 (*HO-1*) pathway via the *miR-24-3p*/hypoxia inducible factor 1 subunit α inhibitor (*HIF1AN*) axis (61). However, some studies have also reported on the protective effect of circRNA in

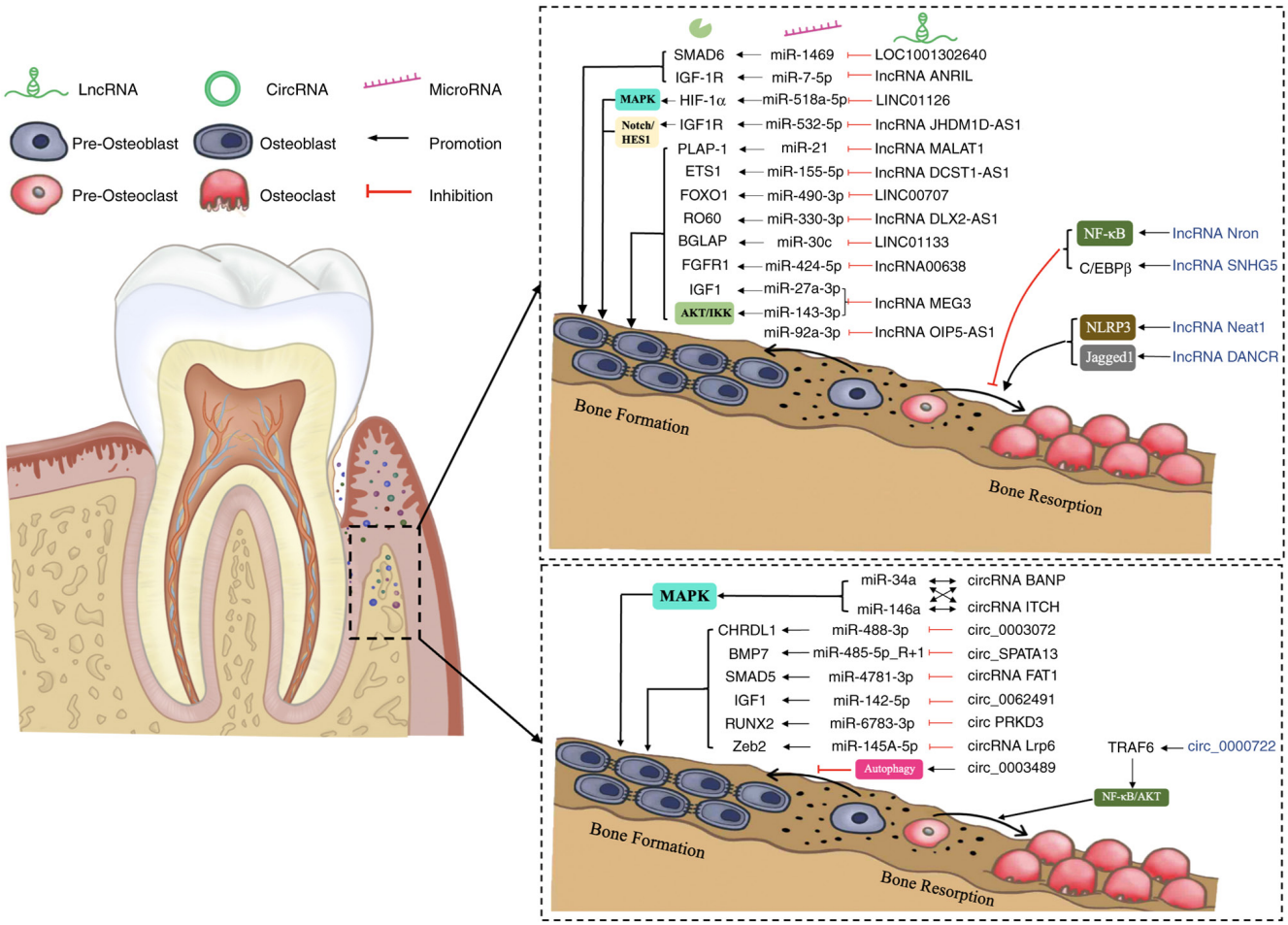

Figure 3. NcRNAs regulate bone homeostasis in periodontitis. LncRNAs and circRNAs promote the osteogenic differentiation of PDLSCs and bone resorption of osteoclasts by adsorbing miRNAs as ceRNAs. The black arrowheads indicate promotion and the red T indicate inhibition. nc, noncoding; lnc, long noncoding; Linc, long intergenic noncoding; circ, circular; PDLSCs, periodontal ligament stem cells; mi, micro; ce, competing endogenous; SMAD6, mothers against decapentaplegic homolog 6; IGF-1R, insulin-like growth factor 1 receptor; HIF-1α, hypoxia inducible factor 1 alpha; MAPK, mitogen-activated protein kinase; HES1, hes family BHLH transcription factor 1; PLAP-1, periodontal-ligament–associated protein-1; ETS1, erythroblast transformation specific 1; FOXO1, forkhead box O1; RO60, Y RNA binding protein; BGLAP, bone gamma-carboxyglutamate protein; FGFR1, fibroblast growth factor receptor 1; IGF1, insulin-like growth factor 1; AKT, protein kinase B; IKK, inhibitor of NF-κB kinase; NF-κB, nuclear factor kappa-B; C/EBP-β, CCAAT-enhancer-binding protein-β; NLRP3, NLR family pyrin domain containing 3; CHRDL1, chordin like 1; BMP7, bone morphogenetic protein 7; SMAD5, mothers against decapentaplegic homolog 5; RUNX2, runt-related transcription factor 2; Zeb2, zinc finger E-box binding homeobox 2; TRAF6, TNF receptor-associated factor 6.

periodontitis. Silencing *Circ_0099630* alleviates LPS-induced PDLC injury by targeting *miR-940/TRAF6/NF-κB* in periodontitis (62). In another RNA-seq study of gingiva from patients with chronic periodontitis, *Circ_0003948* was markedly downregulated; this downregulation conferred protection through the *miR-144-3p*/ nuclear receptor subfamily 2 group F member 2 (*NR2F2*)/phosphatase and tensin homolog (*PTEN*) axis (63). However, in human gingival fibroblasts, *Circ_0138959* was confirmed to inhibit cell viability and promote pyroptosis through the *miR-527*/cysteine-aspartic acid protease/proteinase 5 (*Caspase-5*) axis, aggravating periodontitis (64) (Fig. 2).

