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ORIGINAL RESEARCH

lncRNA RNA AC114812 Regulates the Inflammatory Response of Periodontal Ligament Cells via the miR-181a-5p-SPP1 Axis

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Background: Long noncoding RNAs (lncRNAs) play a significant role in the occurrence and development of periodontitis. We investigate the potential role of the lncRNA AC114812 in the lipopolysaccharide (LPS) induced proliferation, migration and inflammatory response of periodontal ligament cells (PDLCs) via the miR-181a-5p-SPP1 axis.

Methods: Bioinformatics analysis and whole transcriptome sequencing analysis were conducted on the gingival tissues of three pairs of healthy and periodontitis patients to screen out lncRNAs with differential expression in periodontitis and a periodontitis cell model was constructed via stimulation with LPS. The expression levels of the lncRNA AC114812 in tissues and cells were detected via real-time quantitative polymerase chain reaction (qRT-PCR), and the expression localization was detected via fluorescence in situ hybridization (FISH). The role of si-AC114812 in periodontitis was investigated through qRT-PCR, MTT assay and wound healing experiments. Through database screening combined with sequencing results, the competitive endogenous RNA (ceRNA) mechanism of lncRNA AC114812-miR-181a-5p-SPP1 was verified via a dual-luciferase gene reporter assay.

Results: LncRNA AC114812 was highly expressed in periodontitis tissues. Knockdown of lncRNA AC114812 inhibited the expression of inflammatory factors interleukin-1β (IL-1β) and interleukin-6 (IL-6) in PDLCs stimulated by inflammation and improved the proliferation and migration abilities of PDLCs affected by inflammation. FISH assays confirmed that the lncRNA AC114812 was expressed mainly in cytoplasm and may have a sponge effect. The ceRNA mechanism of the lncRNA AC114812-miR-181a-5p-SPP1 was predicted. The dual-luciferase gene reporter assay verified the existence of binding sites among the three genes and their mutual regulatory effects.

Conclusion: By regulating the expression of long non-coding RNA AC114812, the inflammatory response can be alleviated, thereby affecting cell proliferation and migration. The effect may be achieved through the miR-181a-5p-SPP1 axis. These can provide new strategies and intervention targets for the prevention and treatment of periodontal diseases.

Keywords: periodontitis, LncRNA AC114812, inflammatory response

Introduction

Periodontitis is a type of chronic inflammatory disease that occurs in periodontal supporting tissues and is characterized mainly by progressive damage to periodontal supporting tissues. It can lead to a series of clinical symptoms, including gingival bleeding, gingival recession, tooth loosening, and even tooth loss, and is currently the main cause of tooth loss in adults.[1] The pathogenesis of periodontitis is not yet clear. Many studies have shown that periodontitis is caused mainly by pathogenic bacteria affecting the host immune response, leading to immune mechanism disorders in the host, causing the periodontal tissues to be continuously exposed to a local inflammatory environment and inducing pathological changes or complications in the whole body.[2] Disorders of the immune response mechanism are largely regulated by genes.[3] Gene therapy, as an effective treatment method, has received extensive attention in the treatment of chronic diseases such as cardiovascular diseases and diabetes.[4] Many studies have shown that regulating disease-related genes through methods

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such as gene silencing, gene activation, and epigenetic regulation, including regulating lncRNAs, improve treatment efficacy.[5–9]

LncRNAs are noncoding RNAs composed of more than 200 nucleotides and are important biological function transcripts. They can play powerful regulatory roles in various biological functions and activities.[10] Moreover, lncRNAs are immunogenic and participate in the regulation of gene expression in immune cells and pathogenic bacteria.[11–14] For example, Xu et al reported that the lncRNA Sros1 can promote the activation of the IFN-γ-mediated innate immune response by stabilizing Stat1 mRNA.[15]

Recent studies have found that non-coding RNAs play a crucial role in the progression of periodontitis by regulating inflammatory factors, immune cell activation, and bone metabolism imbalance through the ceRNA mechanism.[16] Taking lncRNA as an example, lncRNA can act as a molecular sponge to absorb miRNAs, competitively inhibiting the expression of miRNAs and thereby relieving the inhibition on downstream target gene mRNAs.[17] LncRNA affects the expression of downstream target genes (such as IL-1β, IL-6) by binding to pro-inflammatory or anti-inflammatory miRNAs, regulating the inflammatory response.[18] It also affects alveolar bone destruction through the miRNA-Osteoclast signaling axis (such as the RANKL/OPG pathway) and regulates bone resorption.[19] During the development of periodontitis, many lncRNAs are dysregulated. Some differentially expressed lncRNAs have been proven to be related to many key aspects of periodontitis progression.[20] Studies have shown that ceRNAs also play important roles in the occurrence and development of periodontitis.[21–24] Zhou Mi et al reported that long noncoding RNA 01126 promotes the pathogenesis of periodontitis in human PDLCs through the miR-518a-5p/HIF-1α/MAPK pathway,[25] and Chen Hong et al reported that long noncoding RNA FGD5-AS1 affects the occurrence of periodontitis by regulating the miR-142-3p/SOCS6/NF-κB pathway.[26] The regulatory mechanism of lncRNAs in periodontitis is not yet known and will need to require further exploration.

Currently, high-throughput sequencing is developing rapidly, aiding in discovering key lncRNAs.[27] We conducted whole-transcriptome sequencing on gingival tissues and revealed that the lncRNA AC114812 was differentially expressed in periodontitis. The lncRNA AC114812 is stably expressed in mammals and has a full length of 663 bp, contains two exons, and is located on chromosome 2 and it is a verified antisense lncRNA.[28] Through the association of genomic loci and the co-expression relationship between lncRNAs and mRNAs, it may have a certain association with the UDP-glucuronosyltransferase 1A family (UGT1As). In inflammation, there are significant differences in the expression of UGT1As, and their expression and function may be closely related to the inflammatory response.[29] Therefore, lncRNA AC114812 may have played an important regulatory role in periodontitis. This study revealed that the lncRNA AC114812 was differentially expressed in periodontitis. By exploring its effects on inflammation and the proliferation and migration ability of PDLCs, as well as the possible ceRNA regulatory mechanism, new strategies for the prevention and treatment of periodontitis are provided.

Methods

Gingival Biopsy Collection

Human gingival tissues were obtained from patients with periodontitis (n = 13) and from healthy controls who received gingivectomy or crown lengthening during orthodontic or prosthodontic treatment (n = 13) at the Department of Periodontology of Hebei Medical University. All patients who provided samples provided with informed consent were included, and the collected samples were immediately frozen separately at −150°C. Gingival tissues fromcoronal to the gingival margin (2–4mm) of patients who needed periodontal surgery and were treated at the Stomatological Hospital of Hebei Medical University from January 2022 to August 2023 were collected. Gingival tissues from 13 pairs of patients with healthy and chronic periodontitis were collected. The general conditions of patients with healthy and chronic periodontitis were included. The age of the healthy gingiva group was (35.23 ± 6.11) years, including 5 males and 8 females; the age of the chronic periodontitis group was (40.38 ± 6.01) years, including 7 males and 6 females. There was no statistical significance, and the interference of gender and age on the experimental results was excluded. The inclusion criteria were as follows: ① Good health and no systemic diseases (such as diabetes, heart disease, etc).; ② No bad habits (such as smoking, etc).; ③ No antibiotics were taken in the past six months. The standard for healthy periodontium was

no gingival inflammation, no bleeding on probing, and probing depth ≤ 3 mm, but requiring periodontal aesthetic surgery or crown lengthening surgery. The standard for chronic periodontitis was diagnosed as moderate to severe chronic periodontitis, and after basic treatment, the periodontal probing was still ≥ 5 mm, requiring periodontal surgery.

Whole-Transcriptome Sequencing Analysis

Three pairs of gingival tissues from healthy individuals and patients with periodontitis were selected. Total RNA was extracted, and a strand-specific library was constructed via rRNA depletion. After quality control of the library, sequencing was performed via an Illumina NovaSeq™ 6000, with a sequencing read length of 2*150 bp (PE150). Sequencing was completed by Hangzhou Lianchuan Biotechnology Co., Ltd.

Bioinformatics analysis was conducted to explore the mechanism of action of the lncRNA AC114812. The miRanda 3.3a (http://www.bioinformatics.com.cn/local_miranda_miRNA_target_pred-iction_120) and TargetScan databases (https://www.targetscan.org/vert_61/) were used to predict the targets of the miRNA candidates.

Total RNA Extraction, cDNA Synthesis, and qRT-PCR

Total RNA was extracted from cultured tissues or cells via TRIZOL reagent (Beyotime, Shanghai, China) according to the manufacturer's instructions. cDNA was synthesized from 1 µg of total RNA via a cDNA reverse transcription kit (Thermo Fisher Scientific, Waltham, Massachusetts, USA). qRT-PCR was performed via SYBR Green Master Mix (Takara Biomedical Technology, Kusatsu, Japan) on a QuantStudio 5 Real-time PCR instrument (Thermo Fisher Scientific, Waltham, Massachusetts, USA). The thermal settings were as follows: 95°C for 30s, 95°C for 5 s for 40 cycles, and 60°C for 34s for 40 cycles. The average value of the housekeeping gene GAPDH was used as the internal reference for mRNA, and the small nuclear RNA U6 was used as the internal control for miRNA. Three qRT-PCRs were performed. Table 1 lists the primers used in the experiment, and the results were analyzed via the $2^{-\Delta\Delta Ct}$ relative expression method.

