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The Roles of Non-Coding RNAs in Periodontitis: Regulatory Mechanisms and Clinical Implications

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Abstract. Periodontitis, a chronic inflammatory condition with high global prevalence, presents considerable challenges for early detection and targeted intervention using current diagnostic and therapeutic approaches. This limitation has prompted increasing research interest in non-coding RNAs (ncRNAs) as potential sensitive biomarkers and key regulatory molecules. This review summarizes the current classification of ncRNAs—primarily microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs)—and their respective regulatory functions in the pathogenesis of periodontitis. MicroRNAs (miRNAs), including miR-146a and miR-155, act as key regulators of immune-inflammatory responses and bone homeostasis through post-transcriptional mechanisms. In contrast, long non-coding RNAs (lncRNAs), such as LncSPIRE1 and LBX2-AS1, function predominantly as competitive endogenous RNAs (ceRNAs) to modulate inflammatory networks and osteogenic differentiation. Circular RNAs (circRNAs) play distinct and sometimes opposing roles in the development of periodontitis. Protective circRNAs, such as circCDR1as and circLRP6, facilitate cell proliferation and tissue repair by sequestering specific miRNAs. Conversely, detrimental circRNAs, including circCDK8 and circ_0099630, inhibit osteogenic differentiation and amplify inflammatory responses through diverse molecular pathways. Furthermore, the translational potential of ncRNAs is highlighted by their detectable fluctuations in gingival crevicular fluid, which are clinically informative, reflecting disease progression and therapeutic efficacy, thereby underscoring their utility as diagnostic biomarkers. Thus, elucidating the ncRNA regulatory network holds significant promise for the development of targeted therapies aimed at restoring immune balance and promoting periodontal tissue regeneration.

Keywords: Periodontit, non-coding RNAs, micro RNAs, circular RNAs, long non-coding RNAs

1. Introduction

Periodontitis is a chronic inflammatory disease initiated by a dysbiotic dental plaque biofilm, which triggers infection and inflammation of the periodontal supporting tissues. It affects approximately 11% of the global population, and its incidence has been steadily rising in recent years.

However, conventional methods remain inadequate for early detection and accurate assessment of disease activity. Clinical symptoms and changes in early indicators only become apparent after

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irreversible tissue damage has occurred, hindering precise regulation of the immune-inflammatory process. This clinical challenge underscores the need for earlier, more sensitive biomarkers, generating growing interest in non-coding RNAs (ncRNAs) in recent years.

Non-coding RNAs are RNA molecules that do not encode proteins but play important roles in cellular processes by modulating gene expression. They can be classified based on their structure: microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs). MiRNAs fine-tune gene expression through post-transcriptional suppression, lncRNAs modulate inflammatory networks via transcriptional and epigenetic mechanisms, and circRNAs often function as competitive endogenous RNAs (ceRNAs) to indirectly regulate mRNA stability and translation. Owing to their high sensitivity, strong specificity, non-invasive accessibility, and capacity to dynamically reflect disease activity, ncRNAs offer distinct advantages over conventional diagnostic techniques. Consequently, profiling ncRNA expression signatures holds great potential as a strategy for early disease detection, stratification of disease activity, and prediction of therapeutic outcomes.

Emerging evidence suggests that ncRNAs contribute to the pathogenesis of periodontitis through multiple mechanisms, including competitive receptor binding and transcriptional regulation. For instance, LncSPIRE1 functions as a ceRNA for miR-181a-5p, modulating PRLR and the downstream JAK2/STAT3 signaling pathway, thereby alleviating Th17/Treg-mediated inflammatory responses and bone resorption in periodontitis. Additionally, circRNAs have been shown to influence periodontal homeostasis by regulating programmed cell death in key cells such as periodontal ligament stem cells and gingival fibroblasts. Despite these advances, the precise regulatory mechanisms and molecular pathways linking ncRNAs to periodontitis remain incompletely elucidated.

