Research Article

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Impacts of long noncoding RNA MALAT1 on LPS-induced periodontitis via modulating miR-155/SIRT1 axis

https://doi.org/10.1515/tjb-2022-0077
Received April 13, 2022; accepted July 12, 2022;
published online August 24, 2022

Abstract

Objectives: Periodontitis, a dental disease that causes inflammation of gums is triggered by a bacterial infection. Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (lncRNA MALAT1) has been reported to participate in inflammatory diseases. In the present study, we investigated the effects of lncRNA MALAT1 on periodontal ligament cells (PDLCs) with lipopolysaccharide (LPS) induction.

Methods: MALAT1, microRNA-155 (miR-155), Sirtuin 1 (SIRT1), Bax, and Bcl-2 RNA expressions were detected by using real-time quantitative polymerase chain reaction (RT-qPCR). PDLC viability and apoptosis were assessed by using 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide tetrazolium salt (MTT) assay and flow cytometry. Enzyme-linked immunosorbent assay (ELISA) assessed secretions of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). Luciferase reporter test was applied for confirming the binding of miR-155 with MALAT1 and SIRT1, respectively.

Results: Overexpression of MALAT1 facilitated the LPS-induced periodontitis while MALAT1 suppression restrained LPS-induced injury. Also, miR-155 was expressed in LPS-induced PDLCs. Moreover, MALAT1 negatively regulated miR-155 followed by the up-regulation of SIRT1 which in turn reduced the inflammation in LPS-induced PDLCs.

Conclusions: We concluded that upregulated lncRNA MALAT1 could accelerate periodontitis through the regulation of miR-155/SIRT1. Our findings suggested a novel MALAT1/miR-155/SIRT1 pathway for the treatment of periodontitis.

Keywords: IL-1β; MALAT1; miR-155; periodontitis; SIRT1; TNF-α.

Introduction

Periodontitis is a dental disease caused by various inflammatory factors such as environmental factors and infections of plaque-related bacteria [1]. The *Porphyromonas gingivalis*, *Tannerella denticola*, and *Treponema forsytheia* are the main bacteria causing periodontitis [2]. The periodontitis effects on teeth structures might be causes of tooth loss and alveolar bone resorption [3]. The periodontal regenerations such as attachment of connective tissues, cementum, and new bone formation were stimulated by a periodontal ligament (PDL) [4]. The periodontal development needs the proliferation of PDL cells (PDLCs) which play vitally in mechanical stress, periodontitis, and homeostasis of periodontal tissues [5]. The mechanical stimulation of PDL promoted secretions of proinflammatory cytokines, leading to the osteoclastogenesis of PDLCs [6].

Long non-coding RNAs (lncRNAs) are over 200 nucleotides without protein-coding capacity that have been reported to play critically in the progression of disorders via modulating immune response and inflammation [7]. Previous research has shown that dysregulation of lncRNAs in chronic periodontitis (CP) plays a significant role in regulating periodontitis [8]. However, the mechanisms of lncRNAs in the pathogenesis of periodontitis are still unknown. LncRNA MALAT1 was first discovered to perform its

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function in promoting metastasis, proliferation, and invasion of cell lung cancer and exerted its role in the cell cycle and epigenetic processes [9]. Another study has revealed that MALAT1 participated in progressions of immune-inflammatory diseases as a promoter [10]. MALAT1 has been determined to accelerate inflammatory responses in human middle ear epithelial cells with lipopolysaccharide (LPS) or interleukin 17A via activating the nuclear factor kappa B (NF-κB) signaling pathway [11]. Moreover, MALAT1 could enhance secretions of proinflammatory cytokines by negatively regulating NF-κB [12]. Beyond that, MALAT1 has been detected to facilitate LSP-induced PDLC damage through miR-769-5p/HIF3A axis [13]. However, the underlying mechanism of MALAT1 in modulating PDLC progression after LPS induction still needs to be explored.

In this study, we investigated the impacts of MALAT1 on PDLCs with LPS induction. Roles of abnormal expressed MALAT1 were determined by assessing the rate of cell apoptosis, cell viability as well as secretions of inflammatory cytokines. Moreover, we also examined further molecular mechanisms of MALAT1 in LPS-induced PDLCs to provide a new approach for treating periodontitis.