Cell Culture and Model Construction

Healthy individuals aged 14–29 years who visited the Department of Oral and Maxillofacial Surgery of Hebei Medical University were recruited. The periodontal ligament tissues around the extracted impacted wisdom teeth or orthodontic teeth were collected as the primary cell culture source of PDLCs. The primary cells were cultured in T25 flasks containing high-glucose DMEM (Gibco, San Diego, California, USA), 10% fetal bovine serum (viva cell, Shanghai, China), and 1% double antibody (viva cell, Shanghai, China) at 37°C and 5% CO_2. Cells from the P3 to P5 generations were used for subsequent experiments (Figure S1) The cell source was identified by immunocytochemical staining, and the results were determined by Servicebio (Wuhan, China) (Figure S2). LPS (InvivoGen, San Diego, California, USA) was used to stimulate PDLCs and establish an in vitro inflammatory environment (Figure S3).

Table 1 Primer Sequences

Gene name	Forward Primer	Reverse Primer
GAPDH	CAGGAGGCATTGCTGATGAT	GAAGGCTGGGGCTCATTT
U6	GCTTCGGCAGCACATATACTAAAAT	CGCTTCACGAATTTGCGTGTCAT
IL-6	TTCGGTCCAGTTGCCTTCTCC	TCTGAAGAGGTGAGTGGCTGTC
IL-1β	ATGGCTTATTACAGTGGCAATGAGG	AGTGGTGGTCGGAGATTCGTAG
lncRNA AC114812	TGGGCTTCTGCTGAATGTATGC	GGTGATCCTGGCTGAGTATTTGG
miR-181a-5p	AACATTCAACGCTGTCGGTGAGTAA	GTGCAGGGTCCGAGGT
SPP1	AATGCTGTGTCCTCTGAAGAAACC	AGTCAATGGAGTCCTGGCTGTC
si-NC	UUCUCCGAACGUGUCACGUTT	ACGUGACACGUUCGGAGAATT
si-AC114812	ACAGAAAGUAAAAACCUAGCU	CUAGGUUUUUACUUUCUGUAG
mimic miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	UCACCGACAGCGUUGAAUGUUUU

Plasmid Construction and Extraction

The plasmid was constructed in the vector pmirGLO at Xi'an GeneCarer, China, Ltd. and purified via the TianGen Plasmid Mini Kit (TianGen, Beijing, China). The plasmid was purified and amplified according to the manufacturer's protocol.

Cell Transfection

The small interfering RNA (si-AC114812) and siRNA control (si-NC) were designed by Xi'an GeneCarer, China, Ltd., and the mimic NC and mimic miR-181a-5p were designed by Sangon Biotech (Shanghai, China). According to the manufacturer's protocol, when the cells reached 70%~80% confluence, 100 nM Lipofectamine 3000 (Invitrogen, Carlsbad, California, USA) was used to transfect si-NC and si-AC114812 into PDLCs to construct knockdown models. The purified plasmid was cotransfected with a miR-181a-5p mimic or nc mimic into PDLCs.

MTT Assay

PDLCs were seeded in 96-well plates (1×10^4 cells/well). After various treatments, 5 mg/mL MTT solution (Solarbio, Beijing, China) was added to each well at the designated time point and then incubated at 37°C for 4 h. Afterward, 200 µL of dimethyl sulfoxide solution (Sigma, St. Louis, Missouri, USA) was added to dissolve the reaction product formazan. The optical density was measured at 570 nm via a microplate reader (Bio-Tek PowerWaveXS2).

Wound Healing Experiment

PDLCs were seeded at a density of 2.0×10^5 in each well of a 6-well plate. A scratch was made along the diameter of the cell layer via a 100 µL pipette tip. The wells were washed with PBS, and the medium was replaced with serum-free medium. Images were captured via a microscope (Olympus, Tokyo, Japan) at a magnification of 40× at the specified time. The relative area of the wound was calculated via Image-Pro v1.49.

FISH Assay

The probes for lncRNA AC114812, U6, and GAPDH for RNA FISH were purchased from Servicebio, China, Ltd. Cells were seeded onto slides. The cells were fixed in 4% paraformaldehyde for 15 minutes and treated with 0.1% Triton X-100 for 10 minutes to increase cell permeability. After three washes, the cells were incubated with the prehybridization solution for 60 minutes and then incubated with the hybridization solution containing the lncRNA AC114812 probe overnight at 37°C. After washing, the cells were stained with DAPI, and images were captured via a confocal imaging system (Nikon upright fluorescence microscope, Tokyo, Japan).

Preparation of Cytoplasmic and Nuclear Components

A Cell Cytoplasm and Nucleus Isolation Kit (Thermo Fisher Scientific, Waltham, Massachusetts, USA) was used to collect cytoplasmic and nuclear RNA from PDLCs according to the kit manual. GAPDH was used as the internal control for the cytoplasm, and U6 was used as the internal control for the detection of the nucleus.

Dual-Luciferase Gene Reporter Assay

One nanogram of plasmid was transfected together with 100 nM NC mimic or miR-181a-5p mimic into cells via Lipofectamine 3000. Twenty-four hours after transfection, the Renilla and firefly luciferase activities were measured via the Dual-Luciferase Reporter Assay System (Beyotime, Shanghai, China) according to the manufacturer's instructions. The light intensity of Renilla luciferase was standardized to that of firefly luciferase and expressed as a multiple of induction relative to the basal activity.

Statistical Analysis

The data were analyzed via SPSS 27 statistical software. Statistical significance was set at $P < 0.05$. One-way analysis of variance or *t* tests were used to determine statistical significance. All the assays were independently performed three times.

Results

Abnormal Expression of lncRNAs in Periodontitis

By analyzing the sequencing data, abnormally expressed lncRNAs were obtained. From the 3 pairs of samples, normalization processing was carried out for the two groups of samples via FPKM values, and differential lncRNAs were screened based on the criteria of $P < 0.05$ and $\log_2$(fold change) > 1 or $\log_2$(fold change) < −1. A total of 685 differentially expressed lncRNAs were obtained under the screening conditions, among which 230 were upregulated and 455 were downregulated (Figure 1). Through the Pearson correlation coefficient and free energy value, potential target genes of lncRNAs were predicted. A total of 58,825 potential target genes were obtained, among which 60 differentially expressed target genes with $P < 0.05$ and $\log_2$(fold change) > 1 or $\log_2$(fold change) < −1 were obtained as the threshold. Nine lncRNAs that were differentially expressed and were identified via interaction analysis with mRNAs were also screened out (Figure 2). Among them, the expression of the lncRNA AC114812 was the most significantly different ($\log_2$FC = 12.96).

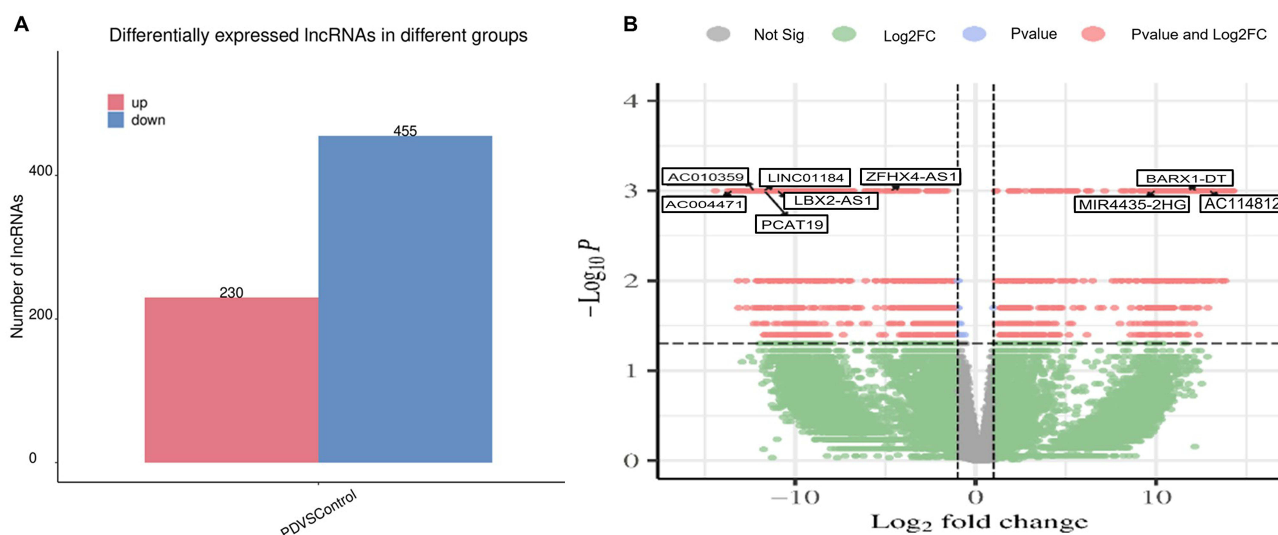

Figure 1 Abnormal expression of lncRNAs in periodontitis.(**A**). The expression trends of differentially expressed lncRNAs. (**B**). The volcano plot was drawn to clearly show the differentially expressed lncRNAs.