This article systematically categorizes ncRNAs based on their structural characteristics and examines the regulatory roles of various ncRNA subtypes in the pathological processes of periodontitis, including disease pathogenesis, inflammatory response, and tissue destruction. Furthermore, it integrates and synthesizes existing research to elucidate the potential applications of ncRNAs in the early diagnosis and clinical management of periodontal disease.

2. miRNA

In the complex pathogenesis of periodontitis, non-coding RNAs (ncRNAs)—regulatory RNA molecules that do not encode proteins—play an indispensable and central role. They extensively influence immune-inflammatory responses, cell fate, and tissue regeneration capacity within periodontal tissues through multi-layered and precise regulation of gene expression.

Based on their structural and functional characteristics, ncRNAs are broadly classified into three major types: microRNAs (miRNAs), which act as key regulators of immune responses and primarily govern post-transcriptional gene regulation; long non-coding RNAs (lncRNAs), which often function as inflammatory modulators to amplify or suppress signaling and maintain bone homeostasis; and circular RNAs (circRNAs), which primarily serve as competitive endogenous RNAs (ceRNAs) by acting as molecular sponges for miRNAs or interacting with RNA-binding proteins. Collectively, these three classes of ncRNAs constitute an intricate regulatory network that profoundly influences the pathogenesis and progression of periodontitis.

Recent studies have identified miRNAs as pivotal regulators in these processes. Key miRNAs, including miR-146a, miR-181a-5p, miR-155, and miR-23a, have been extensively investigated. They primarily function through post-transcriptional regulatory mechanisms to finely modulate relevant signaling pathways and target gene expression, thereby participating in immune-inflammatory responses and tissue repair processes.

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Among these, miR-146a serves as a crucial negative immune regulator in periodontitis. Its primary mechanism involves establishing lipopolysaccharide (LPS) tolerance: when LPS triggers an inflammatory response via activation of the Toll-like receptor (TLR)/NF-κB pathway, miR-146a expression is induced and upregulated. It subsequently executes negative feedback inhibition by targeting and degrading mRNAs of key signaling molecules within this pathway, such as IRAK1 and TRAF6, thereby preventing excessive inflammation. This mechanism helps confine the disease to a chronic, low-responsive state, consequently prolonging the progression of periodontitis during its initial or stable phases [1].

The clinical significance of miR-146a is reflected not only in interindividual expression variability but also in its dynamic correlation with disease progression. Studies have revealed that periodontitis patients diagnosed with "Stomach Fire Flaring Up syndrome" in traditional Chinese medicine—a condition often accompanied by marked oral inflammation—exhibit significantly lower levels of miR-146a in their saliva, suggesting a close relationship between its expression and individual inflammatory status. More importantly, miR-146a levels in gingival crevicular fluid differ between periodontitis patients and healthy individuals and demonstrate consistent changes following initial periodontal therapy. Its dynamic expression is significantly correlated with clinical parameters such as probing depth and clinical attachment loss, highlighting its potential as a biomarker for assessing periodontal inflammatory status and monitoring treatment response [2].

In contrast to the broad anti-inflammatory role of miR-146a, miR-181a-5p primarily exerts a protective function by maintaining immune balance. Research indicates that within the periodontal inflammatory milieu, bone marrow mesenchymal stem cells (BMMSCs) upregulate miR-181a-5p expression via the IL-6/STAT3 signaling axis. This upregulation enhances the immunomodulatory capacity of BMMSCs by fine-tuning the Th17/Treg balance, ultimately promoting periodontal tissue regeneration. Conversely, downregulation of miR-181a-5p disrupts the homeostasis of the IL-6/STAT3/miR-181a-5p pathway, leading to immune imbalance, exacerbated inflammation, and impaired tissue repair. Thus, miR-181a-5p can be regarded as a pivotal molecular switch determining the efficacy of stem cell-based therapies [3].

miR-155 orchestrates the progression of periodontitis through multiple mechanisms, including disrupting the Th17/Treg balance, activating inflammatory signaling pathways such as JAK/STAT, promoting macrophage polarization toward the M1 phenotype, and shifting bone metabolism toward resorption. Clinically, miR-155 expression is significantly upregulated in both periodontal ligament cells and gingival crevicular fluid of patients with chronic periodontitis, with levels positively correlating with the degree of periodontal tissue destruction. This indicates that, like miR-146a, miR-155 holds potential as a biomarker for diagnosing the disease and assessing its severity [4].