CircRNAs regulate bone homeostasis in periodontitis. At present, studies of the mechanism by which circRNAs regulate bone homeostasis in periodontitis are still relatively limited. PDLSCs, as important seed cells for periodontal regeneration, are the main objects of research into periodontal-bone homeostasis. RNA-seq was performed on osteogenesis-induced PDLSCs to construct a circRNA-ceRNA network. It was predicted that the circRNAs B-cell translocation gene 3 (*BTG3*)-associated nuclear protein (BANP) and itchy E3 ubiquitin protein ligase (ITCH) can bind to *miR-34a* and *miR-146a*, respectively and both eventually participate in the MAPK pathway (65). *Circ_0003072* can promote osteogenic differentiation of PDLSCs through the *Circ_0003072/miR-488-3p*/chordin-like 1 (*CHRDL1*) pathway; *Circ_0003072* acted as a sponge for *miR-488-3p*, thereby upregulating *CHRDL1* levels (66). Furthermore, researchers found that the circRNA spermatogenesis-associated 13 (*circ-SPATA13*) functions as a molecular sponge for *miR-485-5p_R+1*, in turn targeting *BMP7* to promote osteogenic differentiation of PDLSCs (67). In another study, the circRNA *FAT1* was involved in regulating PDLSC osteogenic differentiation through the ceRNA network of *miR-4781-3p/Smad5* (68). Similarly, *Circ_0062491* has been found to promote PDLSC osteogenic differentiation through the *miR-142-5p*/insulin-like growth factor 1 (*IGF1*) axis (69). *Hsa-miR-6783-3p* could act as a sponge of the circRNA protein kinase D3 (*circPRKD3*) to indirectly regulate osteogenic

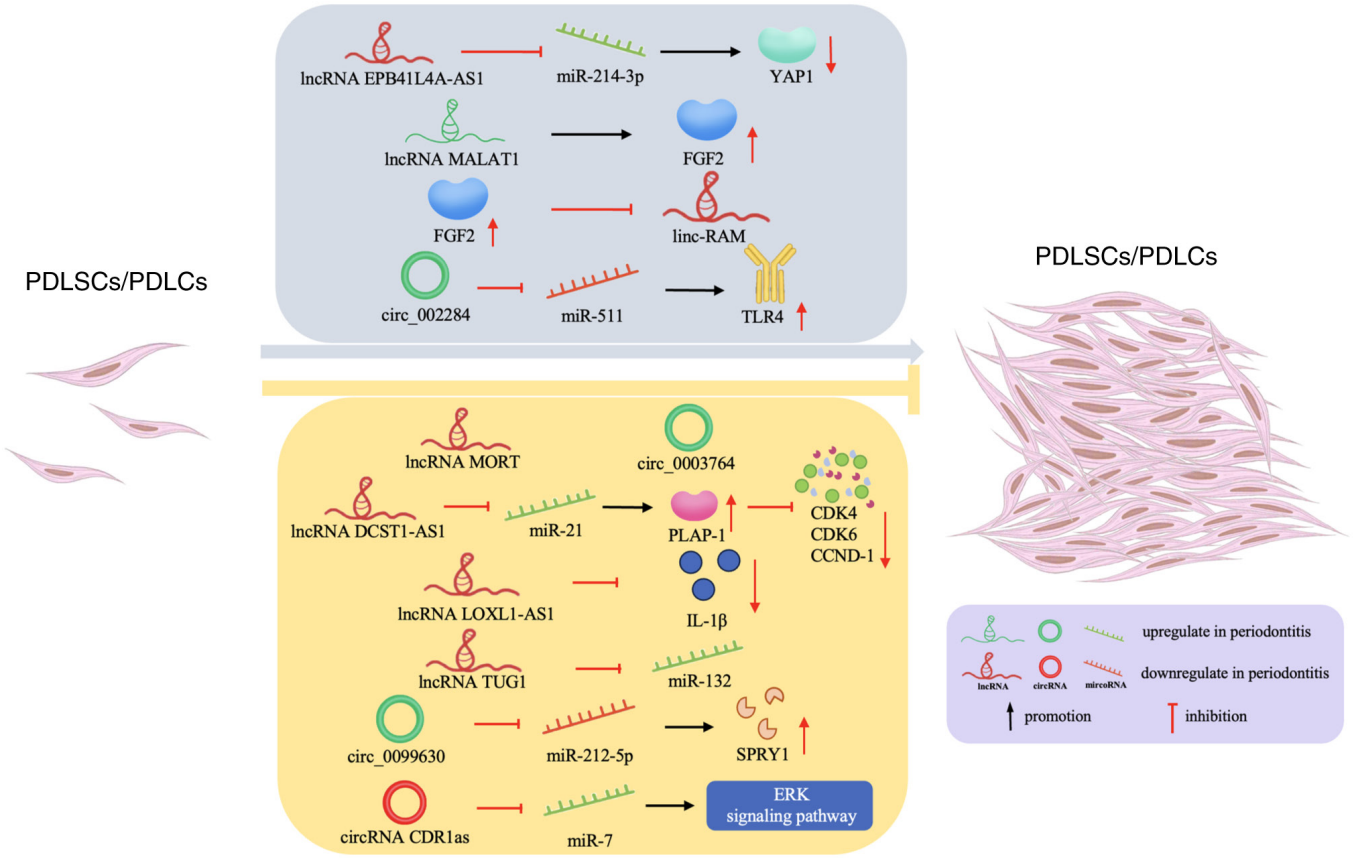

Figure 4. NcRNAs regulate the proliferation of PDLSCs/PDLCs. From left to right of figure shows PDLSCs/PDLCs proliferation. The gray area is the ncRNA that promotes the proliferation of PDLSCs/PDLCs and the yellow area is the ncRNA that inhibits the proliferation of PDLSCs/PDLCs. The black arrowheads indicate promotion and the red T indicate inhibition. Bold red arrowheads indicate the molecules with increased/decreased expression of ncRNA in the process of promoting/inhibiting cell proliferation. nc, noncoding; PDLSCs, periodontal ligament stem cells; PDLCs, periodontal ligament cells; YAP1, yes-associated protein 1; FGF2, fibroblast growth factor 2; TLR4, Toll-like receptor 4; PLAP-1, periodontal-ligament-associated protein-1; CDK4, cyclin-dependent kinase 4; CDK6, cyclin-dependent kinase 6; CCND-1, cyclin D1; SPRY1, sprouty RTK signaling antagonist 1; ERK, extracellular signal-regulated kinase.

differentiation of mechanically stimulated PDLSCs (70). Moreover, it has been found that the circRNA low-density lipoprotein receptor-related protein 6 (*Lrp6*) promotes cementoblastic differentiation through the miR-145A-5p/zinc finger E-box-binding homeobox 2 (Zeb2) axis and plays an important role in the regeneration of periodontal tissues (71). However, it has also been reported that *hsa_Circ_0003489* inhibits osteogenic differentiation of PDLSCs by triggering activation of autophagy in the hypoxic periodontitic microenvironment (72). In addition to its role in the regulation of alveolar-bone remodeling through the ceRNA network, circRNA can directly regulate bone homeostasis by influencing signaling pathways. Exosomal *Circ_0000722* derived from PDLSCs undergoing osteogenic differentiation might promote osteoclastogenesis by upregulating *TRAF6* expression and activating the downstream *NF-κB* and *Akt* signaling pathways (73) (Fig. 3).

