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Review

The Expression Patterns of Non-Coding RNAs in Periodontal Disease

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Abstract: During the last few decades there has been a growing interest in understanding the involvement of epigenetics in the pathogenesis and treatment of periodontal disease. Noncoding RNAs (ncRNAs), including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), may serve as epigenetic modifiers affecting the expression of genes involved in the pathogenesis of inflammatory and autoimmune diseases. There is increasing evidence supporting the idea that the function of all three types of ncRNAs seems to be interdependent. LncRNAs can act as miRNA decoys, while circRNAs can act as miRNA sponges, leading to the re-expression of miRNA target genes. The purpose of this review is to evaluate the expression patterns of ncRNAs in periodontal disease. Studies demonstrate a positive correlation between miRNA expression and periodontitis; however, this cannot be claimed for lncRNAs and circRNAs, which appear to be differentially expressed in periodontitis patients. Several studies have also suggested utilizing ncRNAs as diagnostic and prognostic biomarkers in periodontitis, or even as potential therapeutic targets; Nevetheless, the evidence to support this is premature. Future well-designed research remains necessary to establish the functional role of ncRNAs in the evolution and progression of periodontal disease.

Keywords: noncoding RNAs; epigenetics; periodontal disease

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1. Introduction

Periodontitis is a chronic inflammatory disease characterized by the progressive destruction of the supportive tissues of the teeth [1]. A bacterial infection is considered the main cause of the disease; however, several environmental and genetic parameters may affect both the disease onset and progression [2]. Specifically, periodontal disease is initiated by the activation of the host's inflammatory response against the bacterial stimuli. This response is mediated through the expression of a complex network of proinflammatory cytokines, which in turn lead to cellular activation. Obviously, various extrinsic and intrinsic factors that could modulate the host's inflammatory response mechanisms would affect disease progression. Probably the most studied and recognized examples of such factors include smoking [3], diabetes mellitus [4], and gene polymorphisms [5].

In recent years, there has also been growing interest in understanding the involvement of epigenetics in the pathogenesis and treatment of periodontal diseases [6]. Epigenetics is the study of chemical modifications in DNA and its associated proteins that alter gene expression [7]. The epigenome is dynamically formed by genomic and environmental interactions asserting the unique individual phenotype [8,9]. The main epigenetic modification mechanisms include DNA methylation, histone modification, and gene regulation by nonprotein coding RNAs (ncRNAs).

NcRNAs are a class of RNAs without proteincoding functions that regulate gene expression and cell differentiation at the genomic and chromosomal levels [10–13]. According to their length, they are mainly divided into short-chain ncRNAs or microRNAs

(miRNAs) and long noncoding RNAs (lncRNAs) [14,15]. MiRNAs are 17 to 25 nucleotides long and evolutionarily conserved, stemming from larger transcripts, while lncRNAs are linear RNAs with a length of more than 200 nucleotides [8,15,16].Circular RNAs (circRNAs)are considered a special class of ncRNAs that are different from linear RNAs.They are covalently closed lncRNAs, mainly encountered in the cytoplasm of eukaryotic cells [17].

Early studies comparing the expression profiles of ncRNAs from gingival tissues of healthy and periodontitis patients have revealed significant differences [18,19]. Specifically, using microarray technology, it was demonstrated that 159 miRNAs and 8925 lncRNAs were differentially expressed, indicating a possible role of these ncRNAs in the pathogenesis and development of periodontitis. Since then, many other studies have focused on the expression of specific ncRNAs in periodontal disease, in an attempt to identify potential targets for the treatment of periodontal disease or potential biomarkers for the diagnosis and assessment of periodontitis. In the present review, we summarize the current knowledge regarding the differences in the expression of ncRNAs among periodontitis and healthy individuals.

1.1. MiRNAExpression in Periodontal Disease

The studies that evaluated the expression of miRNAs in periodontitis patients are presented in Table 1. Most of the results derive from studies where the participants suffered from chronic periodontitis, while only a few included patients with aggressive periodontitis [20–23]. Most studies showed a positive correlation in the expression of specific miRNAs and the presence as well as progression of periodontal disease, while only a relatively small number linked miRNA downregulation with periodontitis [24–31].

The only two studies that compared the miRNA expression between chronic and aggressive periodontitis patients revealed no significant differences, although both groups demonstrated an increase in miRNA expression when compared to the periodontally healthy group [21,23].

Interestingly, the study by Fujimori et al., 2019 is the only study that aimed to investigate salivary miRNAs reflecting periodontal condition in chronic periodontitis. This cross-sectional pilot study included 120 participants with mild, moderate, or severe chronic periodontitis. Among the 84 miRNAstested, only hsa-miR-381-3p was significantly upregulatedin the severe periodontitis group. Moreover, as anticipated, there was also a significant correlation between the relative expression of this miRNA and the mean pocket depth [32]. In addition, the same group (Fujimori et al., 2021) also evaluatedmiRNA expression in relation to the progression of periodontitis. Specifically, in this two-year cohort study they assessed the expression of several miRNAs from the saliva in 120 patients undergoing supportive periodontal therapy [33]. According to this study, there was a positive correlation between the expression of several miRNAs and the progression of chronic periodontitis.