Additionally, miR-23a shows abnormally elevated expression in the gingival crevicular fluid of periodontitis patients and is associated with disease severity, further supporting the role of miRNAs as a promising pool of biomarkers for periodontitis. Some reviews have highlighted the dual role of miRNAs in periodontitis: on one hand, miRNAs such as miR-146a, miR-181a-5p, and miR-155 form a complex regulatory network by modulating key signaling pathways and maintaining immune homeostasis, intricately participating in disease pathogenesis and progression; on the other hand, their stable expression and dynamic changes in gingival crevicular fluid offer excellent biomarkers for disease diagnosis and treatment monitoring. Consequently, future therapies targeting specific miRNAs—either enhancing protective miRNA functions or inhibiting pathogenic miRNA expression—hold promise for the development of novel precision therapeutic strategies in periodontitis.

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3. lncRNA

Long non-coding RNAs (lncRNAs) play a decisive role in the pathogenesis of periodontitis, primarily through the regulation of two interconnected biological processes: inflammatory signaling networks and bone homeostasis. Various lncRNAs influence the osteogenic differentiation capacity of periodontal ligament fibroblasts by interacting with immune cells or modulating relevant signaling pathways, thereby contributing to the development and progression of periodontitis.

At the level of immune regulation, lncR-APDC and LncSPIRE1 have been identified as key modulators. lncR-APDC, functioning as a pro-inflammatory factor, modulates the immune response in periodontitis by directly or indirectly interacting with immune cells (e.g., Tff2), thereby influencing disease progression [5]. Similarly, LncSPIRE1 regulates immune homeostasis by balancing Th17/Treg cells. Its downregulation in periodontitis-derived mesenchymal stem cells enhances Th17-driven inflammation and impairs Treg-mediated suppression, ultimately promoting osteoclast differentiation and exacerbating periodontitis [6]. In addition, by sequestering miR-181a-5p as a ceRNA, LncSPIRE1 suppresses Th17/Treg imbalance-induced inflammation and osteoclastogenesis.

In the direct regulation of osteogenic differentiation, LncRNA LBX2-AS1 acts as a dual-function switch. Its mechanism centers on the miR-24/VEGF axis, whereby it promotes osteogenic differentiation of periodontal ligament fibroblasts via VEGF induction, while its inhibition of miR-24 provides a counterbalancing negative regulation. This bidirectional modulation of the same signaling axis allows precise control over periodontal ligament fibroblast function, playing a vital role in periodontal bone remodeling [7].

At the translational level, lncRNAs show considerable potential as diagnostic biomarkers. Studies have revealed that the expression levels of both lncRNA FAS-AS1 and lncRNA FGD5-AS1 in the gingival crevicular fluid of patients with chronic periodontitis are significantly downregulated and positively correlated with clinical severity and pathogenic bacterial load. Therefore, the combined detection of their expression levels holds significant diagnostic value for assessing disease stage.

In summary, multiple lncRNAs regulate periodontitis through a coordinated network by modulating immune responses (e.g., lncR-APDC, LncSPIRE1), disrupting osteogenic differentiation and bone homeostasis (e.g., LBX2-AS1), and serving as diagnostic biomarkers via stable expression changes (e.g., FAS-AS1, FGD5-AS1). Building on these mechanisms, future interventions targeting specific lncRNAs—such as restoring immune balance by promoting LncSPIRE1 expression—pave the way for precise diagnosis and targeted therapy in periodontitis.

4. Circular RNAs (circRNAs)

Circular RNAs (circRNAs) play an indispensable role in the progression of periodontitis, primarily functioning as molecular sponges for miRNAs. By competitively binding to miRNAs, they regulate the expression of downstream target genes.