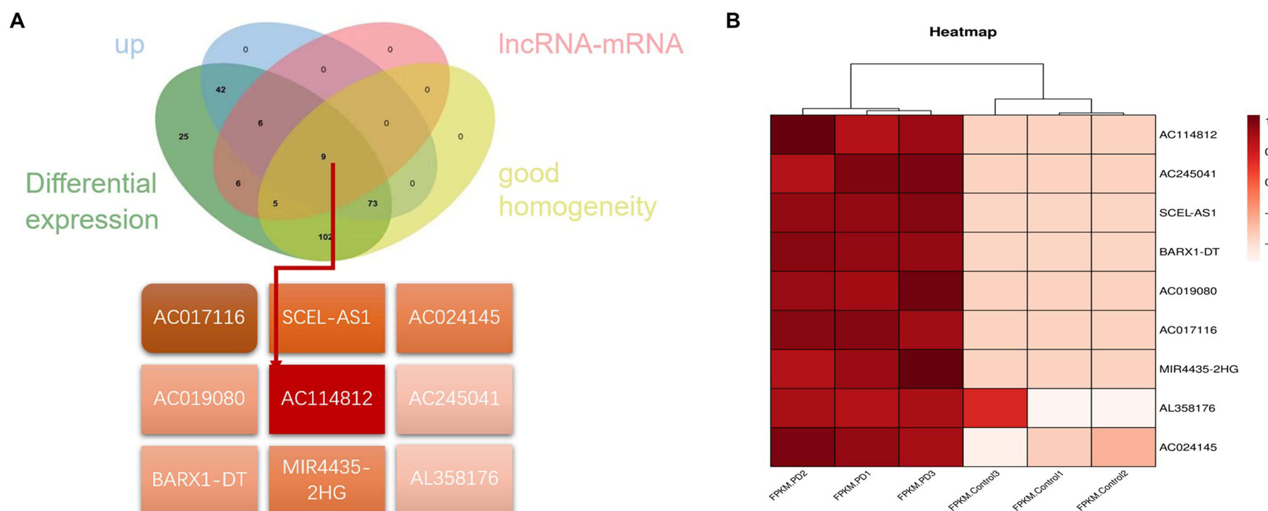

Figure 2 Screening of lncRNAs (**A**). Venn diagram shows the lncRNAs that are differentially expressed and upregulated, which were selected together with 9 lncRNAs that interact with mRNAs for analysis. (**B**). Clustering heatmaps shows that the expression of the lncRNA AC114812 was the most significantly different among the 9 lncRNAs.

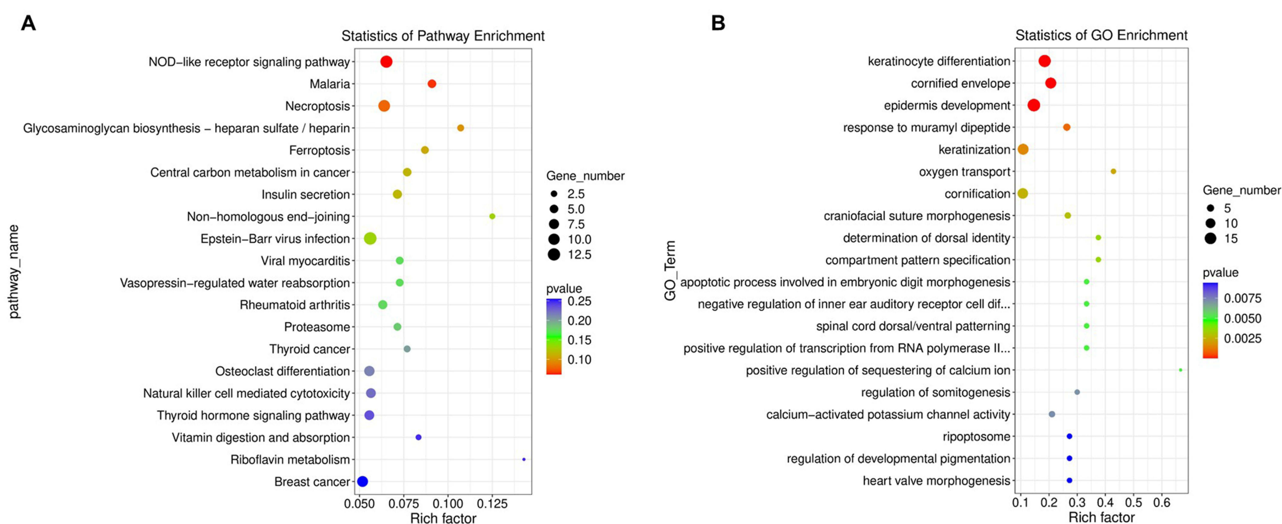

Figure 3 Functional enrichment analysis of lncRNA in periodontitis (**A**). KEGG analysis diagram of lncRNAs with differential expression; (**B**). GO analysis diagram of lncRNAs with differential expression.

The KEGG enrichment analysis results revealed that a total of 253 pathways and related diseases were enriched, among which the most significantly enriched terms related to our study are as follows (Figures 3A): the NOD-like receptor signaling pathway, malaria, necroptosis, ferroptosis, rheumatoid arthritis, cancer, etc. Current studies have confirmed their correlations with periodontitis.[30–35]The GO analysis results indicated that the target genes of the significantly differentially expressed lncRNAs were enriched in a total of 2475 biological processes, 451 cellular components, and 644 molecular functions; among them, 141 biological processes, 14 cellular components, and 35 molecular functions were significantly enriched ($p < 0.05$). The most significantly enriched terms related to our study are shown (Figures 3B) and include functions such as keratinocyte differentiation, oxygen transport, and calcium-activated potassium channel activity. Current studies have confirmed their correlations with periodontitis.[36–38] In conclusion, based on the sequencing results and abnormal expression in periodontal tissues, we hypothesized that the lncRNA AC114812 is highly correlated with the pathogenesis of periodontitis and further verified its role in the pathogenesis of periodontitis. Through qRT-PCR, the expression of the lncRNA AC114812 in gingival samples from patients with periodontitis (n = 10) and healthy controls (n = 10) was compared. At the same time, the genes with differential expressions identified in the sequencing data were randomly selected for further verification of the reliability of the sequencing data. The results showed that their expression levels were consistent with the sequencing results (Figure S4). The expression of the lncRNA AC114812 was significantly increased in the periodontitis group (Figure 4A), further verifying this speculation.

LncRNA AC114812 Affects PDLCs Under Inflammatory Conditions

A periodontal ligament cell model of periodontitis was constructed via the use of LPS from Porphyromonas gingivalis (P. g) to simulate PDLCs in a periodontitis environment. After 12 h of stimulation with 1 μg/mL LPS, the expression of inflammatory factors and the lncRNA AC114812 were detected. The results revealed that LPS promoted the expression of inflammatory factors, including IL-6 and IL-1β (Figures 4C andD), and that the expression of the lncRNA AC114812 was upregulated in PDLCs under inflammatory conditions (Figure 4B).

To further determine the role of the lncRNA AC114812 in periodontitis, a knockdown model of the lncRNA AC114812 was constructed by using a siRNA to knockdown the lncRNA AC114812. The transduction efficiency of PDLCs was greater than 75% (Figure 4E). The qRT-PCR results were used to confirm the transfection effect in PDLCs. After lncRNA AC114812 was knocked down, 12 h of LPS inflammatory stimulation was performed. There was no significant difference in the expression levels of IL-6 and IL-1β after the knockdown lncRNA AC114812. We found that the expression levels of IL-6 and IL-1β were lower than those in the group without lncRNA AC114812 knockdown subjected to LPS inflammatory stimulation (Figures 4F–I). Knocking down lncRNA AC114812 resulted in a significant