Some authors also evaluated how systemic diseases, such as diabetes mellitus [27,34–36], obesity [37–39], rheumatoid arthritis [40], and coronary heart disease [26,41], influence relative miRNA expression levels in patients with a healthy or diseased periodontium. Results from these studies have shown that miRNA expression was significantly upregulated in patients suffering from both periodontal disease and diabetes, rather than exclusively diabetes or periodontitis. Similar results are also observed for obese and coronary heart disease patients with periodontitis [26,37–39,41]. This could lead to the conclusion that the presence of certain systemic diseases synergistically affects the regulation of microRNAs related to periodontal disease. On the other hand, data were inconclusive in patients with chronic periodontitis with or without rheumatoid arthritis [40].

Smoking, a well-established risk factor for periodontal disease, has also been evaluated for its effect on miRNA expression in periodontitis patients. In the study of Öngöz Dede et al., 2022 the expression of six miRNAs in the saliva of smokers and nonsmokers with periodontal disease, before and after nonsurgical periodontal therapy, was determined [42]. Salivary miR-146a, miR-146b, miR142-3p, miR-155, and miR-203 gene expression was significantly upregulated in periodontitis patients compared to the control group both

in smokers and nonsmokers. Moreover, a significant increase in miR-142-3p expression was detected in all groups of smokers compared to nonsmokers. Hence, the authors suggested that smoking may contribute to an increase in the levels of salivary miR-142-3p in periodontal health and disease. Finally, although there was a decrease in miRNA gene expression after periodontal treatment, this was not statistically significant.

Among the plethora of miRNAs examined, MiR-146a is the mostfrequently analyzed [22,26,36,41,43–46]. MiR-146a is involved in the expression of tumor necrosis factor-α (TNF-α), interleukin (IL)-b, and IL-6, and therefore is associated with the pathogenesis of several inflammatory diseases [42,46]. Its upregulation seems to play a functional role in periodontal disease by exhibiting a negative regulation of immune response [47]. Patients with chronic periodontitis exhibit up to a 32,6 timeshigher expression of this miRNA [48]. These findings are also in agreement with the results of the the larger studyin terms of sample size included in this review [45]. Only the study by Rovas et al. found that miR-146a-5p expression levels were significantly lower among patients with periodontal disease [40]. Other frequently studied miRNAs are miR-142-3p, miR-223, miR-155, miR-205, and miR-21. MiR-223 is a modulator in osteoclastogenesis, and its high expression in periodontal disease should be further examined as it might affect alveolar bone loss [49].

Table 1. Summary of publications evaluating miRNA expression in periodontal disease.

Reference	Type of Study	Cases	Type ofSample	Type of Periodontal Disease	Results
Uttamani et al., 2023 [24]	Cohort	CP, 27 Healthy, 27	Gingival biopsy	Chronic periodontitis⬇	⬇miR-26a-5p, FC: 0.38± 0.14; miR-26b-5p, FC:0.41 ± 0.21 in CP
Costantini et al., 2023 [50]	Cross-sectional	CP, 21 Healthy, 15	Gingival crevicular fluid	Chronic periodontitis	⬆miRNA-103a-3p significant differences between mild and severe stages with a variation of 1.27-fold miRNA-23a-3pa fold change of 11.32 in patients with mild periodontitis, while in moderate and severe periodontal disease the expression levels were 1.9- and 1.4-fold, respectively miRNA-15a-5p, miRNA-223-3p, and miR-423-5p severe periodontitis 3.68-fold, in relation to patients with periodontitis in mild (0.39-fold) and moderate stages (0.45-fold)
Liu et al., 2022 [34]	Cross-sectional	G1: CP, 26 G2: T2DM, 24 G3: CP + T2DM,22 G4: healthy, 25	Serum and gingival crevicular fluid	Chronic periodontitis	miR-223, miR-200b high in G1 and G2, and higher in G3