Recent studies have demonstrated that circCDR1as acts as a molecular sponge for miR-7, promoting the proliferation of periodontal ligament cells (PDLCs) via activation of the ERK signaling pathway, thereby exerting a protective effect and mitigating periodontitis. Similarly, circMAP3G11, by sequestering miR-511-3p and positively regulating TLR4 expression, enhances PDLC proliferation and suppresses apoptosis, also contributing to a protective role in periodontitis [8].

Likewise, circLRP6 is significantly upregulated during cementoblast differentiation. It promotes this process by antagonizing miR-145a-5p, subsequently enhancing the osteogenic differentiation

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capacity of periodontal ligament stem cells (PDLSCs) and facilitating periodontal tissue repair [9].

Furthermore, circRASA2 exhibits a dual regulatory role in modulating the proliferation, migration, and osteogenic differentiation of PDLSCs. On one hand, circRASA2 targets and negatively regulates miR-543 expression; overexpression of miR-543 has been shown to promote these cellular activities in LPS-treated PDLCs. On the other hand, TRAF6, a downstream target of miR-543, can be downregulated by circRASA2 knockdown via its sponging effect on miR-543. The inhibitory effects on PDLC proliferation, migration, and osteogenic differentiation induced by circRASA2 knockdown can be reversed by TRAF6 overexpression [10].

The influence of circRNAs on periodontal tissues is dualistic: some promote PDLC proliferation, wound healing, and osteogenesis, while others contribute to cellular damage and apoptosis. For instance, circCDK8 suppresses the osteogenic differentiation of PDLCs by triggering autophagy under hypoxic conditions, disrupting the osteogenic–osteoclastic balance, and promoting periodontitis development.[11] Similarly, circ_0138959, acting via the miR-527/CASP5 axis, inhibits cell viability and induces apoptosis in gingival fibroblasts, thereby functioning as a pro-periodontitis factor [12].

Notably, circ_0099630 inhibits PDLC proliferation and osteogenic differentiation through dual pathways, thereby accelerating periodontitis progression. First, it acts as a sponge for miR-212-5p, leading to increased SPRY1 expression and inhibition of osteogenic differentiation. Second, circ_0099630 promotes the phosphorylation of P65 and IκB-α, enhancing the inflammatory response in periodontitis via the miR-940/TRAF6 axis.[13]

In summary, circRNAs play a dual role in regulating periodontitis progression. While some function as competitive endogenous RNAs (ceRNAs) by sequestering miRNAs to modulate downstream gene expression and delay disease progression, others interact with immune factors or signaling pathways to inhibit PDLSC proliferation and osteogenic differentiation, thereby exacerbating periodontitis.

5. Results and discussions

This review establishes diverse non-coding RNAs (ncRNAs) as central regulators in the pathogenesis and progression of periodontitis.

Our analysis confirms that microRNAs function as essential regulators within immune-inflammatory processes. For instance, miR-146a establishes lipopolysaccharide (LPS) tolerance via a negative feedback mechanism targeting TRAF6 and IRAK1. In contrast, miR-155 enhances pro-inflammatory signaling and stimulates osteoclast-mediated bone loss. These findings illustrate the pivotal role of miRNAs in modulating host defense responses and inflammatory tissue destruction.

Long non-coding RNAs act as key regulators of immune system balance and bone remodeling. For example, LncSPIRE1 influences the equilibrium between T-helper 17 cells and regulatory T cells. Another molecule, LBX2-AS1, controls osteogenic differentiation in periodontal ligament cells via molecular pathways such as the miR-24/VEGF signaling cascade. These regulatory mechanisms demonstrate the functional importance of lncRNAs in maintaining physiological stability and directing cellular development within periodontal tissues, highlighting potential targets for understanding molecular interactions underlying oral biological processes.

Circular RNAs exhibit dual functional roles in the pathogenesis of periodontitis. Certain circRNAs, such as circCDR1as and circLRP6, display protective properties by sponging specific microRNAs, thereby enhancing cell viability and differentiation. Conversely, other circRNAs, including circCDK8 and circ_0099630, act as disease-promoting molecules that inhibit osteogenic capacity and amplify inflammatory signaling. This functional dichotomy underscores the regulatory

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significance of circRNAs in periodontal tissue homeostasis and disease progression, highlighting their context-dependent actions within the molecular network of periodontitis.