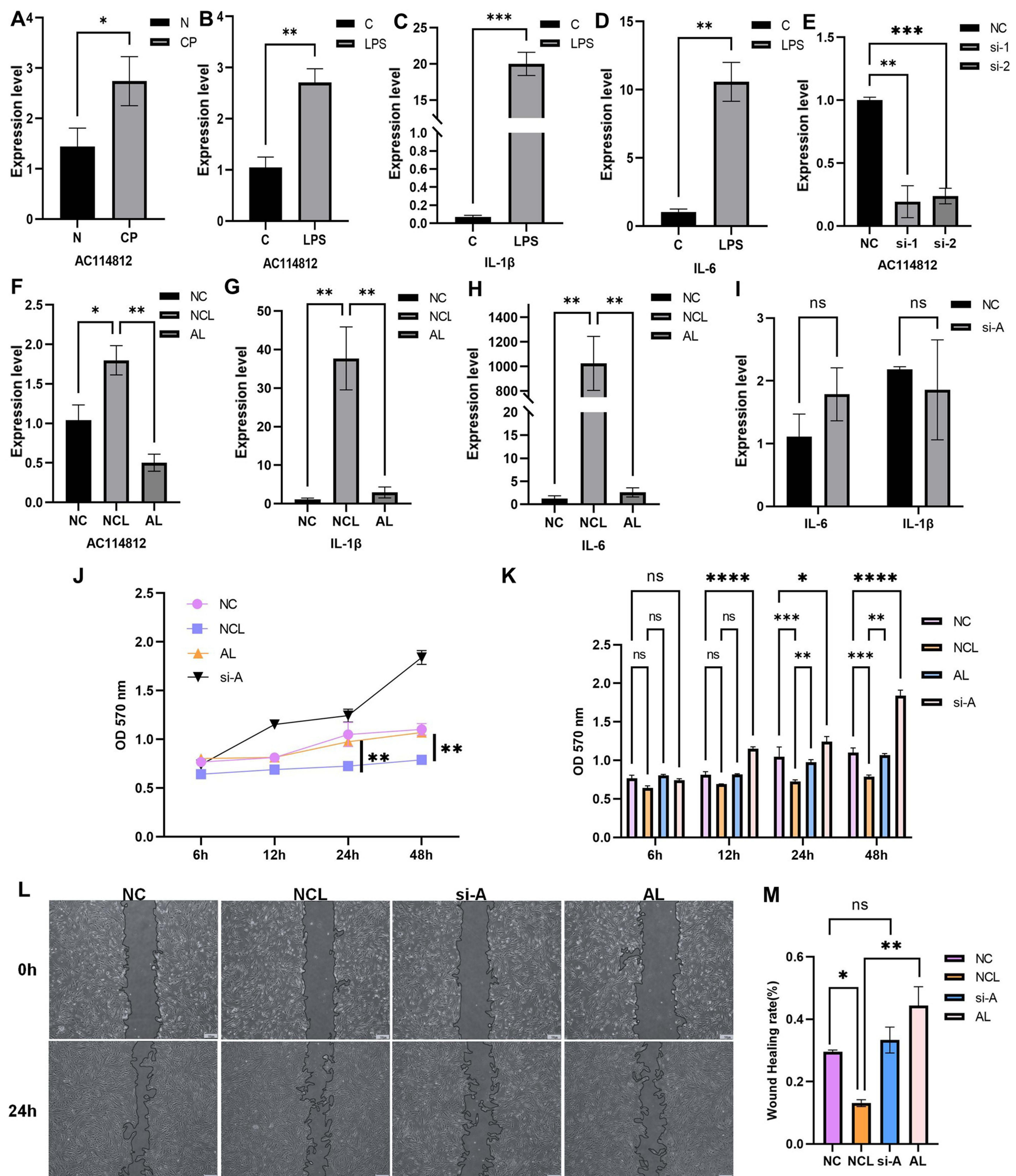

Figure 4 The role played by regulating lncRNA AC114812 expression under inflammatory conditions **(A)**. Verification results of lncRNA AC114812 expression levels in gingival tissues: N represents the healthy control group; CP represents the chronic periodontitis patient group. The CP group was approximately 1.90 times higher than the N group (P = 0.0468). (**B–D**). Verification results of lncRNA AC114812, IL-6, and IL-1β expression levels in PDLCs under inflammatory conditions. C represents the control group; LPS represents the periodontitis modeling group. lncRNA AC114812: LPS group was approximately 2.59 times higher than the C group (P = 0.0076). IL-1β: LPS group was approximately 280.33 times higher than the C group (*P* = 0.0002). IL-6: LPS group was approximately 10.11 times higher than the C group (P = 0.0027). (**E**). Two si-AC114812 constructs, si-1 and si-2, were constructed. The knockdown efficiency was verified via qRT-PCR. The transduction efficiency of si-1 group was approximately 80.67% (P = 0.0033). The transduction efficiency of si-2 group was approximately76.20% (P = 0.0003). For subsequent experiments, si-1 was selected. (**F–I)** qRT-PCR was used to verify the expression levels of the lncRNA AC114812, IL-6, and IL-1β. NC represents the control group, NCL represents the NC + LPS group, si-A represents the si-AC114812 group and AL represents the si-AC114812 + LPS group. lncRNA AC114812:NCL group was approximately 1.73 times higher than NC group (P = 0.0415). AL group was approximately 3.57 times lower than NCL group (P = 0.0036). IL-1β: NCL group was approximately 33.06 times higher than NC group (P = 0.0040). AL group was approximately 12.82 times lower than NCL group (P = 0.0051). IL-6: NCL group was approximately 805.18 times higher than NC group (P = 0.0030). AL group was approximately 394.38 times lower than NCL group (P = 0.0030). Compared with si-A group, there was no statistically significant difference in the expression levels of IL-1β and IL-6 in the NC group. (**J** and **K**). The MTT assay results show the cell proliferation status of the three groups at 6 h, 12 h, 24 h, and 48 h. (**L** and **M**). Wound healing assay results showing the migration ability of the three groups at 24 h.The results are presented as the means ± standard deviations. The scale is 500 μm. (ns p >0.05, *p <0.05, **p <0.01, ***p <0.001, ****p <0.0001).

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increase in cell survival rate and enhanced proliferation ability 12 hours later. By observing the proliferation of PDLCs at 24 h under LPS stimulation, we found that under inflammatory conditions, the survival rate of cells that had the lncRNA AC114812 knocked down was higher compared to those without the knockdown. (Figures 4J and K). At 24 h, the migration rate of the cells was observed. Compared with LPS stimulation alone, the knockdown of lncRNA AC114812 significantly increased the migration rate (Figures 4L and M). These data indicate that PDLCs with knocked down lncRNA AC114812 can significantly resist the increase in inflammatory levels caused by LPS and can also improve the inhibition of cells caused by LPS and reduce the migration rate.

The lncRNA AC114812-miR-181a-5p-SPP1 Axis May Play a Role in Periodontitis

FISH and nuclear-cytoplasmic separation experiments confirmed that the lncRNA AC114812 was expressed mainly in the cytoplasm (Figures 5A and B). We hypothesized that the lncRNA AC114812 mightact as a ceRNA by binding to miRNAs and further competing with mRNAs. Using the databases miRanda 3.3a (https://www.bioinformatics.com.cn/local_miranda_miRNA_target_prediction_120) and TargetScan databases (https://www.targetscan.org/vert_61/) (Figures 5C and D). miR-181a-5p is a downstream candidate target of the lncRNA AC114812, and its expression is different in periodontitis, with a decrease; SPP1 is a downstream candidate target of miR-181a-5p, and its expression is different in periodontitis, with an increase. Through qRT-PCR, the expression levels of miR-181a-5p and SPP1 at the tissue and cellular levels were confirmed to be consistent with the predicted results (Figures 6A–D).

lncRNAs AC114812, miR-181a-5p and SPP1 Have Binding Sites

We constructed luciferase reporter constructs containing the wild-type (AC114812-WT) or mutant (AC114812-MUT) target sites of the lncRNA AC114812 to further determine whether miR-181a-5p could bind to the lncRNA AC114812. The overexpression of miR-181a-5p in PDLCs significantly inhibited the activity of the AC114812-WT reporter construction, whereas the AC114812-MUT reporter construction was unaffected (Figures 7A–C). We subsequently constructed luciferase reporter constructs containing the wild-type (SPP1-WT) or mutant (SPP1-MUT) target sites of SPP1 to further determine whether miR-181a-5p could bind to SPP1. The results revealed that the overexpression of miR-181a-5p in PDLCs significantly inhibited the activity of the SPP1-WT reporter construct, whereas the SPP1-MUT reporter construction was unaffected (Figures 7A–D). Additionally, the qRT-PCR results confirmed the ability of the miR-181a-5p mimics to transfect PDLCs (Figure 7B).

Discussion

With the rapid development of high-throughput sequencing, current sequencing technology has become increasingly mature. By conducting whole transcriptome sequencing and database analysis to identify the differential expression of lncRNAs in periodontitis patients and healthy individuals, and combining related pathway and functional enrichment analysis, the role and regulatory pathways of lncRNAs in the pathogenesis of periodontitis have been explored. This has advanced research on periodontitis and provided a new strategy for precise diagnosis and targeted treatment.

In this study, to explore the regulatory role of lncRNAs in periodontitis, the characteristics of lncRNAs in three pairs of gingival tissues from periodontitis patients and healthy controls were investigated through lncRNA whole-transcriptome analysis. We focused on the lncRNA AC114812, which is abnormally expressed, upregulated, highly uniform, and interacts with mRNAs, to further verify its role in periodontitis. At present, there are very few studies on lncRNA AC114812 in the field of periodontitis. However, the mRNA that interacted with lncRNA AC114812 and was screened from the sequencing data includes UGT1A1, UGT1A6, UGT1A7, etc. These mRNAs belong to the family of glucuronosyltransferase members A and their gene loci. The KEGG and GO analyses revealed that they have related functions with steroid hormones and drug metabolism. Gingival tissues are among the target organs of steroid hormones, and steroid hormones play important roles in inflammation, immunity, and bone metabolism.[39,40] Therefore, exploring the regulatory role of the lncRNA AC114812 in periodontitis is important, as it may be involved in the regulation of inflammation and bone remodeling in periodontitis.