CircRNAs regulate the proliferation of periodontal-ligament cells and stem cells. The functions of various circRNAs in regulating cell proliferation are inconsistent. For example, a study found that *Circ_0099630* curbed PDLC proliferation and osteogenic differentiation through elevating sprouty rhoketin signaling antagonist 1 (*SPRY1*) expression via sponging *miR-212-5p* in periodontitis (74). The circRNA *MAP3K11* (*Circ_002284*) enhances the proliferation and migration of human PDLSCs (hPDLSCs) and reduces their apoptosis through *miR-511*/TLR4 (75). Although *Circ_0003764* regulates osteogenic differentiation of PDLSCs, it can also inhibit the proliferation of PDLSCs (76). Moreover, the *circRNA sponge for miR-7* (*CiRS-7*, also known as *CDR1-AS)* binds to miR-7 to activate the extracellular signal-regulated kinase signaling pathway and mediates the inhibitory effect of LPS on PDLSC proliferation (77). In addition to its regulation of bone homeostasis and PDLSC proliferation (77,78), the binding of *CDR1-AS* to *miR-7* in PDLSCs has been confirmed to inhibit Krüppel-like factor 4 (*KLF4*) expression to maintain expression of stemness-related genes (79). As previous studies reported, *CDR1-AS*/*miR-7* affects different target genes to regulate the biological functions of PDLSCs via a ceRNA mechanism (62,78,79). Furthermore, *CDR1-AS* can also combine with *miR-7* to act on different targets and participate in the regulation of such diseases as pulmonary hypertension (80), abdominal aortic aneurysm (81), breast cancer (82) and hepatocellular carcinoma (83). Therefore, the interaction of *CDR1-AS* with *miR-7* could be an interesting research focus; more studies are needed (Fig. 4).

In general, recent studies have demonstrated that circRNAs play important roles in the regulation of periodontitis. Research on circRNAs in periodontitic pathogenesis has

important clinical significance. Most studies have revealed that ceRNA mechanisms underlie the regulatory role of circRNAs; no other regulatory mechanisms of circRNAs have been found in periodontitis. Furthermore, previous studies on the ceRNA mechanism of circRNAs often did not assess cellular localization of circRNAs; circRNA in cytoplasm can often bind to miRNAs and then regulate target genes. The multiple mechanisms of circRNAs in periodontitis deserve further exploration.

4. Other ncRNAs in periodontitis

In addition to lncRNAs and circRNAs, other ncRNAs are also involved in the progression of periodontitis. Through ncRNA analysis of exosomes in blood samples from healthy individuals and patients with periodontitis, both before and after treatment, it was found that small nucleolar RNAs (SNORD57 and SNODB177) exhibited significant differences (84). This indicates that the expression level of small non-coding RNAs (sRNAs) may serve as a diagnostic indicator for periodontitis in the future. In 2015, Duran-Pinedo *et al* (85) conducted a comprehensive analysis of bacterial sRNAs in the intergenic regions of the oral microbiome in healthy individuals and periodontitis patients. This sequencing analysis found that sRNAs were an important factor in regulating the transformation of the oral microbiome from a symbiotic to a dysbiotic one. These bacterial sRNAs affect bacterial toxicity by regulating changes in the oral microbiome, while at the same time they exert the host's immune response. Therefore, bacterial sRNAs may serve as key regulatory elements in the pathogenesis of periodontitis.

5. New areas of ncRNA research

Secondary structures of ncRNAs. NcRNAs can directly physically bind to other nucleic acid targets or sequence-specific recognition of RNA-binding proteins (RBPs) through base complementary pairing. A ncRNA can also bind with cellular partners through its secondary or tertiary structure (6), which is composed of local stem loops and helices.

In periodontitis, it is common for ncRNAs to directly bind to proteins or genes through their structural features, thereby affecting protein function or the expression of downstream genes. For example, apoptotic vesicles containing miR-143-3p derived from macrophages disrupt periodontal bone homeostasis by binding to insulin-like growth factor-binding protein 5 (IGFBP5) in bone marrow mesenchymal stem cells (BMSCs) (86). Similarly, circLRP6 acts as a binding target of miR-145a-5p, while Zeb2 is a downstream target of the same miRNA during the cementoblastic differentiation process (71). Therefore, circLRP6 regulates the differentiation of cementoblasts in periodontitis by antagonizing the function of miR-145a-5p. The structure of ncRNA determines the ncRNA's mode of interaction with cellular partners; by changing the ncRNA's interactions with proteins or other RNAs, it can perform regulatory functions (87). H19, as one of the earliest-discovered lncRNAs, has been found to have secondary structural changes that might damage lncRNA function, leading to complex diseases such as heart failure (88). The development of sequencing technologies and *in silico* and experimental methods has allowed further exploration of the effects of variations in ncRNAs. For instance, single-nucleotide polymorphisms and indels in lncRNA genes and regulatory regions alter RNA secondary structures, expression levels and target recognition and then confer a predisposition toward cancer on carriers (89). Currently, techniques for RNA structure detection can be divided into two categories, one based on small-molecule modification and the other based on crosslinking and proximity linking. Sequencing is an important detection method used to interpret RNA structure (90): it provides crucial technical support for detecting the secondary structure of ncRNAs, reveals their mysterious spatial structure and proves the close relationship between RNA structure and function. Researchers have even developed RNA structural analyses that enable structural profiling at the transcriptomic scale in living cells (91).

NcRNA-protein interaction. Post-transcriptional regulation (PTR) mediated by ncRNAs is closely related to RBP expression. RBPs, which are critical for maintaining the transcriptome, can also regulate RNA processing and transportation through PTR, including regulation of RNA splicing, polyadenylation, mRNA stability, mRNA localization and translation (92). Recently, accumulating evidence has demonstrated that ncRNA-RBP interactions modulate the pathogenesis of periodontitis. The lncRNA solute carrier family 30, member A4 (*SLC30A4*)-*AS1* binds serine and arginine rich splicing factor 3 (SRSF3) protein to affect the senescence of PDLSCs and the osteogenic-differentiation ability of PDLSCs (93). *LincRNA-EPS* could inhibit the expression of Caspase-11/NLRP3 inflammasome components in periodontal inflammation by compromising the activation of the *NF-κB* signaling pathway via interacting with transformation-associated recombination (TAR) DNA-binding protein 43 (*TDP43*) (94). The lncRNA X-inactive specific transcript (*Xist*) recruited the enrichment of upstream transcription factor 2, C-*Fos* interacting (*USF2*) to the WD repeat-containing protein 72 (*WDR72*) promoter region to promote its transcription and facilitate osteogenic differentiation of PDLSCs (95).