Table 1. *Cont.*

Reference	Type of Study	Cases	Type ofSample	Type of Periodontal Disease	Results
Öngöz Dede et al.,2022 [42]	Cohort	G1: CP + nonsmokers, 15 G2: CP + smokers, 15 G3: gingivitis + nonsmokers, 15 G4: gingivitis + Smokers, 15 G5: periodontically healthy + nonsmokers, 15 G6: periodontically healthy + smokers, 15	Saliva	Chronic periodontitis/gingivitis	Salivary miR-146a, miR-146b, miR142-3p, miR-155, and miR-203in CP Smoking may contribute to an increase in the levels of salivary miR-142-3p in periodontal health and disease
Chaparro et al., 2022 [47]	Case–control	CP, no data Healthy, no data	Gingival biopsy	Chronic periodontitis	⬆miRNA-20a, miRNA-30e, and miRNA-93 in CP
Mogharehabedet et al., 2022 [51]	Sectional	CP, 10 Healthy, 10	Blood sample	Chronic periodontitis	⬆miR-155, FC:64.4 in CP
Huang and Jia, 2022 [25]	Cohort	CP, 76 Healthy, 71	Gingival crevicular fluid PDLCs	Chronic periodontitis	⬇miR-28-5p in CP
Zhu and Zhong, 2022 [52]	Cohort	CP, 80 Healthy, 100	Gingival crevicular fluid	Chronic periodontitis	⬆miR-30b-3p and miR-125b-1-3p may be associated with the pathogenesis of periodontitis
Rovas et al., 2022 [40]	Cross-sectional	CP, 134 Healthy periodontically with or without RA, 76	Gingival crevicular fluid	Chronic periodontitis	miR-140-3p, miR-145-5p, and miR-146a-5p in CP in pt with or without RA
	t				⬆
Rovas et al., 2021 [53]	Cross-sectional	CP, 30 Healthy, 31 Diagnosed with RA, 25	Gingival tissue GCF Saliva Plasma	Chronic periodontitis	miR-199a-5p, miR-483-5p, miR3198, and miR-4299 associated with the presence and/or severity of PD
Mahendra et al., 2021 [26]	Cohort	GP+CAD, 25 CP, 25 Healthy, 25	Oral subgingival plaque	Generalized periodontitis	⬆miRNA-146a and ⬇miRNA-126 in the GP + CAD group
Fujimori et al., 2021 [33]	Cohort	Patients who underwent supportive periodontal therapy, 120	Saliva	Chronic periodontitis	hsa-miR-5571-5p, FC:3.70; hsa-let-7f-5p, FC:7.90; hsa-miR-99a-5p, FC:2.71; hsa-miR-28-5p, FC:6.86; and hsa-miR-320d, FC:4.51 were associated with periodontitis progression
Elazazy et al., 2021 [27]	Cross-sectional	G1:CP, 20 G2: type 2 diabetes CP, 20 G3: healthy, 20	Serum and gingival crevicular fluid	Chronic periodontitis	miR-223 and miR-200bin G1 and G2 miR-203in G1 and G2
Du et al., 2021 [28]	Cohort	CP, 72 Healthy, 50	Gingival crevicular fluid	Chronic Periodontitis	⬇miR-1226 in CP
Lee et al., 2020 [20]	Pilot case–control	AP, 4 Healthy, 4	Saliva	Aggressive periodontitis	⬇hsa-let-7a-5p, FC:3.81; hsa-let-7f-5p, FC:3.40; hsa-miR-181b-5p, FC:5.91; and hsa-miR-23b-3p, FC:3.66 in AP

Table 1. *Cont.*

Reference	Type of Study	Cases	Type ofSample	Type of Periodontal Disease	Results
Gonçalves Fernandes et al., 2020 [29]	Cohort	LAP, no data Healthy, no data	Blood sample	Localized aggressive periodontitis	miRNAs miR-9-5p, FC:2.23; miR-155-5p, FC:2.01; 203a-3p, FC:2.17; miR-147a, FC:2.11; miR-182-5p, FC:2.46; and miR-183-5p, FC:2.48 in LAP
Jia et al., 2020 [54]	Cross-sectional	CP, 24 Healthy, 18	Gingival biopsy	Chronic periodontitis	miRNA 210 in CP
Al-Rawi et al., 2020 [43]	Pilotcross-sectional	DM, 24 Healthy, 29 Each group was subdivided into periodontally healthy or having periodontitis, specific data unknown	Saliva	Chronic periodontitis	⬆miRNAs-146a/b, FC:4.3/12.3; miR-155, FC:13.7 for periodontitis diabetic pt, and miR-203, FC:5.9 higher in patients with CP and/or DM
Nisha et al., 2019 [55]	Cross-sectional	CP, 16 Healthy, 16	Saliva	Chronic periodontitis	⬆miR-143-3pin CP, FC:5.82
Ou et al., 2019 [35]	Cross-sectional	CP, 45 Healthy, 50 DM, 40 CP+ DM, 63	Gingival biopsy +GCF	Chronic periodontitis	miR-214in diabetes-associated periodontitis patients
Amaral et al., 2019 [21]	Cross-sectional	CP, 9 AP, 9 Healthy, 66	Gingival biopsy	Chronic periodontitis and aggressive periodontitis	No differences in the miRNA expression profiles between CP and AP ⬆hsa-miR-1274b, hsa-let-7b-5p, hsa-miR-24-3p, hsa-miR-19b-3p, hsa-miR-720, hsa-miR-126-3p, hsa-miR-17-3p, and hsa-miR-21-3p
Zhang et al., 2019 [56]	Cross-sectional	CP, 29 Healthy, 21	Gingival crevicular fluid	Chronic periodontitis	⬆miR-23a in CP potential biomarker
Zhao et al., 2019 [44]	Cross-sectional	CP, 38 Healthy, 30	Serum	Chronic periodontitis	⬆miRNA-146ain CP
Fujimori et al., 2019 [32]	Cross-sectional	G1: no/mild CP, 26 G2: moderate CP, 58 G3: severe CP, 36	Saliva	Chronic periodontitis	⬆miRNA hsa-miR-381-3p in CP, FC:3,63
Bagavad Gita et al., 2019 [41]	Case–control	G1: CHD no CP, 66 G2: CHD + CP, 66 G3: healthy + CP, 66 G4: healthy no CP, 66	Blood sample	Chronic periodontitis	⬆miRNA 146 overexpressed in G1, G2, and G3 with no significant differences between them
Naqvi et al., 2019 [37]	Cross-sectional	G1: Obesityno/+ CP, 14 G2: Healthy no/+ CP, 14	Gingival biopsy	Chronic periodontitis	Significant differences in miRNA expression levels between healthy and obese subjects and periodontal and nonperiodontal patients