Materials and methods

Cell culture

PDLCs were obtained from the healthy periodontal ligament of the periodontal membrane root as described in previous research [14]. Dulbecco's modified eagle medium (DMEM) (Thermo Fisher, NJ, USA) containing 1,000 mg/L glucose, and 10% fetal bovine serum (FBS) (Thermo Fisher, NJ, USA) was used to culture PDLCs followed by the cultivation of cells with 5% CO_2 at 37 °C. After cells reached 90% confluency, *P. gingivalis* LPS (100 ng/mL; InvivoGen, Pak Shek Kok, Hong Kong) was used to treat PDLCs to induce inflammatory responses.

Cell transfection

A 6-well plate at a density of 2×10^5 cell/well was used to seed PDLCs. Overexpression of MALAT1 was conducted using the pcDNA 3.1 vector (Invitrogen, CA, USA) named pc-MALAT1. Besides that, suppression of MALAT1 (si-MALAT1#1 and siMALAT1#2) and its control (siNC) were provided by GenePharma (Shanghai, China). GenePharma also provided NC/miR-155 mimics and SIRT1 shRNA (sh-SIRT1) and its control (sh-NC). After the confluence of cells reached 80%, transfection was performed by using Lipofectamine 3,000 (Invitrogen, USA) based on instructions of the manufacturer. Primer sequences are listed in Table 1. Real-time quantitative polymerase chain reaction (RT-qPCR) was used to detect cell transfection after 48 h of cultivation.

Table 1: Primer sequences in cell transfection.

si-MALAT1#1	5′-CCUCAGACAGGUAUCUCUU-3′
si-MALAT1#2	5′-GAUCCAUAAUCGGUUUCAA-3′
si-NC	5′-UUCUCCGAACGUGUCACGUTT-3′
NC mimics	5′-UUUGUACUACACAAAAGUACUG-3′
MiR-155 mimics	5-UCACAACCUCCUAGAAAGAGUAGA-3′
sh-NC	5′-ACGTCTATACGCCA-3′
sh-SIRT1	5′-CCATTCTTCAAGTTTGCAA-3′

MTT assay

96-well plates (1×10^6 cell/well) were used to seed PDLCs followed by adding 0.1 mL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide tetrazolium salt (MTT) and DMEM containing 10% FBS into each well. After incubating for 4 h, 200 μL of dimethyl sulfoxide solution was added to each well to melt the reaction product. The iMark Microplate Absorbance Reader (Bio-Rad, CA, USA) evaluated absorbance at 570 nm.

Flow cytometry

Flow cytometry was applied for examining PDLCs apoptosis. Cells were collected and rinsed twice with cold Phosphate Buffer Saline (PBS) which was mixed with 10× Annexin binding buffer (50 mL). Fluorescein isothiocyanate (FITC) (0.5 mL) and propidium iodide (PI) double staining solutions (2 mL) purchased from BD Biosciences (NJ, USA) were used to incubate cells without light at 23 °C for 15 min. A flow cytometer (Biocompare, CA, USA) validated the PDLCs apoptosis rate.

RT-qPCR

Total RNA was segregated from PDLCs using TRIzol reagent (Thermo Fisher, NJ, USA) on the instructions of the manufacturer. PrimeScript RT Master Mix kit (Takara, CA, USA) was applied for reverse transcribing total RNA into cDNA. The RT-qPCR assay was performed by using SYBR Premix Ex Taq kit (Takara, CA, USA) U6 and GAPDH was taken as a reference for miRNAS and RNAs respectively. The relative expressions were analyzed by using the $2^{-\triangle\triangle Ct}$ method. The primers used are given in Table 2.

Dual-luciferase reporter assay

To explore luciferase activities of 3′-UTR regions in MALAT1 or SIRT1 sequences having putative binding spots with miR-155 were inserted into the pmirGLO vector (Promega, Wisconsin, USA) to produce luciferase reporter plasmids (MALAT-wt/mt or SIRT1-WT/MUT). Lipofectamine 3,000 (Invitrogen, CA, USA) was applied for co-transfection in PDLCs with reporter plasmids (MALAT-wt/mt or SIRT1-WT/MUT) and miR-155 vectors (miR-155 mimics, NC mimic). A dual luciferase activity assay kit (BioVision, CA, USA) examined fluorescence in each group.