To uncover the interaction between RNA and RBPs, researchers have developed various experimental methods and predictive tools. In the process of experimental research, a larger range can be narrowed down to screen out candidate RBPs with greater potential. For example, the binding of the lncRNA gastric-cancer-associated transcript 2 (*GACAT2*) to pyruvate kinase muscle isozyme M1/M2 (PKM1/2) proteins was tested using chromatin isolation by RNA purification (ChIRP) sequencing (96). In a recent study on periodontitis, an RNA pull-down assay identified the RBP to the lncRNA *NR_045147* as integrin subunit β3 binding protein (*ITGB3BP*). Co-immunoprecipitation (CoIP) and ubiquitination-IP assays found that *NR_045147* maintains protein stability by competing with ubiquitination (97). Lu *et al* (98) used the *cat*RAPID algorithm to predict the potential protein partners of lncRNA *Lockd* and RNA pull-down to confirm *Lockd*'s interaction with SUZ12 polycomb repressive complex 2 subunit (*SUZ12*), thereby affecting the binding of SUZ12 to the key regulatory regions of osteogenic genes in the inflammatory microenvironment. This experimental approach might very well reflect the interactions of lncRNAs and proteins

in vivo. The aforementioned methods have important reference value in exploring regulation of interactions between ncRNA and RBP in periodontitis.

NcRNA-encoded peptides or proteins. The traditional view is that ncRNA does not encode proteins. In fact, however, small open reading frames (sORFs) can encode small bioactive peptides (99,100). NcRNAs can have one or more sORFs that can be translated into peptides of <100 amino acids. However, by default, the traditional gene annotation process filters out proteins with <100 amino acids and treats them as noise or false positives, leading some ncRNAs with coding functions to be ignored. With the advancement of ribosome sequencing and protein translation techniques, as well as improvements in precision and accuracy, a number of ncRNAs have been found to translate into bioactive peptides or proteins (101). In the last decade, an increasing number of ncRNAs have been identified as encoding and functioning through peptides; these ncRNAs play important roles in a number of diseases (102,103). For example, human leukocyte antigen complex P5 (HCP5)-132aa, a microprotein encoded by *HCP5* harboring this ORF, is highly expressed in gastric-cancer (GC) cells and tissues and can promote proliferation of GC cells by inhibiting ferroptosis (104). The lncRNA *181-Rik* is translated into the conserved micropeptide short transmembrane mitochondrial protein 1 (Stmp1), located in mitochondria, which regulates retinal ischemia/reperfusion-induced retinal ganglion cell (RGC) death by modulating microglial inflammatory response (105). Cell division cycle 42 (CDC42)-165aa protein, encoded by *circCDC42*, promotes excessive activation of the pyrin inflammasome and aggravates lung injury caused by pyroptosis of alveolar macrophages (106).

At present, multiple bioassay software applications have been developed to predict the coding capacity of ncRNAs. Liang *et al* (107) developed the MicroProteinDB database, which offers and visualizes extensive knowledge to aid retrieval and analysis of computationally predicted and experimentally validated microproteins originating from various ncRNA types. Although these applications can predict coding capacity using different algorithms, experimental verification is the most convincing method. Researchers can construct an ncRNA-ORF mutant fusion protein vector with green fluorescent protein (GFP) to detect whether GFP fusion protein can be expressed and verify the protein coding ability of an ncRNA (108). Antibodies (Abs) that bind specifically to ncRNA-translated peptides can also be designed and prepared to verify whether ncRNA-translated peptides can be detected (109). For example, anti-*Linc00263-P* Ab was customized to explore the function of the new microprotein encoded by *Linc00263* in promoting osteolytic bone metastasis in breast cancer (110). Although there is currently no relevant report in the field of periodontitis, the regulation of periodontitis by ncRNAs can be further explored based on the mechanisms of ncRNA-encoded proteins.

NcRNAs and single-cell sequencing. Unlike traditional sequencing technology, single-cell sequencing technology can sequence the genome or transcriptome of a single cell type, more accurately detect cell clustering and identify cell heterogeneity, which is of great significance for disease prevention, diagnosis and individualized treatment (111,112). The use of single-cell sequencing to detect ncRNA in periodontal tissues could offer new perspectives on the epigenetic regulation of periodontitic pathogenesis. Single-cell RNA sequencing of periodontitic gingival tissue revealed that in *lncR APDC* knockout mice, the proportions and functions of immune cells changed, including T and B cells, macrophages and neutrophils (113). However, there are relatively few reports on using single-cell sequencing to detect ncRNAs in periodontal tissues. Exploring the expression profile of ncRNAs at the single-cell level could reveal unique cell clusters in periodontitis and provide insights into the heterogeneity of the disease. In summary, as a new technology, single-cell sequencing can more accurately analyze the transcriptome profile of a single cell and enable researchers to further study the molecular characteristics of the heterogeneity of periodontitis.

Diagnostic potential of ncRNAs in periodontitis. NcRNA expression level is closely related to disease progression and has tissue specificity. NcRNAs in tissues or body fluids are emerging as potential new biomarkers because the levels of free ncRNAs in body fluids are stable and renewable. Numerous studies have indicated that ncRNAs have outstanding advantages as diagnostic markers, while lncRNAs and circRNAs in particular show high diagnostic value (114,115).

In recent years, the receiver operating characteristic (ROC) curve has been widely used to find prognostic disease markers and evaluate the reliability of diagnostic markers. In studies of ncRNAs as diagnostic markers, the research flowchart mainly includes screening differentially expressed genes by sequencing, predicting target genes using relevant databases, performing functional clustering and analysis via Gene Ontology/Kyoto Encyclopedia of Genes and Genomes and evaluating diagnostic markers using an ROC curve. Finally, verification methods such as quantitative reverse-transcription polymerase chain reaction (RT-qPCR) and western blotting are used to evaluate the accuracy of these markers (Fig. 5).

Serum and urine are becoming the main sample sources due to the noninvasiveness of their collection and their renewability. Changes in blood components are closely related to systemic diseases. Several studies have proven the potential of lncRNAs in serum as diagnostic tools in multiple systemic diseases (116). The lncRNA cholesterol cytochrome P450 family 1 subfamily B member 1 (*CYP1B1*)-*AS1* promotes inflammation and apoptosis by targeting *miR-18a-5p*; *CYP1B1-AS1* in serum serves as a biomarker for sepsis diagnosis and poor prognosis (117). Expression of circulating *Linc01094* as detected by RT-qPCR can differentiate osteoporotic patients from healthy ones and those with osteoporotic fractures from those without (118). LncRNAs in urine are also extremely important in the diagnosis of systemic diseases. The exosomal lncRNA *MALAT1* in urine is regarded as a diagnostic marker for Wilms tumor and high expression of *SNHG16* can potentially serve as a diagnostic biological marker for bladder cancer (119,120). Expression of circRNAs is abundant, stable and conservative and specific to tissue and developmental stage, making them ideal biomarkers (121). CircRNAs in bodily fluids show strong potential as diagnostic markers in systemic diseases, including