Table 1. *Cont.*

Reference	Type of Study	Cases	Type ofSample	Type of Periodontal Disease	Results
Yoneda et al., 2019 [57]	Case-control	CP, 30 Healthy, 30	Blood sample	Chronic periodontitis	⬆miR-555, FC:1.85; miR-130a-5p, FC:1.71; miR-664a-3p, FC:1.54; miR-501-5p, FC:1.57; miR-6770-5p, FC:0.65; miR-4717-5p, FC:0.64; miR21-3p, FC:0.63 in CP
Micó-Martínez et al., 2018 [30]	Cross-sectional	CP, 9 Healthy, 9	Gingival crevicular fluid	Chronic periodontitis	⬇miRNA 1226, FC:15.8 in CP
Venugopal et al., 2018 [58]	Cross-sectional	CP, 100 Healthy, 100	Gingival biopsy	Chronic periodontitis	⬆Let/a, miRNA-21, FC:2; miRNA-100 in CP
Li et al., 2019 [59]	Cross-sectional	CP, 16 Healthy, 16	Gingival biopsy	Chronic periodontitis	⬆miRNA 144 in CP
Ghotloo et al., 2019 [22]	Cross-sectional	AP, 18 Healthy, 10	Gingival biopsy	Aggressive periodontitis	⬆miRNA 146, FC:17.8 in AP
Radović et al., 2018 [36]	Cohort	G1: T2DMno CP, 24 G2: T2DM+ CP, 24 G3: healthy no CP, 24 G4: healthy + CP, 24	Gingival crevicular fluid	Chronic periodontitis	⬆miRNA 146 and 155 in CP
Saito et al., 2017 [23]	Cross-sectional	CP, 7 AP, 2 Healthy, 11	Gingival crevicular fluid	Chronic and aggressive periodontitis	⬆miR-223-3p, miR-203a, and miR-205-5p in CP and AP
Na et al., 2016 [31]	Cross-sectional	CP, no data Healthy, no data	Gingival biopsy	Chronic periodontitis	miR-128, miR-34a, and miR-381in CP miR-15b, miR211, miR-372, and miR-656 in CP
Motedayyen et al., 2015 [48]	Cross-sectional	CP, 20 Healthy, 10	Gingival biopsy	Chronic periodontitis	miRNA 146a expression 32,6 times greaterin CP
Kalea et al., 2015 [38]	Cross-sectional	Normal-weight subjects with severe periodontitis, 17 Obese subjects with severe periodontitis, 19	Gingival biopsy	Severe periodontitis CP or AP	⬆miR200b, FC:1.27 in obese periodontitis subjects
Ogata et al., 2014 [60]	Cross-sectional	CP 3 Healthy 3	Gingival biopsy	Chronic periodontitis	⬆miRNA 150, 223, and 200b, FC: >2.72 in CP
Kadkhodazadeh et al., 2013 [45]	Cohort study	CP 75 PI:38 Healthy 84	Blood sample	Chronic periodontitis Peri-implantitis	⬆miRNA 146a and 499 in CP and PI
Perri et al., 2012 [39]	Cross-sectional	G1: periodontically healthy + non-obese 5 G2: CP + non-obese, 5 G3: periodontically healthy + obese, 5 G4: CP + obese, 5	Gingival biopsy	Chronic periodontitis	⬆G3: miR-18a, FC:1.5; miR-30e, FC:2.1 ⬆G2: miR-30e, FC:4.4; miR-106b, FC:4.9 ⬆G4: miR-15a, FC:2.7; miR-18a, FC:1.5; miR-22, FC:3.1; miR-30d, FC:2.2; miR-30e, FC:4.9; miR-103, FC:1.5; miR-106b, FC:6.4; miR-130a, FC:4.6; miR-142-3p, FC:5.3; miR-185, FC:3.6; and miR-210, FC:2.3
Lee et al., 2011 [61]	Cross-sectional	No data	Gingival biopsy	Chronic periodontitis	⬆miR-181b, miR-19b, miR-23a, miR-30a, miR-let7a, and miR-301a