Table 2: Primers sequences in the real-time quantitative polymerase chain reaction.

	Primer sequences	
	Forward	**Backward**
MALAT1	GGAAGGAGCGAGTGCAATTT	ATATTGCCGACCTCACGGAT
miR-155	UUAAUGCUAAUCGUGAUAGGGGU	ACCCCUAUCACGAUUAGCAUUAA
SIRT1	GCAGCAGCCAGATAACCTTC	TCTACAGCAAGGCGAGCATA
TNF-α	AGGACACCATGAGCACTGAA	CCGATCACTCCAAAGTGCAG
IL-1β	CTCTCTCCTTTCAGGGCCAA	GCGGTTGCTCATCAGAATGT
Bax	GGCCTGAGTCCAGCTCTTTA	GTCCTGGAGACAGGGACATC
Bcl-2	CCTCGCTGCACAAATACTCC	TGGAGAGAATGTTGGCGTCT
β-Actin	ACCCAGAAGACTGTGGATGG	TCAGCTCAGGGATGACCTTG

ELISA

To evaluate proinflammatory cytokines densities after LPS induction, Human tumor necrosis factor-α (TNF-α) ELISA Kit (ab181421, Abcam, UK) and Human interleukin-1β (IL-1β) Antibody Pair Kit (ab217608) were applied in accordance with manufacturer's protocols. Protein densities were validated at 450 nm using the iMark Microplate Absorbance Reader (Bio-Rad, CA, USA).

Statistical analysis

All the experiments were run in triplicates. Analyses of data were performed using SPSS 19.0 (IBM, USA) and GraphPad Prism 7.0 (GraphPad Software, USA). For the difference between two groups or different groups, Student's t-test and one-way ANOVA were performed. $p<0.05$ was taken as meaningful.

Results

MALAT1 level is promoted in LPS-stimulated PDLCs

To detect MALAT1 expressions in periodontitis, RT-qPCR was performed. Results indicated that MALAT1 expression was increased in PDLCs induced by LPS (Figure 1A). Additionally, PDLC viability and apoptosis were examined, showing that LPS induction reduced the cell viability but accelerated the apoptosis rate (Figure 1B and C). Thereafter, apoptotic biomarkers were examined, and RT-qPCR results indicated that Bcl-2 was downregulated by LPS treatment while Bax was promoted (Figure 1D). Moreover, proinflammatory cytokines were analyzed. ELISA results revealed that TNF-α and IL-1β protein densities were increased by LPS induction (Figure 1E).

Effects of MALAT1 on LPS-stimulated PDLCs

Next, overexpression and downregulation of MALAT1 were applied for examining the impacts of MALAT1. RT-qPCR results showed that MALAT1 expression was enhanced in the pc-MALAT1 group, which was downregulated in si-MALAT1#1 and #2 groups (Figure 2A). We selected si-MALAT1#2 in the following experiments as it had strong inhibition efficiency compared to that of si-MALAT#1. Beyond that, the cell viability was decreased while the rate of cell apoptosis was promoted by the overexpression of MALAT1 in LPS-induced PDLCs (Figure 2B and C). In contrast, si-MALAT1#2 promoted PDLC viability and hampered apoptosis after LPS induction (Figure 2B and C). Moreover, MALAT1 over expression downregulated Bcl-2 expression and increased Bax expression, but siMALAT1#2 prompted Bcl-2 and reduced Bax (Figure 2D). Additionally, ELISA results indicated that TNF-α and IL-1β protein densities were inhibited by siMALAT1#2 but elevated with MALAT1 upregulation (Figure 2E). These results suggested that overexpressed MALAT1 facilitated the apoptosis and inflammatory reactions after LPS-induction.