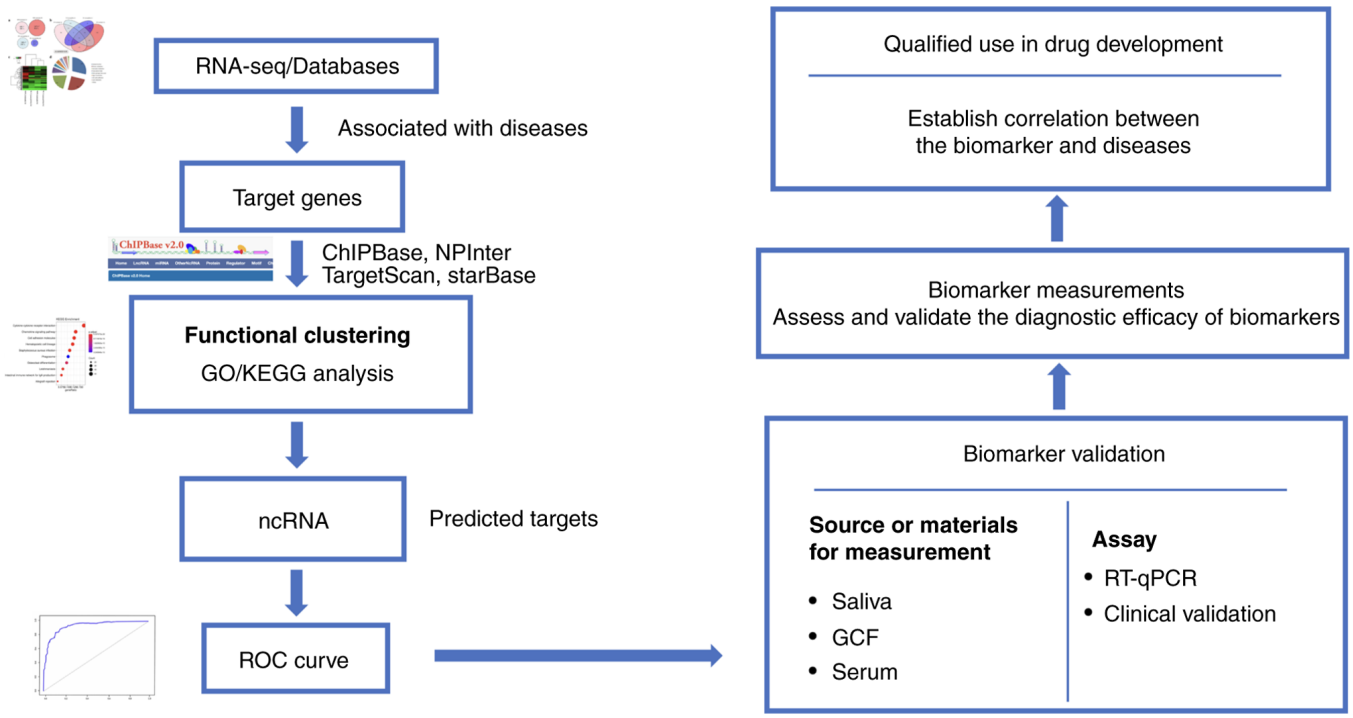

Figure 5. ROC curve was used to screen biomarkers for early diagnosis of the disease. Firstly, the predicted ncRNA biomarkers were obtained by RNA-seq or database analysis. ROC curve was used to evaluate the reliability of diagnostic biomarkers. The biomarker can be verified clinically to evaluate its diagnostic efficacy. If the biomarker is reliable, it can be prepared as a drug for disease diagnosis. ROC, receiver operating characteristic; nc, noncoding; RNA-seq, RNA-sequences; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; GCF, gingival crevicular fluid; RT-qPCR, reverse transcription quantitative PCR.

autoimmune diseases, cardiovascular diseases, cancers and ischemic stroke (122,123). Therefore, related studies mainly have focused on systemic diseases or those that pose a great threat to life. In summary, exploring the diagnostic ability of ncRNAs can aid early prevention, guide treatment and assess prognosis. Furthermore, it can improve survival rates and reduce social burdens.

At present, the diagnosis of periodontitis is mainly based on clinical measurements, including bleeding assessment, periodontal-pocket depth and X-ray. However, these indicators have certain deficiencies in the early diagnosis, staging, progression prediction and prognosis evaluation of the disease. In addition to serum, diagnostic markers for periodontitis can be found in saliva and gingival crevicular fluid (GCF). These samples are simple to obtain, can be taken noninvasively way to prevent further tissue damage during clinical diagnosis and are plentiful (124).

Current studies on ncRNAs as diagnostic markers for periodontitis are mainly limited to miRNAs, whose ability to serve as such has been proven (15,125). Due to their stable properties, the use of circRNAs as diagnostic markers for periodontitis warrants further exploration (Fig. 6).

Therapeutic potential of ncRNAs in periodontitis. NcRNAs play important regulatory roles in systemic diseases, but discovering the mechanisms underlying these roles should not be the endpoint of relevant research. The ultimate goal is to transform ncRNAs into clinical treatment, with the expectation of achieving safe, accurate gene therapy. There are mainly two strategies in ncRNA treatment: Targeting ncRNAs to inhibit their expression and function; and restoring the expression or function of the target ncRNA. Techniques may involve antisense oligonucleotides (ASOs), ASO therapeutic circRNAs, anti-microRNAs (anti-miRs), siRNAs, miRNA sponges, miRNA mimics, short hairpin RNAs and clustered regularly interspaced short palindromic repeats-Caspase-9-based gene editing (126).

Clinical application of ncRNAs must be accurate and safe. At present, the limited bioavailability of ncRNAs *in vivo* presents a major challenge to said clinical application (127). Therefore, selecting the appropriate ncRNA vector and system is vitally important. Nanoparticles (NPs), ncRNA modification and the oncolytic-adenovirus strategy have become research hotspots. A number of studies have focused on gene therapy using NPs to deliver relevant ncRNAs, including diseases of the digestive, respiratory and circulatory systems (128-130). Currently, siRNA or ASO drugs are the focus of research into nucleic acid drugs; no miRNA, lncRNA, or circRNA has been clinically employed. At present, gene intervention studies using biological vectors (adenovirus, adeno-associated virus and lentivirus) are limited to laboratory studies due to safety issues such as immune origin and gene recombination; a number of problems remain to be solved before human experiments can be conducted.