The results revealed that the lncRNA AC114812 was highly expressed in the gingival tissues of periodontitis patients. The results of in vitro experiments indicated that the knockdown of lncRNA AC114812 in PDLCs significantly improved

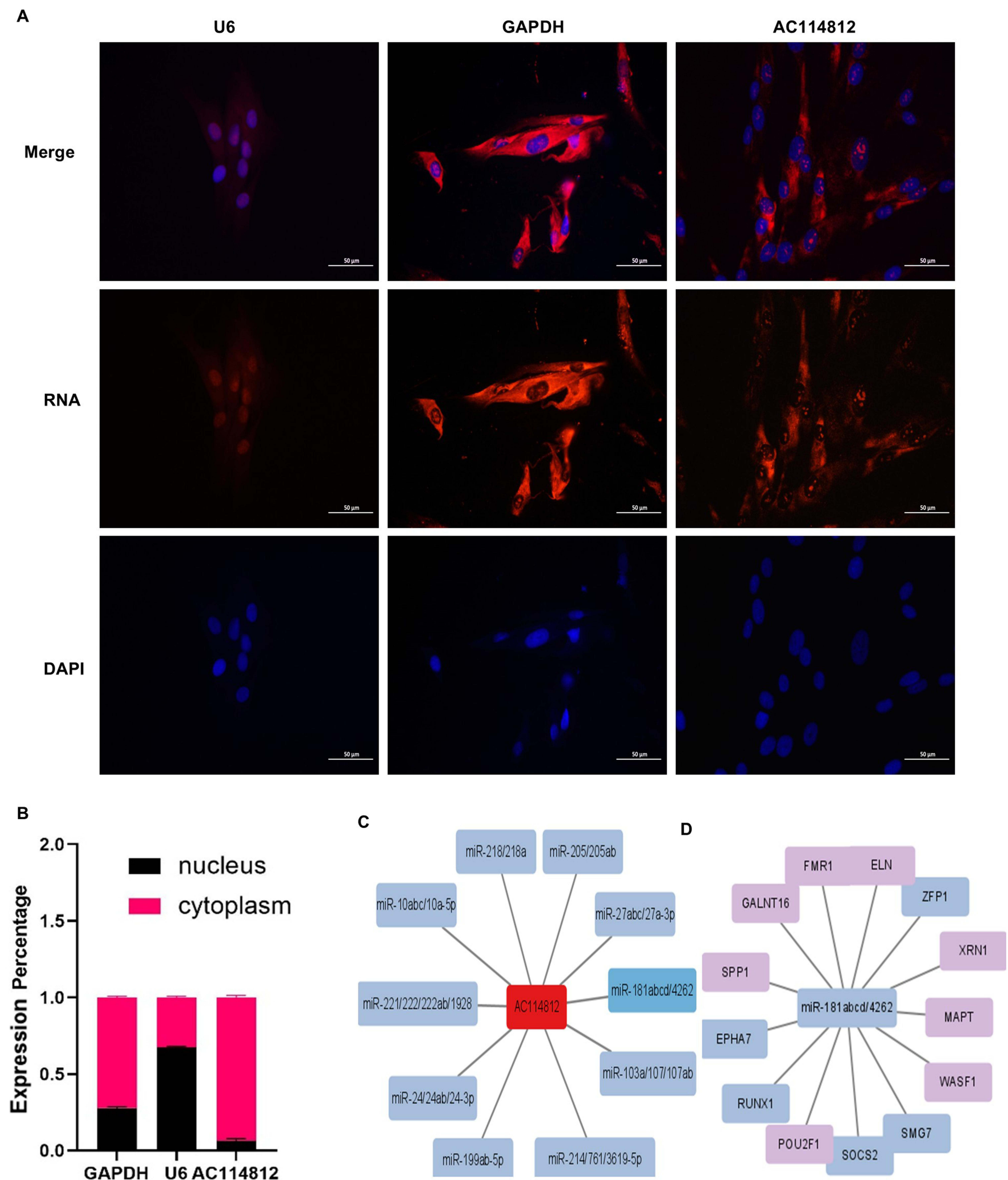

Figure 5 lncRNA AC114812-miR-181a-5p-SPP1 axis may play a role in periodontitis. (**A**). FISH experiment: U6 is the nuclear reference, GAPDH is the cytoplasmic reference, DAPI is blue, and the probe is red; (**B**). qRT-PCR results after the nuclear-cytoplasmic separation experiment; pink represents the cytoplasmic proportion, black represents the nuclear proportion; (**C**). miRNAs with binding sites for lncRNA AC114812 screened from the database, with a final focus on miR-181a-5p; (**D**). Downstream target genes of miR-181a-5p screened from the database compared with sequencing data, with a focus on SPP1.

the proliferation inhibition and elevated inflammatory levels caused by inflammation. For the treatment of periodontitis, maintaining the active proliferation ability and anti-inflammatory and anti-inflammatory effects of PDLCs is crucial.[41] In the pathogenesis of periodontitis, IL-1β and IL-6 act as key pro-inflammatory cytokines, constituting the core molecular

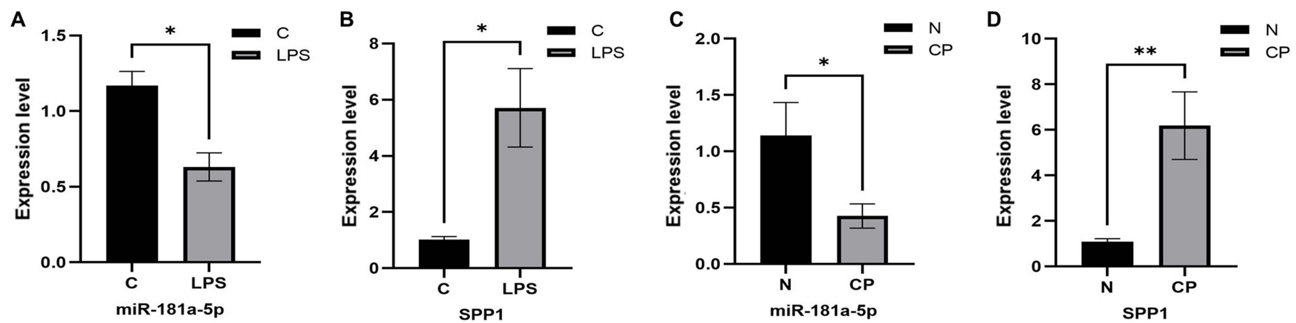

Figure 6 miR-181a-5p and SPP1 expression levels in periodontitis.(**A** and **B**). qRT-PCR verification of miR-181a-5p and SPP1 expression levels in PDLCs; miR-181a-5p: LPS group was approximately 1.85 times lower than the C group (P = 0.0148). SPP1: LPS group was approximately 5.63 times lower than the C group (P = 0.0285). (**C** and **D**). qRT-PCR verification of miR-181a-5p and SPP1 expression levels in tissues. miR-181a-5p: The CP group was approximately 2.67 times lower than the N group (P = 0.0371). SPP1: The CP group was approximately 5.67 times higher than the N group (P = 0.0030). The results are expressed as the means ± standard deviations (**p* <0.05, ***p* <0.01).