MALAT1 modulated progressions of LPS induction via sponging miR-155

Using the bioinformatic tool, ENCORI (https://starbase.sysu.edu.cn/), binding spots of miR-155 with MALAT1 were provided (Figure 3A). Moreover, MALAT1-wt and miR-155 mimics had the lowest fluorescence, indicating that miR-155 was sponged by MALAT1 (Figure 3B). Additionally, RT-qPCR results showed that miR-155 expression was decreased by MALAT1 overexpression but elevated by

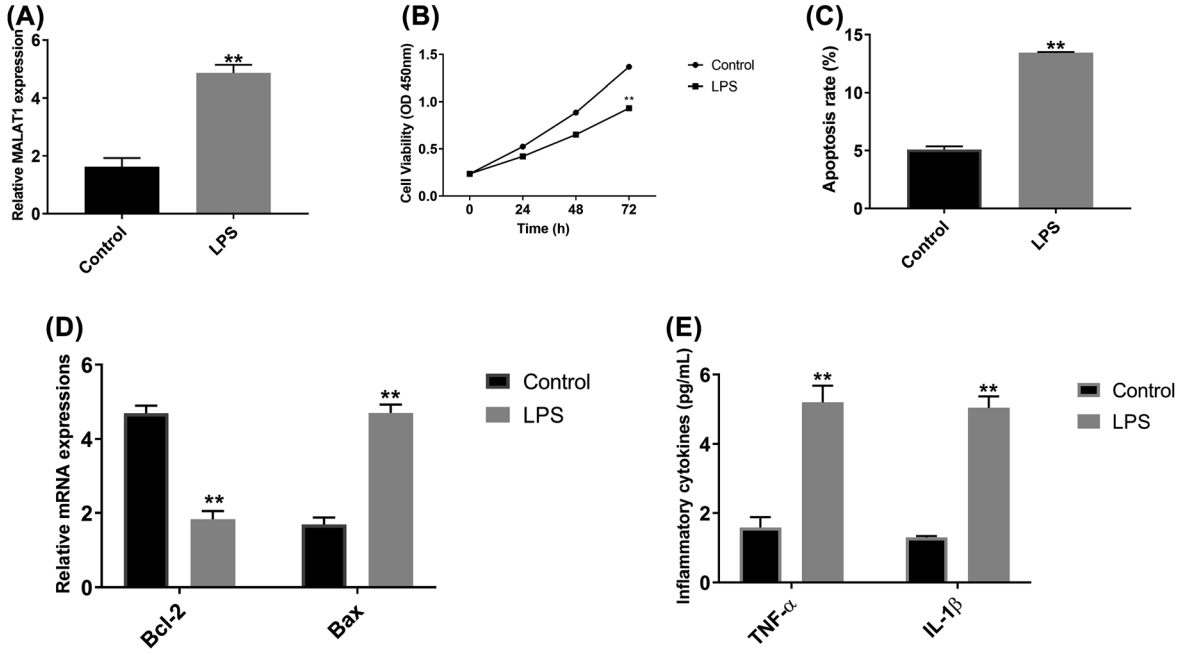

Figure 1: Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (lncRNA MALAT1) was upregulated in lipopolysaccharide (LPS) stimulated periodontal ligament cells (PDLCs).
(A) MALAT1 expressions were measured by using RT-qPCR. (B, C) PDLC viability and apoptosis were measured using MTT assay and flow cytometry, respectively. (D) Bax and Bcl-2 mRNA expressions were assessed by RT-qPCR. (E) ELISA measured TNF-α and IL-1β protein densities in LPS-induced PDLCs. **p<0.05 was statistically significant.