However, current research on the role of ncRNAs in periodontitis remains insufficient in several respects. First, the generally limited sample sizes in existing studies constrain the broader applicability of the findings. Second, the precise regulatory mechanisms within the complex interaction networks involving different ncRNAs and coding RNAs are still poorly characterized. Third, most preliminary observations lack sufficient functional experimental validation, necessitating further investigations to establish causal relationships and verify underlying mechanisms.

Investigations into ncRNA biomarkers in biofluids, such as gingival crevicular fluid, face considerable methodological challenges. A primary issue is the notable absence of standardized protocols for their detection and quantitative analysis, leading to substantial variability across laboratories. Many studies are constrained by limited cohort sizes, which diminishes statistical power and compromises the reliability and generalizability of conclusions. Another significant complication arises from the insufficient characterization of confounding variables—including systemic conditions, pharmacological treatments, smoking, and oral microbiome composition—which can significantly influence ncRNA expression levels. A comprehensive understanding of these influences is essential for accurate data interpretation and the establishment of robust, clinically relevant biomarker signatures.

Furthermore, current analytical approaches for identifying and measuring ncRNAs in biofluids suffer from a lack of uniform protocols. This methodological heterogeneity complicates cross-study comparisons and undermines the reproducibility of findings. Many published reports are further limited by modest cohort sizes, reducing statistical power and generalizability. The impact of confounding variables, such as systemic disease status, medication use, smoking habits, and oral microbiome composition, remains inadequately characterized, hindering accurate interpretation of biomarker data.

Finally, ongoing studies of ncRNAs remain predominantly observational, revealing associations rather than causal relationships. A substantial knowledge gap persists regarding the definitive biological functions and precise operational mechanisms of many reported ncRNA species. For instance, the specific molecular binding partners and downstream signaling pathways regulated by lncRNAs such as FAS-AS1 continue to be poorly understood. These proposed models require rigorous validation through systematic in vivo perturbation studies, employing both gain-of-function and loss-of-function methodologies. Only such direct experimental evidence can substantiate their physiological relevance and clarify the detailed regulatory networks involved, thereby advancing beyond purely correlative observations.

6. Conclusion

In summary, this analysis definitively confirms that non-coding RNA species—particularly microRNAs, long non-coding RNAs, and circular RNAs—constitute essential components of the molecular framework governing periodontal disease pathology. These diverse transcripts form an intricately interconnected network that exerts precise, multi-level regulation over central biological processes. This regulatory system meticulously coordinates immune and inflammatory responses, maintains alveolar bone metabolic equilibrium, and directs the complex cellular activities underlying soft tissue regeneration and repair. Notably, numerous individual ncRNAs exhibit functional duality, exerting either protective or destructive effects depending on specific microenvironments and disease stages, thereby adding considerable complexity to their mechanistic contributions.

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The disruption of this sophisticated RNA network represents more than a secondary consequence of tissue destruction; it constitutes an upstream causative factor in disease initiation and progression. Aberrant expression patterns collectively establish a self-reinforcing pathological circuit that perpetuates chronic inflammation and facilitates progressive tissue damage. This paradigm fundamentally shifts our understanding of periodontitis etiology from a primarily bacterially driven process to one that incorporates critical host-derived molecular dysregulation.

Consequently, investigating these regulatory molecules provides crucial insights into the fundamental mechanisms driving periodontal destruction, while simultaneously revealing a broad spectrum of potential clinical applications. Distinct expression signatures detected in accessible biofluids offer substantial promise for developing sensitive diagnostic and prognostic biomarkers capable of refining disease classification. Furthermore, the molecular specificity of these transcripts positions them as attractive targets for innovative therapeutic strategies. Future efforts may focus on developing RNA-based interventions, including antisense oligonucleotides and molecular sponges, designed to selectively modulate pathogenic ncRNA activities. Although challenges related to tissue-specific delivery and stability remain, these approaches open new avenues for personalized treatment paradigms in oral healthcare, moving beyond conventional strategies toward mechanism-targeted biological solutions.

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