To date, synthetic carriers mainly include lipid, polymer and inorganic NPs, which have been explored for delivery of siRNA to the target site. Lipid NPs are excellent nucleic acid delivery systems, with strong tissue penetration and low cytotoxicity and immunogenicity (131). Tong *et al* (132) have optimized a lipid NP (LNP) formulation (C2) and modified the

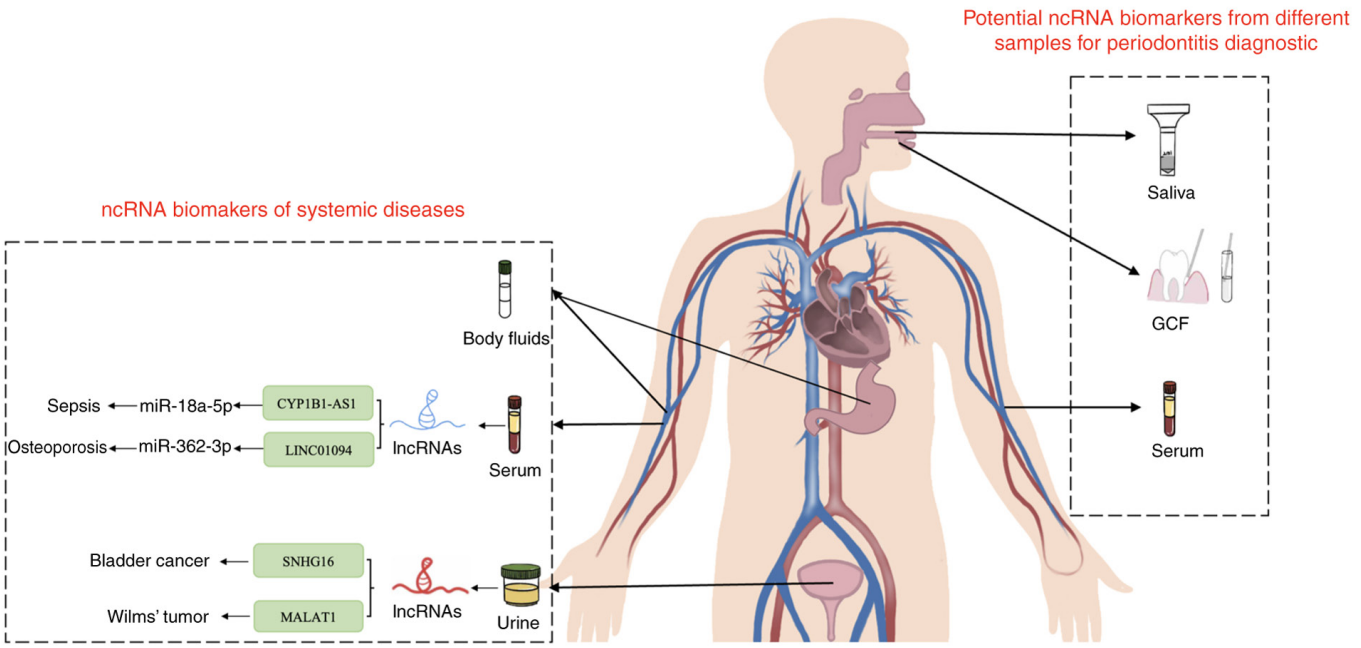

Figure 6. Diagnostic potential of ncRNA in periodontitis. NcRNAs in human tissues or various types of body fluids (including serum and urine) can be used as diagnostic markers for systemic diseases. Similarly, different samples such as serum, saliva and GCF can also be used as sources of ncRNAs, which could be used as potential biomarkers. nc, noncoding; GCF, gingival crevicular fluid.

LNPs with the Angiopep-2 peptide. This work demonstrates the efficacy of a brain-targeted siRNA delivery system in glioblastoma multiforme treatment.

Polymer NPs can effectively wrap negatively charged nucleic acids mainly through their positive charge; their ability to alter charge, degradability and molecular weight makes them excellent delivery systems. Construction of both engineered exosomes and polymers as nucleic acid carriers should have the advantages of i) biocompatibility, ii) effective delivery of nucleic acids and avoidance of nucleic acid degradation, iii) delivery to target organs, iv) biodegradability, v) stable properties and vi) commercial production. Inorganic nanocarrier delivery systems mainly include gold, magnetic, mesoporous silica and calcium phosphate NPs.

As aforementioned, lncRNAs and circRNAs as nucleic acid drugs remain in the animal research stage. Administration of *Lnc-RAINY* encapsulated in Food and Drug Administration (FDA)-approved NPs into a lung cancer patient-derived xenograft model markedly reduces tumor progression, demonstrating therapeutic potential (133). An intranasal LNP delivery system carrying the circRNA Scm polycomb group protein homolog 1 (*circSCMH1*) promoted and enhanced sensorimotor and cognitive-function recovery in post-stroke mice (134). In recent years, nanomedicine has used biomaterials and biomedical-engineering innovations to overcome biological barriers and patient heterogeneity to achieve precise treatment and improve patient-specific therapeutic responses. At the same time, research on NP delivery systems and in particular nucleic acid therapy have entered a period of rapid development (135). In particular, the construction of the ASP8-PU lncRNA *NRON* system targeting osteoclasts is highly valuable (52). In this system, *NRON* mainly serves to inhibit osteoclast formation and reduce bone resorption. PU is a nanoscale polymer that can encapsulate nucleic acids via electrostatic interactions, offering excellent biocompatibility and effective transport capacity. The loading of asp-8 enables nanodrugs to directly target the surface of the absorbed bone, achieving periodontitis treatment in mice (136). Nevertheless, nucleic acid therapy is still not widely used in clinical settings, as it has failed to achieve safe and efficient treatment in a number of diseases and research into using it for periodontitis has also not progressed. Although the regulatory mechanism of new ncRNAs in periodontitis has not been fully explored, the mainstream view is that local administration is the most suitable method of treatment. Consequently, the study of an appropriate NP delivery system to achieve targeted treatment of periodontitis has obvious clinical-application prospects (Fig. 7).

6. Perspectives

Due to continuous innovations in sequencing technology, research on the periodontitis transcriptome has been greatly expanded. A number of ncRNA regulatory mechanisms have been revealed, unknown ncRNAs have been discovered and identified, a ceRNA network under different disease states has been constructed and a more comprehensive profile of ncRNA has been drawn. Research on ncRNAs in periodontitis is gradually increasing. However, the current dataset on the role of ncRNA in periodontitis has various limitations, such as incomplete clinical information, differences in disease progression and incomplete data on different types of periodontitis. No single database contains all ncRNA datasets relevant to this disease. A relatively complete and large database, The Cancer Genome Atlas database (TCGA), has been constructed in the field of tumor research. TCGA contains the genome maps of almost all human cancers. Systematic analysis

Table I. Summary of protective ncRNA in periodontitis.