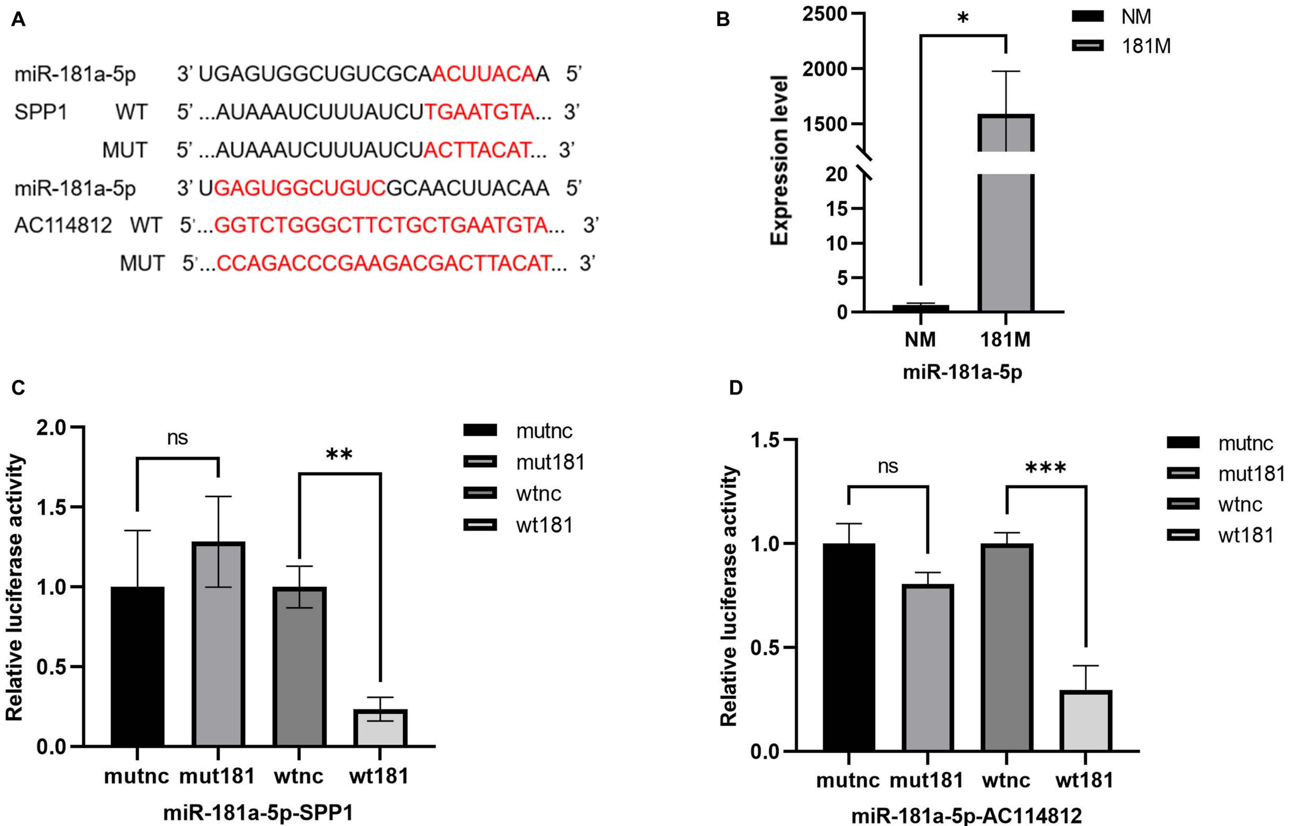

Figure 7 There are binding sites among the lncRNAs AC114812-miR-181a-5p and SPP1. (**A**). Wildtype and mutant plasmids were constructed based on the predicted sites according to the design. The red highlighted positions represent the binding sites of miR-181a-5p with the wild type and the mutated base sites in the mutant type. (**B**). A miR-181a-5p mimic was constructed and verified via qRT-PCR; The 181M group was approximately1494.37 times higher than NM group (P = 0.0143). (**C** and **D**). The results of dual-luciferase gene reporter assays. The results are presented as the means ± standard deviations (ns p >0.05, *p < 0.05, **p < 0.01, ***p < 0.001).

basis for the destruction of periodontal tissues.[42] When pathogenic microorganisms (such as P.g) and their toxic components (such as LPS) in the plaque biofilm invade the gingival tissue, they activate the pattern recognition receptors of the host immune system, triggering a series of intracellular signaling pathways, ultimately leading to excessive production of pro-inflammatory cytokines.[43,44] IL-1β and IL-6 not only serve as key effector molecules in the pathological process of periodontitis, but their detection concentrations also become important biomarkers for disease diagnosis, activity assessment, and prognosis judgment.[45] Compared to traditional clinical indicators (such as probing depth and bleeding index), these molecular markers can provide more objective and earlier disease information. The

research results in this study found that simply knocking down lncRNA AC114812 had no significant change migration rate and in inflammatory factors IL-1β and IL-6, but had a significant effect on cell proliferation. This phenomenon might be due to the fact that knocking down the gene may have inhibited the signaling pathways necessary for cell migration, but it did not affect or even promoted the cell's proliferation ability. The cells proliferated abundantly near the scratch edge, but because of the impaired migration ability, they were unable to effectively fill the blank area of the scratch.[46] Interestingly, knocking down lncRNA AC114812 in LPS-stimulated periodontal ligament cells could significantly improve proliferation inhibition caused by inflammation and the increase in inflammatory factors IL-1β and IL-6 levels. Knocking down lncRNA AC114812 can reduce the expression of inflammatory factors, enhance proliferation to resist proliferation inhibition caused by inflammation and the migration rate inhibited by inflammation. This phenomenon is speculated to be related to non-classical inflammatory pathways.[47] The lncRNA AC114812, as an inflammation-related gene, may affect cell proliferation and migration in a resting state through non-inflammatory pathways, without relying on cytokine secretion. It triggers a feedback compensatory mechanism, and after knocking down lncRNA AC114812, other pathways (such as growth factor receptor signaling) are compensatory activated, but do not reach the threshold to trigger an inflammatory response.[48] Thus, it avoids the imbalance of the basal homeostasis. The results indicate that lncRNA AC114812 is expected to become a new target for the treatment of periodontitis, providing a new idea for the treatment of periodontitis.

The localization of lncRNA is related to its functional expression. In the nucleus, it mainly plays roles in epigenetic regulation, transcriptional regulation, etc. While in the cytoplasm, it mainly regulates the stability and translation of mRNA, including the ceRNA mechanism and direct binding to mRNA.[49] In this study, through FISH and nuclear-cytoplasm separation experiments, it was found that lncRNA AC114812 is in the cytoplasm of periodontal ligament cells. We hypothesize that lncRNA AC114812 may function as a sponge for miRNA, and further explore its sponge effect.

Through database and sequencing data, it was predicted that the lncRNA AC114812 has binding sites for miR-181a-5p. It has been reported that miR-181a-5p is bound by multiple noncoding RNAs and is a potential biomarker in periodontitis. Its expression level in periodontitis is not exact, but it is closely related to the inflammatory response.[50–57] Recent studies have shown that miR-181a-5p plays a role in periodontitis through its ability to sponge lncRNAs. The lncRNA SPIRE1 is involved in the JAK/STAT17 pathway in mandibular bone marrow mesenchymal stem cells and regulates the Th3/Treg immune balance in periodontitis through the SPIRE1-miR-181a-5p/PRLR axis, and miR-181a-5p regulates the expression of PRLR, thereby affecting the activity of the JAK/STAT3 signaling pathway and ultimately regulating the Th17/Treg balance, thereby influencing the inflammatory response in periodontitis.[52] In this study, we verified that miR-181a-5p was downregulated in periodontitis and that the lncRNA AC114812 might negatively regulate the expression of miR-181a-5p. This finding was further confirmed by a dual-luciferase gene reporter assay.

SPP1 is the gene encoding osteopontin (OPN), also known as secreted phosphoprotein 1. The protein encoded by this gene participates in the attachment of osteoclasts to the mineralized bone matrix, which is a key step in bone resorption. The encoded protein is secreted and binds to hydroxyapatite with high affinity. The osteopontin receptor is present on the cell membrane and may participate in binding with this protein. This protein is also a cytokine that can upregulate the expression of interferon-γ and interleukin-12, thereby promoting the occurrence of inflammation.[58,59] Moreover, the expression and localization of this protein in alveolar bone are obvious, and it regulates the development and mineralization of alveolar bone[60–62] In this study, through database prediction, it was predicted that miR-181a-5p might have binding sites with SPP1 and that there might be a targeting relationship between them. Many studies have shown that miR-181a-5p targets multiple bone-related genes downstream,[63] such as miR-181a-5p, which targets DDX3X through the NF-κB signaling pathway to inhibit the progression of osteoarthritis. CircPVT1 is upregulated by regulating the Smad7/TGFβ signaling pathway via miR-21-5p to alleviate steroid-induced femoral head osteonecrosis, etc.[64,65] The upregulation of SPP1 in periodontitis was verified in gingival tissues and cells, and the possible targeting relationship was further confirmed via a dual-luciferase gene reporter assay. miR-181a-5p might negatively regulate the expression of SPP1. Thus, we concluded that the lncRNA AC114812 might regulate the occurrence and development of periodontitis through the miR-181a-5p/SPP1 axis and might play an important role in bone metabolism.

The ceRNA mechanism involves more than one molecule, and its dynamic changes can better reflect the immune status and bone metabolism imbalance of periodontitis.[66] It plays an important role in dynamic monitoring and

recurrence warning.[67] Exploring the role of the lncRNA AC114812-miR-181a-5p-SPP1 axis in periodontitis and jointly detecting gene changes can improve diagnostic accuracy and further significance for recurrence prediction.

The limitations of the study lie in the fact that only the binding sites of lncRNA AC114812/miR-181a-5p/SPP1 axis were verified. In the future, downstream target gene rescue experiments and experiments to verify the role of bone metabolism will be conducted to further prove the role of lncRNA AC114812 in periodontitis through the miR-181a-5p/SPP1 axis. The downstream targets of lncRNA AC114812 may not be limited to the miR-181a-5p/SPP1 axis, and further research is needed to explore other downstream targets of lncRNA AC114812 to better understand the role of lncRNA AC114812 in the pathogenesis of periodontitis. In addition, in further experiments, in vivo studies should be conducted to verify the results of in vitro studies. At the same time, the whole transcriptome sequencing only used 3 pairs of samples, which may lead to a high false positive rate in the screening of differentially expressed genes. The subsequent verification experiments were expanded to 10 pairs, but the statistical power was still limited, and there were certain limitations in the verification of the expression level of this gene. The results of this study indicate that knocking down lncRNA AC114812 can improve the inflammatory level induced by lipopolysaccharide and inhibit the proliferation of periodontal ligament cells in chronic periodontitis. Mechanistically, the lncRNA AC114812/miR-181a-5p/SPP1 axis may provide a basis for periodontal treatment based on lncRNA AC114812.