Table 1. *Cont.*

Reference	Type of Study	Cases	Type ofSample	Type of Periodontal Disease	Results
Stoecklin-Wasmer et al., 2012 [18]	Cross-sectional	CP, 86	Gingival biopsy	Chronic periodontitis	⬆hsa-miR-451, FC:2.63; hsa-miR-223, FC:2.53; hsa-miR-486-5p, FC:2.46; and hsa-miR-3917, FC:2.08 ⬇hsa-miR-1246, FC:0.33; hsa-miR-1260, FC:0.44; hsa-miR-141, FC:0.46; hsa-miR-1260b, FC:0.44; hsa-miR-203 and hsa-miR-210, FC:0.46; and hsa-miR-205*, FC:0.49
Xie et al., 2011 [46]	Cross-sectional	CP, 10 Healthy, 10	Gingival biopsy	Chronic periodontitis	⬆hsa-miRNA-146a, hsa-miRNA-146b, and hsa-miRNA-155

Abbreviations: CP: chronic periodontitis; GP: generalized periodontitis, AP: aggressive periodontitis; LAP: localized aggressive periodontitis; T2DM: type 2 diabetes mellitus; DM: diabetes mellitus; GCF: gingival crevicular fluid; CHD: coronary heart disease; CAD: coronary artery disease; PI: peri-implantitis; PDLCs: periodontal ligament cells; RA: rheumatoid arthritis; G: group; and FC: fold change, ⬆ upregulation, ⬇ downregulation.

1.2. LncRNAExpression in Periodontal Disease

The studies that evaluated the expression of lncRNAs in periodontitis patients are presented in Table 2. As with miRNAs, most of the studies are performed in patients suffering from chronic periodontitis;however, in most cases the severity of periodontal disease is not specified. Thus, from this set of studies it is not safe to link disease severity and progression with the level of lncRNA expression. Moreover, there is great variability in the lncRNAs evaluated, which renders comparisons among studies challenging. In addition, the interpretation of the outcomes is complex considering the inconsistent results. Thus, 9 of the studies show that the downregulation of the expression of specific lncRNAs is linked to periodontal disease [62–70], while 7 studies associate periodontitis with the upregulation of the expression of lncRNAs [71–77]. The best example includes MALAT1. Although this is the most frequently analyzed lncRNA, it is evaluated only in three studies [65,74,77]. From these studies, Li et al., 2020 [74] found an increase in the expression of MALAT1 in gingival biopsies derived from patients with periodontitis stage III grade C. Similarly, Chen et al., 2019 [77] also concluded that MALAT1 was upregulated in periodontal ligament cells from chronic periodontitis patients. On the other hand, the study by Gholami et al., 2020 [65] did not support these findings and showed no difference in MALAT1 expression levels from gingival biopsies and blood samples among healthy individuals and chronic periodontitis patients.

Since lncRNAs may interact with miRNAs, several investigators have also tried to assess the relationship between the expression profiles of certain miRNAs and lncRNAs [67,69]. Interestingly, those two studies concluded that lncRNA expression is inversely correlated with miRNA expression. Specifically, the expression of miR-27a-3p [67] and miR-142-3p [69] was increased in periodontitis patients, while the respective expression of the lncRNAs (MEG3, and FDG5-AS1) was downregulated.

Finally, another interesting finding was that one study [73] showed that the expression of lncRNA PACER was significantly higher in blood samples of female subjects when compared to male subjects with chronic periodontitis, concluding that there may be sex-specific functions to lncRNA levels and inflammatory control.

Table 2. Summary of publications evaluating lncRNA expression in periodontal disease.