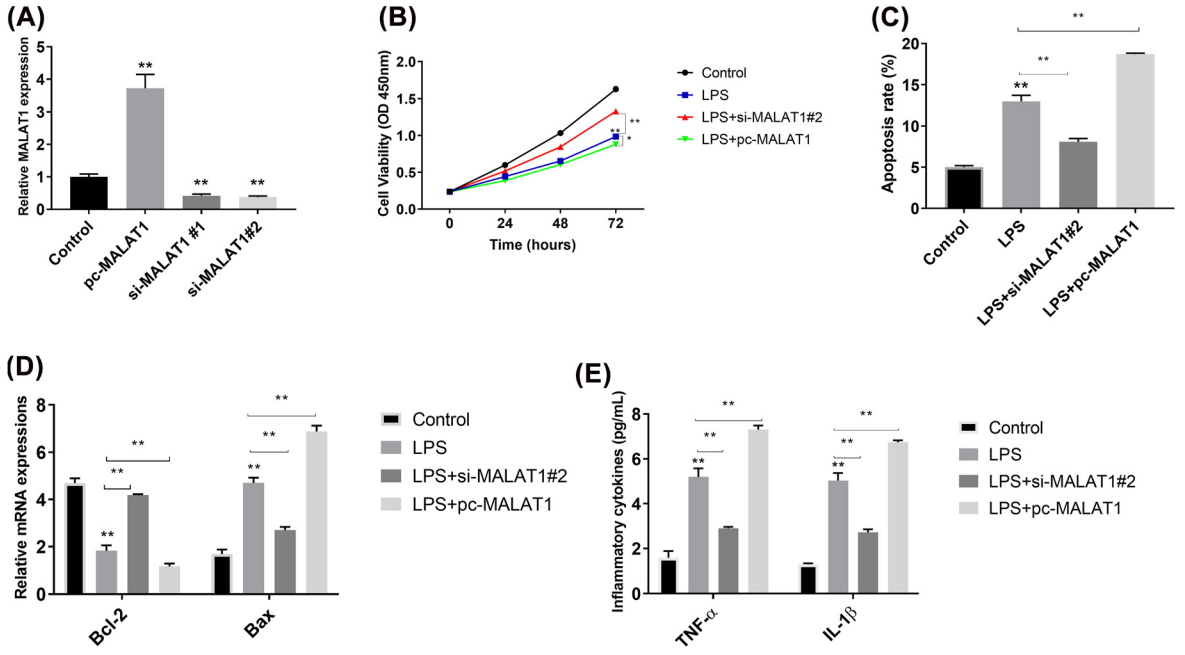

Figure 2: Impacts of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) on modulating progressions of periodontal ligament cells (PDLCs) with lipopolysaccharide (LPS) treatment.
(A) MALAT1 expressions were examined by RT-qPCR after transfected by overexpressed or inhibited MALAT1. (B) MTT analyzed PDLC viability after transfection. (C) Flow cytometry evaluated apoptosis. (D) Bax and Bcl-2 expressions were validated using RT-qPCR. (E) ELISA detected TNF-α and IL-1β protein densities. **p<0.05 was statistically significant.