Names	Types	Functions
PTCSC3	lncRNA	Reduces inflammation by downregulating TLR4
NEAT1	lncRNA	Downregulates IL-6, IL-1β and TNF-α; and reduces inflammation and apoptosis in PDLCs
LOXL1-AS1	lncRNA	Inhibits IL-1β expression in PDLSCs
ZFY-AS1	lncRNA	Inhibits the release of inflammatory factors in periodontitis by regulating the miRNA-129-5P/ DDX3X axis
SNHG5	lncRNA	Influences the expression of inflammatory cytokines through the NF-κB signaling pathway; inhibits differentiation of osteoclasts during OTM by combining with C/EBP-β
Loc1001302640	lncRNA	Plays important roles in the process of osteogenic differentiation through MAPK signaling pathway
ANRIL	lncRNA	Regulates the osteogenic differentiation of PDLSCs by adsorbing miRNAs as ceRNAs
JHDM1D-AS1	lncRNA	
Linc01126	lncRNA	
DCST1-AS1	lncRNA	
MALAT1	lncRNA	
Linc00707	lncRNA	
LncRNA00638	lncRNA	
DLX2-AS1	lncRNA	Restrains inflammatory response and apoptosis of PDLCs by binding with microRNA-330-3p to regulate Ro60
OIP5-AS1	lncRNA	Inhibits the lipopolysaccharide-induced inflammatory response and promotes osteogenic differentiation of hPDLSCs
Linc01133	lncRNA	Promotes osteogenic differentiation of hPDLCs via microRNA-30c / bone gamma-carboxyglutamate protein axis
MEG3	lncRNA	Regulates osteogenic differentiation of PDLSCs through the PI3K/Akt or Akt/IKK pathways
NRON	lncRNA	Inhibit osteoclastic- and alveolar-bone resorption and corrects the imbalance of bone metabolism
MORT	lncRNA	Inhibits PDLSC proliferation and reduces recurrence of periodontitis
linc-RAM	lncRNA	Inhibits proliferation of PDLSCs
PLAP-1	lncRNA	Combines with miR-21 precursor to reduce expression of CDK4, CDK6 and CCND-1 and inhibits PDLC proliferation
LOXL1-AS1	lncRNA	Inhibits the proliferation of PDLSCs and improves periodontitis
TUG1	lncRNA	Mediates LPS-induced proliferative inhibition of hPDLCs by sponging miR-132
circ_0062491	circRNA	Sponges miR-584 in THP-1 cells treated with P. gingivalis; targets miR-498/SOCS6 to alleviate periodontitis
circ_0099630	circRNA	Silencing circ_0099630 can alleviate LPS-induced PDLC injury by targeting miR-940/TRAF6/NF-κB in periodontitis
circ_0003948	circRNA	Downregulated in gingiva from patients with chronic periodontitis through the miR-144-3p/NR2F2/PTEN axis
circ_0003072	circRNA	Promotes osteogenic differentiation of PDLSCs as a sponge for miR-488-3p
circ-SPATA13	circRNA	Sponges miR-485-5p_R+1 to promote osteogenic differentiation of PDLSCs
circRNA FAT1	circRNA	Regulates PDLSC osteogenic differentiation through the ceRNA network of miR-4781-3p/Smad5
circ_0062491	circRNA	Promotes PDLSC osteogenic differentiation through the miR-142-5p/IGF1 axis
PRKD3	circRNA	Regulate osteogenic differentiation of mechanically stimulated PDLSCs
Lrp6	circRNA	Promotes cementoblastic differentiation through miR-145A-5p/Zeb2 and plays an important role in the regeneration
circ_0099630	circRNA	Curbed PDLC proliferation and osteogenic differentiation through elevating SPRY1 expression via sponging miR-212-5p

Table I. Continued.

Names	Types	Functions
circ_0003764	circRNA	Regulates osteogenic differentiation and inhibits the proliferation of PDLSCs
CiRS-7/CDR1-AS	circRNA	Binds to miR-7 to mediate the inhibitory effect of LPS on PDLSC proliferation; inhibits KLF4 expression to maintain expression of stemness-related genes
SLC30A4-AS1	lncRNA	Binds SRSF3 protein to affect the senescence of PDLSCs and the osteogenic-differentiation ability of PDLSCs
LincRNA-EPS	lncRNA	Inhibits the expression of Caspase-11/NLRP3 inflammasome components in periodontal inflammation
Xist	lncRNA	Facilitate osteogenic differentiation of PDLSCs by promoting the transcription of USF2 to WDR72 promoter region
NR_045147	lncRNA	Maintains protein stability by competing with ubiquitination
Lockd	lncRNA	Affects the regulation of osteogenic genes in the inflammatory microenvironment by interacting with SUZ12

nc, noncoding; lnc, long noncoding; PTCSC3, papillary thyroid carcinoma susceptibility candidate 3; TLR4, Toll-like receptor 4; PDLCs, periodontal ligament cells; PDLSCs, periodontal ligament stem cells; mi, micro; DDX3X, DEAD-box helicase 3 X-linked; NF-κB, nuclear factor kappa-B; OTM, orthodontic tooth movement; C/EBP-β, CCAAT-enhancer-binding protein-β; MAPK, mitogen-activated protein kinase; ce, competing endogenous; Ro60, Y RNA binding protein; hPDLSCs, human periodontal ligament stem cells; hPDLCs, human periodontal ligament cells; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; IKK, inhibitor of NF-κB kinase; PDLSC, periodontal ligament stem cell; CDK4, cyclin-dependent kinase 4; CDK6, cyclin-dependent kinase 6; CCND-1, cyclin D1; PDLC, periodontal ligament cell; circ, circular; THP-1, tohoku hospital pediatrics-1; SOCS6, suppressor of cytokine signaling 6; TRAF6, TNF receptor-associated factor 6; NR2F2, nuclear receptor subfamily 2 group F member 2; PTEN, phosphatase and tensin homolog; Smad5, small mother against decapentaplegic family member 5; IGF1, insulin-like growth factor 1; Zeb2, zinc finger E-box-binding homeobox 2; SPRY1, sprouty rhoketin signaling antagonist 1; KLF4, Krüppel-like factor 4; SRSF3, serine and arginine rich splicing factor 3; NLRP3, NOD-like receptor family pyrin domain containing 3; USF2, upstream transcription factor 2; WDR72, WD repeat-containing protein 72; SUZ12, SUZ12 polycomb repressive complex 2 subunit.