Reference	Type of Study	Cases	Type of Sample	Type of Periodontal Disease	Results
Zhang et al., 2022 [71]	Case–control	CP, 28 Healthy, 20	Gingival biopsy	Chronic periodontitis	⬆LncRNA NEAT1 in CP
Yang et al., 2022 [62]	Case–control	P, 7 Healthy, 8	Gingival biopsy	Not specified	⬇LncRNA GAS5 in P downregulated by 50%
Han et al., 2022 [63]	Case–control	P, 12 Healthy, 10	Gingival biopsy	Not specified	⬇LncRNA SNHG5 in P
					⬇
Wang et al., 2021 [64]	Case–control	SP, 30 Healthy, 30	PDLCs from extracted teeth	Stable periodontitis	⬇LncRNA DCST1-AS1 in SP
Zhou et al., 2021 [72]	Case–control	P, 47 Healthy, 19	Gingival biopsy	Not specified	⬆LncRNA LINC01126 in P1080 lncRNAs significantly differentially expressed with fold changes greater than 1.5
Sayad et al., 2020 [73]	Case–control	Gingival biopsy: CP, 30 Healthy, 30 Blood samples: CP, 23 Healthy, 18	Gingival biopsy and blood sample	Chronic periodontitis (stages II to IV)	⬆LncRNA PACER in blood samples in CP especially in female subjects
Li et al., 2020 [74]	Case–control	CP, 20 Healthy, 20	Gingival biopsy	Chronic periodontitis (stage III, grade C)	⬆LncRNA MALAT1 in CP
Guo et al., 2020 [75]	Case–control	P, 5 Healthy, 5	PDLCs from extracted teeth	Not specified	⬆LncRNA H19 in P1080 lncRNAs significantly differentially expressed with fold changes greater than 1.5
Gholami et al., 2020 [65]	Case–control	CP, 30 Healthy, 30	Gingival biopsy and blood sample	Chronic periodontitis	⬇LncRNA ANRIL in blood samples in CP Expression of lncRNA MALAT1 is the same in both groups
Dong et al., 2020 [66]	Case–control	P, 25 Healthy, 25	PDLCs from extracted teeth	Not specified	⬇LncRNA MEG3 in P
Wang et al., 2019 [76]	Cohort	P, 80 Healthy, 66	Blood sample	Not specified	⬆LncRNA AWPPH in P Correlated with high recurrence rate
Liu et al., 2019 [67]	Case–control	P, 20 Healthy, 20	PDLCs from extracted teeth	Not specified	⬇LncRNA MEG3 in P, while miR-27a-3p was upregulated
Liu et al., 2019 [68]	Case–control	P, 34 Healthy, 34	PDLCs from extracted teeth	Not specified	⬇LncRNA PTCSC3 in P
Chen et al., 2019 [77]	Case–control	CP, 12 Healthy, 12	PDLCs from extracted teeth	Chronic periodontitis	⬆LncRNA MALAT1 in CP

Table 2. *Cont.*

Reference	Type of Study	Cases	Type of Sample	Type of Periodontal Disease	Results
Chen et al., 2019 [69]	Case–control	CP, 26 Healthy, 20	Gingival biopsy	Chronic periodontitis	⬇LncRNA FGD5-AS1 in CP, while miR-142-3p was upregulated
Wang et al., 2016 [70]	Case–control	SP, 10 Healthy, 10	PDLCs from extracted teeth	Stable periodontitis	⬇LncRNA POIR in SP
Zou et al., 2015 [19]	Cross-sectional	CP, 30 Healthy, 15	Gingival tissues	Chronic periodontitis	8925 differently expressed lncRNAs ⬆4313 lncRNAs ⬇4612 lncRNAs

Abbreviations: CP: chronic periodontitis; P: periodontitis; SP: stable periodontitis; PDLCs:periodontal ligament cells; NEAT1:nuclear paraspeckle assembly transcript 1; GAS5:growth arrest specific transcript 5; SNHG5:small nucleolar RNA host gene 5; PACER: p50-associated COX-2 extragenic RNA; MALAT1:metastasis-associated lung adenocarcinoma transcript 1; ANRIL: antisense noncoding RNA in the INK4 locus; MEG3:maternally expressed gene 3;and PTCSC3:papillary thyroid carcinoma susceptibility candidate 3, ⬆ upregulation, ⬇ downregulation.

1.3. CircRNAExpression in Periodontal Disease

The studies that evaluated the expression of circRNAs in periodontitis patients are presented in Table 3. Most of these studies were designed to explore, in vitro, the role of circRNAs in periodontitis and secondarily evaluated the levels of expression of circRNAs in periodontitis patients. The data suggest no clear pattern in the expression of various circRNAs. All three studies that evaluated the expression of Circ_0099630 found upregulation in patients with periodontitis [78–80]. In the study by Wang et al. [78], circ_0099630 upregulation was correlated with the downregulation of miR_212-5p, while in the study by Zhao et al. [80], miR-940 was downregulated.

On the contrary, in two other studies the expression of various circRNAs was downregulated [81,82] in periodontitis patients, with the authors suggesting a possible protective action of these circRNAs against periodontitis. Finally, DNA sequencing in the study of Li et al. [83] showed that 1304 circRNAs were differentially expressed in chronic periodontitis patients.

All these findings should be interpreted with caution due to the small number of studies, the small sample size of the included studies, and the lack of a clear definition and characterization of periodontal disease severity.

Table 3. Summary of publications evaluating circRNA expression in periodontal disease.

Reference	Type of Study	Cases	Type of Sample	Type of Periodontal Disease	Results
Wang et al.2023 [78]	Case control	P, 10 Healthy, 10	PDLCs from extracted	Not specified	⬆circ_0099630 in P 3-fold higher
Pan et al. 2022 [84]	Case–control	P, 30 Healthy, 30	PDLCs from extracted teeth	Not specified	⬆circ_0138959 in P
Wei et al. 2022 [79]	Case–control	P, 60 Healthy, 20	hPLFs from extracted teeth	Not specified	⬆circ_0099630 in P
Zhao et al. 2022 [80]	Case–control	P, 26 Healthy, 21	Periodontal tissues	Not specified	⬆circ_0099630 in P linked with lower miR-940 expression
Wang et al. 2021 [81]	Case–control	P, 21 Healthy, 21	Gingival tissues	Not specified	⬇circ_0081572 in P
Yu et al. 2021 [85]	Case–control	P, 20 Healthy, 10	PDLCs from extracted teeth	Not specified	⬆circ_002284 (circMAP3K11) in P