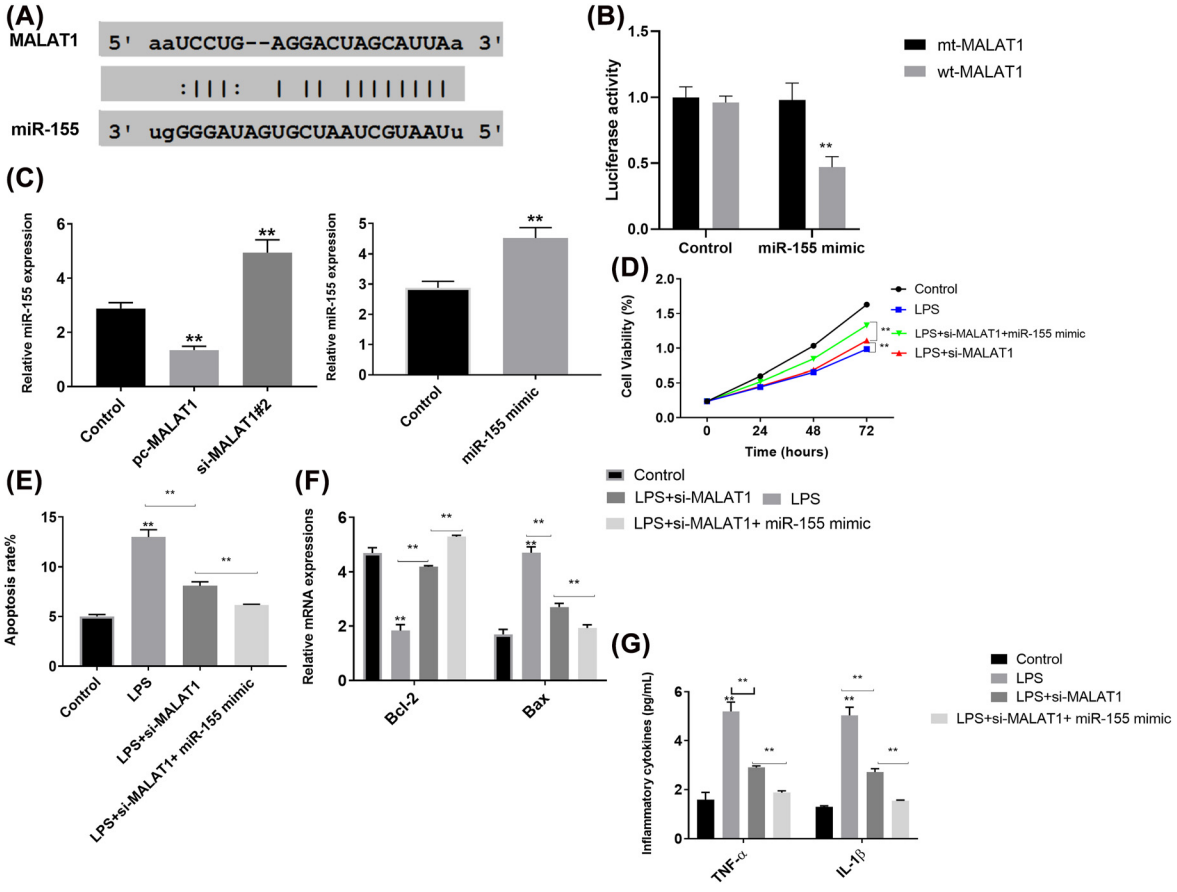

Figure 3: Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) sponged miR-155 to regulate progressions of lipopolysaccharide (LPS) induction in periodontal ligament cells (PDLCs).
(A) Binding spots of miR-155 with MALAT1. (B) Luciferase activities in NC/miR-155 mimic MALAT1-wt/mut. (C) MiR-155 expressions with MALAT1 overexpression or suppression and miR-155 mimics. (D, E) Cell viability and apoptosis with si-MALAT1 and siMALAT1 with miR-155 mimics. (F) Bax and Bcl-2 with si-MALAT1 and siMALAT1 with miR-155 mimics. (G) TNF-α and IL-1β with si-MALAT1 and siMALAT1 with miR-155 mimics.
**p<0.05 was statistically significant.

si-MALAT#2, which was also increased by miR-155a mimics (Figure 3C). Furthermore, miR-155 mimics with si-MALAT1 caused higher PDLC viability and lower apoptosis than siMALAT1 only (Figure 3D and E). Beyond that, miR-155 mimics with si-MALAT1 upregulated Bcl-2 and reduced Bax expression compared with siMALAT1 only (Figure 3F). TNF-α and IL-1β protein concentrations were lower in siMALAT1 with miR-155 mimics than siMALAT1 (Figure 3G).

MiR-155 targeted SIRT1 to modulate progressions of LsPS-induced PDLCs

ENCORI also offered binding spots of miR-155 with SIRT1 (Supplemental Figure 1A). Furthermore, the fluorescence was lower in the miR-155 mimics with the SIRT1-wt group than other three (Supplemental Figure 1B). Then, RT-qPCR results indicated that SIRT1 mRNA expression was upregulated by LPS induction while miR-155 mimics inhibited its expression (Supplemental Figure 1C and D). Meanwhile, SIRT1 suppression also decreased its expression in PDLCs with LPS induction (Supplemental Figure 1E). Beyond that, PDLC viabilities promoted by miR-155 mimics were upregulated by miR-155 mimics with sh-SIRT1 (Supplemental Figure1F). PDLC apoptosis decreased by miR-155 mimics was also reduced by miR-155 mimics with sh-SIRT1 (Supplemental Figure 1G). Upregulated Bcl-2 and inhibited Bax caused by miR-155 mimics were prompted and suppressed by miR-155 mimics with sh-SIRT1, respectively (Supplemental Figure 1H). Additionally, protein concentrations of TNF-α and IL-1β were both suppressed by miR-155 mimics, whose concentrations became lower in

miR-155 mimics with the sh-SIRT1 group (Supplemental Figure 1I). Our findings elucidated that miR-155 could restrain LPS induction in PDLCs by targeting SIRT1.

Discussion

It has been extensively shown that lncRNA plays a critical role in many human diseases [15]. We explored the impacts of MALAT1 on LPS-induced PDLCs and our results showed that MALAT1 overexpression aggravated LPS induction, which was alleviated by the suppression of MALAT1. Moreover, MALAT1 negatively regulated miR-155, and miR-155 mimics attenuated the cell injury induced by LPS. Furthermore, our findings demonstrated that SIRT1 was targeted directly by miR-155 and miR-155 mitigated the LPS-induced PDLCs injury by targeting SIRT1.