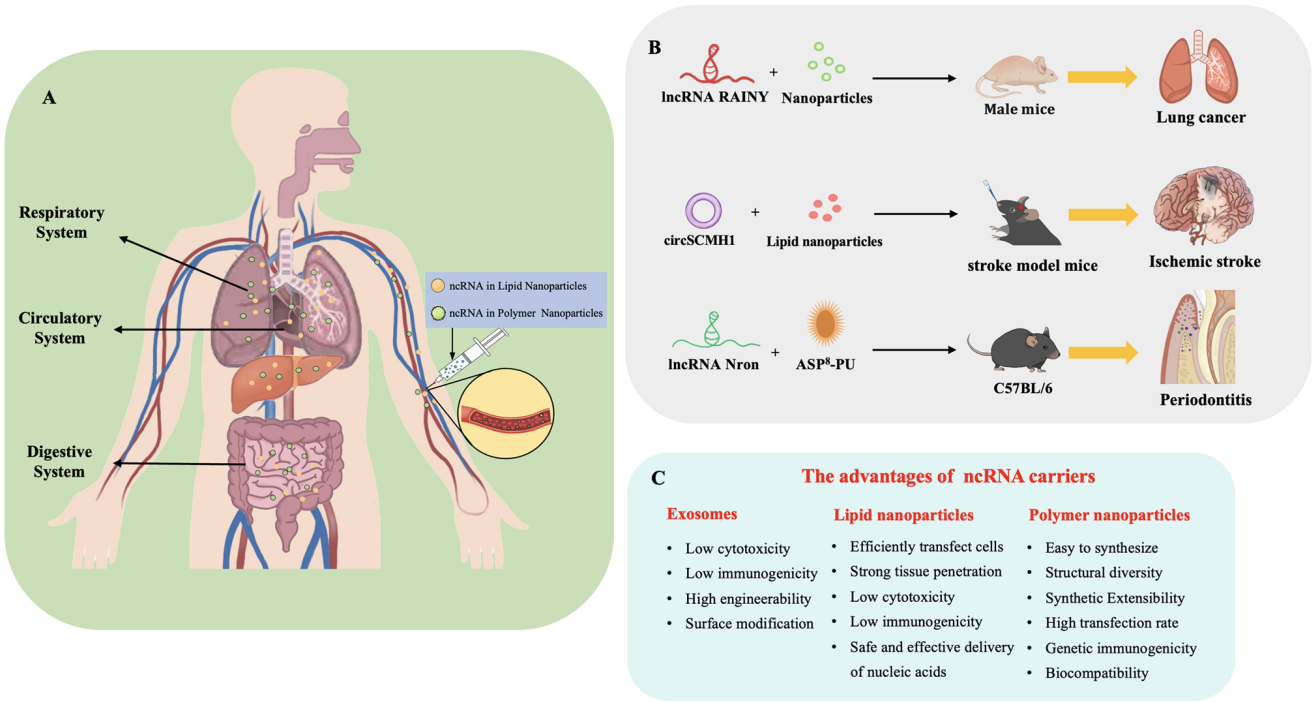

Figure 7. Therapeutic potential of ncRNAs. (A) Nucleic acid delivery systems deliver ncRNA for the treatment of digestive, respiratory and circulatory system diseases. (B) Animal researches on ncRNA as nucleic acid drugs for disease treatment. (C) The advantages of ncRNA carriers (exosomes, lipid nanoparticles, polymer nanoparticles). nc, noncoding.

of this database allows key cancer genes to be found, which is of great significance for understanding the mechanisms governing the occurrence and development of cancer cells and realizing early diagnosis and targeted therapy. It is necessary

Table II. Summary of aggressive ncRNA in periodontitis.

Names	Types	Functions
MFG-AS1	lncRNA	Promotes inflammation by upregulating TLR4
Linc00616	lncRNA	Promotes iron death through the miRNA-370/TfR axis in LPS-induced PDLSCs
NEAT1	lncRNA	Activates the classic NLRP3 inflammasome activation pathway to exacerbate bone destruction in periodontitis
DANCR	lncRNA	Increase stress-induced osteoclast formation and root absorption by upregulating Jagged1
EPB41L4A-AS1	lncRNA	Enhances the proliferation and osteogenic differentiation of hPDLCs by targeting expression of miR-214-3p
MALAT1	lncRNA	Promotes proliferation of PDLSCs in periodontitis and disease progression by upregulating FGF2
Linc01126	lncRNA	Suppresses proliferation while promoting apoptosis and the secretionof inflammatory factors in hPDLCs by sponging miR-518a-5p; promotes inflammation and JAK2/STAT3 pathway activation as a sponge for miR-655-3p
circPVT1	circRNA	Promotes periodontitic progression by modulating Nrf-2/ HO-1 pathway
Circ_0138959	circRNA	Inhibits cell viability and promote pyroptosis through the miR-527/ Caspase-5 axis
hsa_Circ_0003489	circRNA	Inhibits osteogenic differentiation of PDLSCs by triggering activation of autophagy in the hypoxic periodontitic microenvironment
Circ_0000722	circRNA	Promotes osteoclastogenesis by upregulating TRAF6 expression and activating the NF-κB and Akt signaling pathways
Circ_002284	circRNA	Enhances the proliferation and migration of hPDLSCs and reduces apoptosis through miR-511/TLR4

nc, noncoding; lnc, long noncoding; Toll-like receptor 4; TfR, transferrin receptor; PDLSCs, periodontal ligament stem cells; NLRP3, NOD-like receptor family pyrin domain containing 3; hPDLCs, human periodontal ligament cells; mi, micro; FGF2, fibroblast growth factor 2; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; circ, circular; Nrf-2, nuclear factor (erythroid-derived 2)-like 2; HO-1, heme oxygenase-1; TRAF6, TNF receptor-associated factor 6; NF-κB, nuclear factor kappa-B; Akt, protein kinase B; hPDLSCs, human periodontal ligament stem cells.

to build a similar gene information system for periodontitis. As more studies are conducted, additional key gene information in periodontitis is expected to be revealed and exploration of same will help researchers gain a deeper understanding of the disease's pathogenesis and further guide clinical diagnosis and treatment.

LncRNAs and circRNAs, newly discovered types of ncRNAs, are known to play key roles in systemic diseases through a variety of molecules and pathways. However, studies on their mechanisms in the field of periodontitis are limited to those ncRNAs that play regulatory roles as ceRNAs; additional mechanisms of action remain to be explored. Summaries of the ncRNAs relevant to the pathogenesis of the periodontitis are provided in Tables I and II. As ncRNAs regulate a variety of complex biological behaviors in systemic diseases, research on these RNAs in the field of periodontitis must be expanded beyond immune inflammation, autophagy, bone homeostasis and cell proliferation. It is worth affirming that the regulatory mechanisms of ncRNA in periodontitis are being explored more widely and deeply. Greater future recognition of ncRNAs' clinical applications as diagnostic markers and therapeutic targets in periodontitis is needed.

As the role of ncRNAs in periodontitis becomes more detailed, researchers have begun to pay attention to their potential as biomarkers and nucleic acid drugs in clinical applications. At present, the diagnosis of periodontitis is mainly based on clinical symptoms, which is relatively subjective and thus deficient for early screening and diagnosis. As biomarkers, ncRNAs can overcome the limitations of these clinical indicators and provide more objective, accurate and timely results. Using ncRNA in saliva or GCF as a diagnostic marker not only is noninvasive but also facilitates objective evaluation of patient progress. As aforementioned, ncRNAs are considered to have good application prospects as targets for the early diagnosis and treatment of periodontitis.

Currently, nucleic acid drugs approved by the FDA are mainly siRNAs or ASOs; no miRNA, lncRNA, or circRNA has been applied in clinical treatment. As nucleic acid drugs, ncRNAs have great potential and improved advantages in the treatment of various diseases. As naturally occurring molecules in human cells, they have all the required mechanisms for processing and downstream target selection. In addition, ncRNAs work by targeting multiple genes in a single pathway, leading to a broader and more specific response. At present, the clinical application of ncRNA drugs is still limited by the problems of off-target effects, delivery failure and tolerance. Successful application of ncRNA-based therapies requires a multidisciplinary effort, including technological advances in molecular biology, immunology, pharmacology, chemistry and nanotechnology.

Despite the challenges, ncRNA-based drug therapies will eventually become available as technology and research advance in the treatment of periodontitis.

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Availability of data and materials

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Authors' contributions

YF reviewed the literature and wrote the manuscript. XG collected and analyzed the existing data from the previously published research articles. YY and WQ wrote and revised the manuscript and constructed figures. ZC and FF conceived the study and revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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