Table 3. *Cont.*

Reference	Type of Study	Cases	Type of Sample	Type of Periodontal Disease	Results
Zheng et al. 2020 [86]	Case–control	CP, 6 Healthy, 6	PDLCs from extracted teeth	Chronic periodontitis	⬆circ_0003489 (circCDK8) in CP 2-fold higher
Li et al. 2019 [83]	Case–control	CP, 4 Healthy, 4	Gingival tissues	Chronic periodontitis	1304circRNAs were differentially expressed in CPby greater than a 2-fold change ⬇circ_0062491 and ⬆circ_0095812in CP
Wang et al., 2019 [82]	Case–control	CP, 10 Healthy, 11	PDLCs from extracted teeth	Chronic periodontitis	⬇circRNA CDR1as in CP

Abbreviations: CP: chronic periodontitis; P: periodontitis; PDLCs:periodontal ligament cells, ⬆ upregulation, ⬇ downregulation.

1.4. Interactions of ncRNAs in Periodontitis

Since their discovery, miRNAs have attracted more attention than their longer non-coding counterparts; therefore, the number of studies concerning miRNAs is significantly higher than those for lncRNAs and circRNAs. Overall, there seems to be a positive correlation between miRNA expression and periodontal disease. MiRNAs play a crucial role in the pathogenesis of periodontitis by regulating various signaling pathways involved in inflammatory responses, bone remodeling, and stem cell differentiation [33,87–90].

Hence, several miRNAs, such as miR-146a, miR-155, and miR-223, regulate various aspects of the innate and adaptive immune responses against periodontal pathogens, including the targeting components of signaling pathways like NF-κB [87,88]. MiR-99a-5p may affect periodontitis progression through the MAPK signaling pathway, which is involved in regulating cellular processes like inflammation, proliferation, and differentiation [33]. Additionally, miR-132 and miR-222 can regulate the osteogenic differentiation of periodontal ligament stem cells (PDLSCs) by modulating the Wnt/β-catenin and BMP signaling pathways, respectively [89]. MiR-146a, miR-155, and miR-223 can also modulate the signaling pathways involved in osteoclastogenesis and osteoblast differentiation, which are key processes in periodontal bone loss [90].

However, there is increasing evidence supporting that the function of miRNAs is regulated, at least in part, by the other two ncRNAs, ielncRNAs and cirRNAs. Probably the most studied interaction between ncRNAs in relation to periodontitis includes the ability of some lncRNAs and circRNAs to act as sponges/decoys for miRNAs through miRNA reaction elements. Hence, they both serve as competitive endogenous RNAs (ceRNAs) against miRNAs for binding sites in mRNA [91–93]; therefore, lncRNAs can modulate signaling pathways central to periodontitis pathogenesis, such as Wnt, NF-κB, and MAPK, by acting as ceRNAs that sponge miRNAs or by directly targeting pathway components. For example, the lncRNA POIR acts as a sponge for miR-182, which binds to the 3′ UTR of FOXO1. FOXO1 inhibits the canonical Wnt signaling pathway, suggesting that POIR lncRNA may regulate Wnt signaling in periodontitis [94,95]. Moreover, the overexpression of the lncRNA OIP5-AS1 is thought to inhibit the lipopolysaccharide (LPS)-induced inflammatory response in human periodontal ligament stem cells (PDLSCs) by sponging miR-92a-3p, which likely involves the NF-κB pathway [96]. In addition, differentially expressed lncRNAs in periodontitis are predicted to target genes enriched in the MAPK signaling pathway, suggesting their potential role in regulating this pathway [33]. Finally, the relationship among miRNAs, lncRNAs, and circRNAs in periodontal disease involves a network of interactions that regulate the osteogenic differentiation of PDLCs/PDLSCs [97,98], which is important to alveolar bone regeneration. It becomes clear

that the interplay between these noncoding RNAs represents an emerging area of research in understanding the molecular mechanisms underlying periodontitis. Therefore, looking only into the expression levels of only one ncRNA may be misleading.

1.5. Significance of Sample Source in ncRNA Expression

The ncRNA profiling occurred from the analysis of samples originating from various sources, such as blood, serum, plaque, gingival biopsies, gingival crevicular fluid (GCF), saliva, and periodontal ligament cells. This may raise a question as to whether the results are comparable, since the proximity to the diseased periodontal tissues and the effect of systemic influences may differ. It is reasonable to suggest that gingival biopsies present tissue sensitivity and specificity, since they include the diseased site. GCF is the sample source with closer proximity to the gingival tissues and becomes an inflammatory exudate containing a great number of proteins and peptides deriving from host inflammatory cells, oral bacteria, and structural cells of the periodontium and periodontal pocket [99]. Therefore, the analysis of the GCF constituents is considered to reflect the disease status of periodontitis [100]. On the other hand, saliva, serum, and blood samples derive from more distant sites and thus could underestimate the actual level of disease in the gingiva. Therefore, fold changes in the expression of ncRNAs observed from different sample sources may not be directly comparable. In a recent systematic review and meta-analysis by Asa'ad et al., 2020 [101] the authors attempted to assess this issue; however, a statistical analysis was not possible for evaluating differences between methods of sample collection as tissue biopsies were the procedure of choice in the majority of the included studies.