Conclusion

By regulating the expression of long non-coding RNA AC114812, the inflammatory response can be alleviated, thereby affecting cell proliferation and migration. This effect may be achieved through the miR-181a-5p-SPP1 axis. But more experiments are needed for further verification. These provide new strategies and intervention targets for the prevention and treatment of periodontal diseases.

Abbreviations

lncRNA, long non-coding RNA; qRT-PCR, reverse transcription quantitative polymerase chain reaction; LPS, lipopolysaccharide; ceRNAs, lncRNA-miRNA-mRNAs; FISH, Fluorescence in situ hybridization; siRNA, Small interfering RNA; si-NC, siRNA Negative Control; PDLCs, Periodontal Ligament Cells; UGT1As, Uridine Diphosphate Glucuronosyltransferase 1A Subfamily; miRNA, MicroRNA; DMSO, Dimethyl sulfoxide; IL-1β, Interleukin-1β; IL-6, Interleukin-6; WT, wild type; Mut, mutation; P.g, Porphyromonas gingivalis; MTT, Methylthiazolyldiphenyl-tetrazolium bromide; OPN, Osteopontin.

Data Sharing Statement

All data are available in the main text or the extended data. The protocols and datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Human Ethics and Consent to Participate Declarations

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the School of Stomatology, Hebei Medical University. The ethical review number is [2024] 054.

Consent to Participate

The authors certify that they have obtained all appropriate patient consent forms. All patients agreed to participate in the scientific study and allowed their clinical information to be published in the journal.

The minor participants involved have obtained written informed consent from themselves and their parents/guardians.

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Disclosure

The authors declare that they have no competing interests.

References

1. Slots J. Periodontitis: facts, fallacies and the future. *Periodontol*. 2017;75(1):7–23. doi:10.1111/prd.12221
2. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nat Rev Immunol*. 2015;15(1):30–44. doi:10.1038/nri3785
3. Meyle J, Chapple I. Molecular aspects of the pathogenesis of periodontitis. *Periodontol*. 2000;69(1):7–17. doi:10.1111/prd.12104
4. Schaefer AS. Genetics of periodontitis: discovery, biology, and clinical impact. *Periodontol*. 2018;78(1):162–173. doi:10.1111/prd.12232
5. Sudhakar V, Richardson RM. Gene therapy for neurodegenerative diseases. *Neurotherapeutics*. 2019;16(1):166–175. doi:10.1007/s13311-018-00694-0
6. Culver KW, Blaese RM. Gene therapy for cancer. *Trends Genet*. 1994;10(5):174–178. doi:10.1016/0168-9525(94)90095-7
7. Coan M, Haefliger S, Ounzain S, Johnson R. Targeting and engineering long nonnon-coding RNAs for cancer therapy. *Nat Rev Genet*. 2024;25(8):578–595. doi:10.1038/s41576-024-00693-2
8. Ishikawa K, Weber T, Hajjar RJ. Human cardiac gene therapy. *Circ Res*. 2018;123(5):601–613. doi:10.1161/CIRCRESAHA.118.311587
9. Barzel A, Flotte TR. New horizons for immune gene therapy. *Hum Gene Ther*. 2019;30(4):379–380. doi:10.1089/hum.2019.29085.aba
10. Xu X, Lang GP, Chen ZL, Wang JL, Han YY. The dual role of non-coding RNAs in the development of periodontitis. *Biomed Environ Sci*. 2023;36(8):743–755. doi:10.3967/bes2023.079
11. Wu Z, Liu X, Liu L, et al. Regulation of lncRNA expression. *Cell Mol Biol Lett*. 2014;19(4):561–575. doi:10.2478/s11658-014-0212-6
12. Ferrer J, Dimitrova N. Transcription regulation by long non-coding RNAs: mechanisms and disease relevance. *Nat Rev Mol Cell Biol*. 2024;25(5):396–415. doi:10.1038/s41580-023-00694-9
13. Barczak W, Carr SM, Liu G, et al. Long non-coding RNA-derived peptides are immunogenic and drive a potent anti-tumour response. *Nat Commun*. 2023;14(1):1078. doi:10.1038/s41467-023-36826-0
14. Ashrafizadeh M, Zarrabi A, Mostafavi E, et al. Non-coding RNA-based regulation of inflammation. *Semin Immunol*. 2022;59:101606. doi:10.1016/j.smim.2022.101606
15. Xu H, Jiang Y, Xu X, et al. Inducible degradation of lncRNA Sros1 promotes IFN-γ-mediated activation of innate immune responses by stabilizing Stat1 mRNA. *Nat Immunol*. 2019;20(12):1621–1630. doi:10.1038/s41590-019-0542-7
16. Suzuki S, Yamada S. Epigenetics in susceptibility, progression, and diagnosis of periodontitis. *Jpn Dent Sci Rev*. 2022;58:183–192. doi:10.1016/j.jdsr.2022.06.001
17. Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition. *Nature*. 2014;505(7483):344–352. doi:10.1038/nature12986
18. Ma Y, Zhu Y, Shang L, et al. LncRNA XIST regulates breast cancer stem cells by activating proinflammatory IL-6/STAT3 signaling. *Oncogene*. 2023;42(18):1419–1437. doi:10.1038/s41388-023-02652-3
19. Liu J, Wang B, Chen H, Yu X, Cao X, Zhang H. Osteoclast-derived exosomes influence osteoblast differentiation in osteoporosis progression via the lncRNA AW011738/ miR-24-2-5p/ TREM1 axis. *Biomed Pharmacother*. 2024;178:117231. doi:10.1016/j.biopha.2024.117231
20. Zur Bruegge J, Einspanier R, Sharbati S. A long journey ahead: long non-coding RNAs in bacterial infections. *Front Cell Infect Microbiol*. 2017;7:95. doi:10.3389/fcimb.2017.00095
21. Ahmad I, Naqvi RA, Valverde A, Naqvi AR. LncRNA MALAT1/microRNA-30b axis regulates macrophage polarization and function. *Front Immunol*. 2023;14:1214810. doi:10.3389/fimmu.2023.1214810
22. Zhang X, Ren L, Yan X, et al. Identification of immune-related lncRNAs in periodontitis reveals regulation network of gene-lncRNA-pathway-immunocyte. *Int Immunopharmacol*. 2020;84:106600. doi:10.1016/j.intimp.2020.106600
23. Li J, Wang M, Song L, Wang X, Lai W, Jiang S. LncRNA MALAT1 regulates inflammatory cytokine production in LPS-stimulated human gingival fibroblasts through sponging miR-20a and activating TLR4 pathway. *J Periodontal Res*. 2020;55(2):182–190. doi:10.1111/jre.12700
24. Li J, Jin F, Cai M, Lin T, Wang X, Sun Y. LncRNA Nron inhibits bone resorption in periodontitis. *J Dent Res*. 2022;101(2):187–195. doi:10.1177/00220345211019689
25. Zhou M, Hu H, Han Y, et al. Long non-coding RNA 01126 promotes periodontitis pathogenesis of human periodontal ligament cells via miR-518a-5p/HIF-1α/MAPK pathway. *Cell Prolif*. 2021;54(1):e12957. doi:10.1111/cpr.12957
26. Chen H, Lan Z, Li Q, Li Y. Abnormal expression of long noncoding RNA FGD5-AS1 affects the development of periodontitis through regulating miR-142-3p/SOCS6/NF-κB pathway. *Artif Cell Nanomed B*. 2019;47(1):2098–2106.
27. Mattioli K, Volders PJ, Gerhardinger C, et al. High-throughput functional analysis of lncRNA core promoters elucidates rules governing tissue specificity. *Genome Res*. 2019;29(3):344–355. doi:10.1101/gr.242222.118
28. Li W, Li Y, Ma W, Zhou J, Sun Z, Yan X. Long noncoding RNA AC114812.8 promotes the progression of bladder cancer through miR-371b-5p/FUT4 axis. *Biomed Pharmacother*. 2020;121:109605. doi:10.1016/j.biopha.2019.109605
29. Shiu TY, Huang TY, Huang SM, et al. Nuclear factor κB down-regulates human UDP-glucuronosyltransferase 1A1: a novel mechanism involved in inflammation-associated hyperbilirubinaemia. *Biochem J*. 2013;449(3):761–770. doi:10.1042/BJ20121055
30. Zhao Y, Ye Q, Feng Y, et al. Guo Y. *Prevotella* genus and its related NOD-like receptor signaling pathway in young males with stage III periodontitis. *Front Microbiol*. 13:1049525. doi:10.3389/fmicb.2022.1049525
31. Khan S, Gupta ND. Acute gingival bleeding and falciparum malaria. *J Indian Soc Periodontol*. 2014;18(2):131. doi:10.4103/0972-124X.131297
32. Zhang K, Chen X, Zhou R, et al. Inhibition of gingival fibroblast necroptosis mediated by RIPK3/MLKL attenuates periodontitis. *J Clin Periodontol*. 2023;50(9):1264–1279. doi:10.1111/jcpe.13841
33. Bartold PM, Lopez-Oliva I. Periodontitis and rheumatoid arthritis: an update 2012-2017. *Periodontol*. 2020;83(1):189–212. doi:10.1111/prd.12300
34. Baima G, Minoli M, Michaud DS, et al. Periodontitis and risk of cancer: mechanistic evidence. *Periodontol*. 2024;96(1):83–94. doi:10.1111/prd.12540
35. Easter QT, Fernandes MB, Beldorati SG, et al. Single-cell and spatially resolved interactomics of tooth-associated keratinocytes in periodontitis. *Nat Commun*. 2024;15(1):5016. doi:10.1038/s41467-024-49037-y