LncRNAs have been shown to exert their functions in the progression of diseases by sponging miRNAs [16]. LncRNA MALAT1 has been found to act as an oncogene in various types of cancers [17]. MALAT1 promoted the osteoblast differentiation of interstitial cells in the human aortic valve by sponging miR-204 and via up-regulation of Smad24 [18]. Another piece of evidence has revealed that MALAT1 inhibited the miR-155 expression and activated the function of F-box and WD repeat domain containing 7 to impede the pathogenesis of glioma [19]. Also, MALAT1 enhanced the level of TNF-α and IL-12 in tumor-associated macrophages [20]. Additionally, the effects of MALAT1 on inflammatory diseases have been explored as well. MALAT1 suppressed the protective effects of miR-146 in human microvascular endothelial cells, resulting in elevated NF-κB activation and increased inflammatory injury after LPS induction [21]. In this study, we have established LPS-induced PDLCs to figure out the impact of lncRNA MALAT1. After LPS induction, MALAT1 expressions in PDLCs were upregulated. Meanwhile, cell viability was suppressed while apoptosis was facilitated. Moreover, elevated TNF-α and IL-1β revealed that inflammatory reactions were also promoted with LPS induction. Furthermore, functions of MALAT1 were examined later, showing that overexpressed MALAT1 accelerated apoptosis and inflammatory response but restrained cell viability while MALAT1 downregulation promoted cell viability but hampered cell apoptosis and inflammatory reactions with LPS induction. Based on our detections, MALAT1 could facilitate LPS-induced inflammation in PDLCs.

Our study has also revealed that MALAT1 negatively regulated miR-155. Also, miR-155 mimics with si-MALAT1 alleviated LPS-induced PDLCs injury compared to si-MALAT1 only, suggesting MALAT1 worked as a promoter in modulating periodontitis via negatively regulating miR-155. MiR-155 has been detected to be downregulated by LPS in BEAS-2B cells, whose overexpression promoted cell proliferation and inhibited cell apoptosis and inflammatory cytokines levels [22]. Moreover, miR-155 downregulated LPS-induced caspase-3 mRNA expressions to restrain cell apoptosis, implying a protective role of miR-155 in inflammation [23]. In this study, miR-155 was also verified to protect PDLCs from LPS induction.

SIRT1 is considered an anti-aging gene playing vitally in preventing endothelial senescence. Endothelial senescence has been reported to promote vascular dysfunction and inflammation. Also, the expression of SIRT1 was modulated by various miRNAs such as miR-23b-3p, miR-34a, and miR-132-3p [24]. Another study revealed that SIRT1 was suppressed in endothelial cells (ECs) by high glucose, TNF-α, and LPS [25]. However, the exact molecular mechanism of SIRT1 is unclear. miRNAs are small noncoding RNAs that modulate the stability, modulation of gene expression, and destruction of mRNA translation via binding through 3′ UTR of target mRNAs [26]. MiR-155 performed its function in the regulation of inflammatory signaling pathways *in vitro* model of atherosclerosis [27]. Moreover, the overexpression of miR-155 increased IL-6 and IL-8 expressions and promoted the rate of apoptosis, and reduced proliferation in human coronary artery endothelial cells (HCAECs) to regulate the pathogenesis of atherosclerosis [28]. However, how miR-155 exerts its function in periodontitis is still unknown. In our study, SIRT1 expressions were upregulated in LPS-induced PDLCs. Moreover, after the knockdown of SIRT1 and inhibition of miR-155, a reverse effect was observed on LPS-induced PDLC injury. Also, the progression of LPS-induced periodontitis was accelerated by silencing SIRT1 suggesting that miR-155 might prevent LPS-induced periodontitis by direct targeting SIRT1.

Our study demonstrated that upregulated MALAT1 accelerated periodontitis through modulating the miR-155/SIRT1 axis. Hence, this study suggested a novel MALAT1/miR-155/SIRT1 axis for the diagnosis and treatment of periodontitis.

Research funding: This work was supported by the Initial Scientific Research Fund of Chengdu Textile College and Natural Science Foundation of Sichuan Province (2022NSFSC0383).

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: The authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: This study was carried out with the approval of Chengdu Textile College in accordance with the Declaration of Helsinki.

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Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/tjb-2022-0077).