In addition, the direct comparison of the expression levels of ncRNAs among different sample sources in the same population was very scarce. In the study by Elazazy et al., 2021 [27] there was a significant overexpression of miR-223 in both the serum and GCF of chronic periodontitis patients with and without diabetes type 2 as compared to the controls. Furthermore, in both patient groups the GCF levels of miR-223 were significantly elevated in comparison with the corresponding serum levels. On the other hand, miR-200b was also overexpressed in both the serum and GCF of both patient groups, although expression was significantly higher in the serum. Since elevated levels of miR-200b are involved in the increased pancreatic β-cell apoptotic rate [102], the authors suggested that miR-200b is more implicated in the pathomechanism of diabetes;therefore, it is possible that systemic diseases may affect the expression of specific ncRNAs, which may become more obvious in serum samples.

Finally, in the study by Rovas et al., 2021 [53] the authors evaluated the expression of miRNAs in gingival tissue, GCF, saliva, and plasma from patients with or without periodontitis. The relative quantities of selected miRNAs (miR-199a-5p, miR-483- 5p, miR-3198, and miR-4299) were significantly different between GCF, saliva, and plasma samples. The level of miR-3198 was 12.5-fold higher in GCF than in saliva and 85.8-fold higher in plasma ($p< 0.001$). Meanwhile, the miR-199a-5p level was 139.7-fold higher in plasma compared to saliva and 6.6-fold higher than in GCF ($p< 0.001$). Again, this study highlights the differences in the expression of miRNAs depending upon the sample source and type of miRNA.

1.6. NcRNAExpression and Its Use as a Biomarker for Periodontitis

Since miRNAs display stability in biofluids, and can be easily detected in tissue samples, investigators have considered them potential biomarkers for the diagnosis and assessment of periodontitis;therefore, a number of studies support the idea that miR-223, miR-200b, miR-28-5p, miR-23a, miR-146a, hsa-miR-381-3p, miR-1226, miRNA-155, miR143-3p, hsa-miR-664a-3p, hsa-miR-501-5p, and hsa-miR-21-3p could serve as biomarkers for the diagnosis and assessment of periodontitis [97,98], while miRNA-146a and miRNA-126 may serve as risk biomarkers for coronary artery disease and generalized periodontitis [26].

In addition, a small number of clinical studies have also explored the diagnostic and prognostic value of lncRNAs in chronic periodontitis. A notable example is the study

by Wang et al. [76] in which the levels of AWPPH lncRNA before and after periodontal treatment were measured, and investigators found that high levels of AWPPH had high prognostic value for chronic periodontitis recurrence.

1.7. Limitations of the Studies

All aforementioned studies compared the expression of ncRNAs between periodontitis patients and healthy individuals;however, not all of them used the same classification system to define periodontitis. The majority of studies categorized patients according to the classification proposed in the International Workshop held in 1999, but the most recent studies employed the latest classification of 2017 [103,104]. Moreover, specific clinical measurements and indices concerning periodontal status are missing in most of the studies;therefore, it is difficult to link the expression of certain ncRNAs to the severity of the disease. In addition, in almost all studies patients with periodontital disease were pooled into one diseased group irrespective of the severity of periodontitis. This may have a significant impact on the outcomes of the studies, since milder periodontitis may have a washout effect.

Another limitation, regarding mainly the lncRNAs and circRNAs, is the relatively small number of studies available. This in combination with the wide variability in ncRNAs examined, which in most studies do not overlap, weakening the association between specific ncRNAs and periodontitis and not permitting the extraction of solid conclusions. Finally, there seems to be significant variation in terms of the sample size among studies, ranging from 4 to 256 participants. This aspect should be taken into consideration when interpreting the results, especially those of the smaller studies.

2. Conclusions

In conclusion, the altered expression of ncRNAs was identified in periodontitis patients, highlighting their potential role in disease pathogenesis and treatment., In general, there seems to be a positive correlation between miRNA expression and periodontal disease, with miR-146a and miRNA-142-3p being consistently upregulated in patients with periodontitis; therefore, it is reasonable to suggest that these two miRNAs may have the best potential to serve as diagnostic biomarkers for periodontal disease activity. Regarding the lncRNAs and circRNAs, the available evidence does not support a clear expression pattern in periodontitis; however, due to methodological limitations, these outcomes should be interpreted with caution. Larger, well-designed studies using uniform definitions for periodontitis and examining similar ncRNAs seem necessary for the future.

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