36. Lee X, J RSH, Wallet SM, et al. Single-cell and spatially resolved interactomics of tooth-associated keratinocytes in periodontitis. *Nat Commun*. 15 (1):5016.
37. Özçelik H, Batool F, Corre M, et al. Characterization of a hyaluronic acid-based hydrogel containing an extracellular oxygen carrier (M101) for periodontitis treatment: an in vitro study. *Int J Pharm*. 2021;605:120810. doi:10.1016/j.ijpharm.2021.120810
38. Valverde P, Kawai T, Taubman MA. Potassium channel-blockers as therapeutic agents to interfere with bone resorption of periodontal disease. *J Dent Res*. 2005;84(6):488–499. doi:10.1177/154405910508400603
39. Mariotti A, Mawhinney M. Endocrinology of sex steroid hormones and cell dynamics in the periodontium. *Periodontol*. 2013;61(1):69–88. doi:10.1111/j.1600-0757.2011.00424.x
40. Shiau HJ, Aichelmann-Reidy ME, Reynolds MA. Influence of sex steroids on inflammation and bone metabolism. *Periodontol*. 2014;64(1):81–94. doi:10.1111/prd.12033
41. Polimeni G, Xiropaidis AV, Wikesjö UM. Biology and principles of periodontal wound healing/regeneration. *Periodontol*. 2006;41:30–47. doi:10.1111/j.1600-0757.2006.00157.x
42. Relvas M, Mendes-Frias A, Gonçalves M, et al. IL-6, and IL-10 Are Key Biomarkers of Periodontitis Severity. *Int J Mol Sci*. 2024;25(15):8401. doi:10.3390/ijms25158401
43. Azuma MM, Samuel RO, Gomes-Filho JE, Dezan-Junior E, Cintra LT. The role of IL-6 on apical periodontitis: a systematic review. *Int Endod J*. 2014;47(7):615–621. doi:10.1111/iej.12196
44. Grigoriadou ME, Koutayas SO, Madianos PN, Strub JR. Interleukin-1 as a genetic marker for periodontitis: review of the literature. *Quintessence Int*. 2010;41(6):517–525.
45. Reinhardt RA, Masada MP, Kaldahl WB, et al. Gingival fluid IL-1 and IL-6 levels in refractory periodontitis. *J Clin Periodontol*. 1993;20 (3):225–231. doi:10.1111/j.1600-051X.1993.tb00348.x
46. Sun R, Xie HY, Qian JX, et al. FBXO22 possesses both protumorigenic and antimetastatic roles in breast cancer progression. *Cancer Res*. 2018;78 (18):5274–5286. doi:10.1158/0008-5472.CAN-17-3647
47. Yeung YT, Aziz F, Guerrero-Castilla A, Arguelles S. Signaling pathways in inflammation and anti-inflammatory therapies. *Curr Pharm Des*. 2018;24(14):1449–1484. doi:10.2174/1381612824666180327165604
48. Daser A, Mitchison H, Mitchison A, Müller B. Non-classical-MHC genetics of immunological disease in man and mouse. The key role of pro-inflammatory cytokine genes. *Cytokine*. 1996;8(8):593–597. doi:10.1006/cyto.1996.0079
49. Bridges MC, Daulagala AC, Kourtidis A. LNCcation: lncRNA localization and function. *J Cell Biol*. 2021;220(2):e202009045. doi:10.1083/jcb.202009045
50. Baru O, Pop L, Raduly L, et al. The Evaluation of a 5-miRNA panel in patients with periodontitis disease. *JDR Clin Trans Res*. 2025;10(1):34–43. doi:10.1177/23800844241252395
51. Luan X, Zhou X, Trombetta-eSilva J, et al. MicroRNAs and periodontal homeostasis. *J Dent Res*. 2017;96(5):491–500. doi:10.1177/0022034516685711
52. Shao B, Zhou D, Wang J, Yang D, Gao J. A novel LncRNA SPIRE1/miR-181a-5p/PRLR axis in mandibular bone marrow-derived mesenchymal stem cells regulates the Th17/Treg immune balance through the JAK/STAT3 pathway in periodontitis. *Aging*. 2023;15(14):7124–7145. doi:10.18632/aging.204895
53. Jiang M, Dai J, Yin M, Jiang C, Ren M, Tian L. LncRNA MEG8 sponging miR-181a-5p contributes to M1 macrophage polarization by regulating SHP2 expression in Henoch-Schonlein purpura rats. *Ann Med*. 2021;53(1):1576–1588. doi:10.1080/07853890.2021.1969033
54. Wang J, Song J, Li Y, Shao J, Xie Z, Sun K. Down-regulation of LncRNA CRNDE aggravates kidney injury via increasing MiR-181a-5p in sepsis. *Int Immunopharmacol*. 2020;79:105933. doi:10.1016/j.intimp.2019.105933
55. Zhou Y, Long MY, Chen ZQ, Huang JW, Qin ZB, Li L. Downregulation of miR-181a-5p alleviates oxidative stress and inflammation in coronary microembolization-induced myocardial damage by directly targeting XIAP. *J Geriatr Cardiol*. 2021;18(6):426–439. doi:10.11909/j.issn.1671-5411.2021.06.007
56. Guo L, Wang D, Alexander HY, Ren X, Ma H. Long non-coding RNA H19 contributes to spinal cord ischemia/reperfusion injury through increasing neuronal pyroptosis by miR-181a-5p/HMGB1 axis. *Aging*. 2022;14(13):5449–5463. doi:10.18632/aging.204160
57. Guzeldemir-Akcakanat E, Sunnetci-Akkoyunlu D, Balta-Uysal VM, Özer T, Işik EB, Cine N. Differentially expressed miRNAs associated with generalized aggressive periodontitis. *Clin Oral Investig*. 2023;28(1):7. doi:10.1007/s00784-023-05404-5
58. Foster BL, Ao M, Salmon CR, et al. Osteopontin regulates dentin and alveolar bone development and mineralization. *Bone*. 2018;107:196–207. doi:10.1016/j.bone.2017.12.004
59. Reinholt FP, Hultenby K, Oldberg A, Heinegård D. Osteopontin–a possible anchor of osteoclasts to bone. *Proc Natl Acad Sci U S A*. 1990;87 (12):4473–4475. doi:10.1073/pnas.87.12.4473
60. Giachelli CM, Steitz S. Osteopontin: a versatile regulator of inflammation and biomineralization. *Matrix Biol*. 2000;19(7):615–622. doi:10.1016/S0945-053X(00)00108-6
61. Weber GF, Cantor H. The immunology of Eta-1/osteopontin. *Cytokine Growth Factor Rev*. 1996;7(3):241–248. doi:10.1016/S1359-6101(96)00030-5
62. MacNeil RL, Berry J, D'Errico J, Strayhorn C, Somerman MJ. Localization and expression of osteopontin in mineralized and nonmineralized tissues of the periodontium. *Ann N Y Acad Sci*. 1995;760:166–176. doi:10.1111/j.1749-6632.1995.tb44628.x
63. Sufianov A, Beilerli A, Begliarzade S, et al. The role of noncoding RNAs in the osteogenic differentiation of human periodontal ligament-derived cells. *Noncoding RNA Res*. 2022;8(1):89–95. doi:10.1016/j.ncrna.2022.11.003
64. Zhao P, Ma G, Ma L. miR-181a-5p targets DDX3X to inhibit the progression of osteoarthritis via NF-KB signaling pathway. *J Orthop Surg Res*. 2023;18(1):606. doi:10.1186/s13018-023-04073-0
65. Hao Y, Lu C, Zhang B, Xu Z, Guo H, Zhang G. CircPVT1 up-regulation attenuates steroid-induced osteonecrosis of the femoral head through regulating miR-21-5p-mediated Smad7/TGFβ signalling pathway. *J Cell Mol Med*. 2021;25(10):4608–4622. doi:10.1111/jcmm.16294
66. Huang C, Xiao Y, Qing L, Tang J, Wu P. Exosomal non-coding RNAs in the regulation of bone metabolism homeostasis: molecular mechanism and therapeutic potential. *Heliyon*. 2025;11(2):e41632. doi:10.1016/j.heliyon.2025.e41632
67. Wang Y, Zhang XH, Xie SH, et al. Identification of key novel lncRNAs *RP11-400N13.3* and *RP11-197K6.1* that construct ceRNA networks associated with recurrence and metastasis in colon cancer. *Front Biosci*. 2023;28(10):276. doi:10.31083/j.fbl2810276

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