Alpha-Lipoic Acid inhibits NF-κB signal transduced inflammatory cytokines secretion in LPS-induced Human Gingival Fibroblasts

Hiroaki Michael Ishii*1, Etsuko Murakashi*1, Hiroko Igarashi-Takeuchi*1, Hirofumi Shoji*2 and Yukihiro Numabe*1

*1Department of Periodontology, Nippon Dental University, School of Life Dentistry at Tokyo
*2Oral and Maxillofacial Surgery, Nippon Dental University Hospital
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Abstract: Alpha-lipoic acid (ALA) is a known anti-inflammatory agent that can be used as a pharmacological agent in adjunctive therapy to inhibit the recurrence of periodontitis. This study investigated the inflammatory regulation effect of pre-administered ALA on human gingival fibroblasts (HGFs) stimulated with Escherichia coli-derived lipopolysaccharide (LPS). HGFs were administered ALA and then stimulated with LPS. Western blot analysis was used to investigate activation of the nuclear factor-kappa B (NF-κB) signaling pathway. Analysis of NF-κB p65 nuclear translocation was performed using an immunofluorescence assay and inflammatory cytokine (TNF-α, IL-1β, IL-6, and IL-8) secretion analysis was conducted using an enzyme-linked immunosorbent assay. NF-κB signaling pathway expression was increased by LPS stimulation. However, increased NF-κB signaling pathway expression was down-regulated by ALA pre-administration. Further, NF-κB p65 was translocated to the nucleus by LPS stimulation. However, NF-κB p65 translocation was inhibited by ALA pre-administration. The secretion of TNF-α, IL-1β, IL-6, and IL-8 was increased by LPS stimulation but down-regulated by ALA pre-administration. The results of this study demonstrated that ALA regulated the secretion of inflammatory cytokines via regulation of NF-κB signaling pathway activation in HGFs, which suggests that ALA has the potential to regulate periodontal tissue inflammation.


Key words: Alpha-Lipoic acid, human gingival fibroblasts, LPS, NF-κB signaling pathway, inflammatory cytokine

Introduction

Mechanical plaque control is the principal method for removing dental plaque, which is the main cause of periodontitis. However, numerous types of adjunctive therapies, in addition to mechanical plaque control, have recently been investigated. One of these adjunctive therapies is host modulation therapy (HMT), which is used to inhibit the secretion of inflammatory cytokines to prevent destruction of periodontal tissue. Acidic non-steroidal anti-inflammatory drugs (NSAIDs), which are anti-inflammatory therapeutic agents, are effective for periodontitis treatment. However, the use of these drugs is associated with serious side effects, such as digestive ulceration and inhibition of platelet aggregation.

Alpha-lipoic acid (ALA) is a sulfur-containing high-fat acid that functions as a cofactor of mitochondrial enzymes and is an essential factor in metabolism. The therapeutic potential of ALA reportedly includes anti-oxidative effects, heavy-metal detoxification ef-
fects, and clinical therapeutic effects against diabetes mellitus-derived polyneuropathy\(^6\). ALA has also been studied for its potent preventive effects against hypertension\(^7\), diabetes mellitus\(^8\), and ischemia-reperfusion injury\(^9\). Further, as compared with conventional anti-inflammatory therapeutic agents, such as acidic NSAIDs, ALA is expected to have fewer harmful side effects\(^10\). In addition, the anti-inflammatory effects of ALA were recently reported\(^11, 12\). The anti-inflammatory mechanism of ALA is unlike that of conventional acidic NSAIDs as it inhibits the NF-κB signaling pathway, which is the main pathway activated in the inflammation signaling process\(^13, 14\).

Periodontitis is an inflammatory disease of the periodontal tissue that is caused by dental plaque\(^15\). Dental plaque is formed by multiple microorganisms, especially periodontal pathogenic microorganisms, such as *Porphyromonas gingivalis*, *Tannerella forsythensis*, and *Treponema denticola*, which are strongly associated with the progression of periodontitis\(^16\). The outer membrane of these periodontal pathogenic microorganisms contains lipopolysaccharide (LPS), which is composed of an O-antigen, the core (R) antigen, and lipid A. LPS is involved in several bioactivities\(^17\). LPS binds to cell surface CD14 receptors and is then recognized by antigen-recognition Toll-like receptors (TLRs), which mediate signal transduction by the phosphorylation of multiple proteins, leading to inflammation\(^18, 19\).

Although many pathways are involved in the inflammatory response, the NF-κB signaling pathway is the most strongly activated by periodontitis-derived inflammation\(^20, 21\). The NF-κB signaling pathway, which consists of the NF-κB p50/p65 heterodimer and is inhibited by the suppressive protein inhibitor kappa B (IκB), is present in the cytosol in an inactive form. Upon production of inflammatory signals, IκB is phosphorylated and degraded by the ubiquitin-proteasome system, leading to NF-κB phosphorylation and translocation into the nucleus. In the nucleus, NF-κB activates inflammation-related DNA promoters and initiates transcription\(^22\). After mRNA transcription, this leads to periodontal tissue cells secrete inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8, which destroy the periodontal tissue\(^23\)–\(^27\).

The gingival crevicular fluid (GCF) and periodontal tissue of periodontitis patients have a higher concentration of inflammatory cytokines than those of healthy patients\(^28\)–\(^31\). These inflammatory cytokines are secreted by LPS-stimulated periodontinum including HGF\(^32, 33\). Thus, ALA may be a potential adjunctive therapeutic agent to prevent the recurrence of periodontitis. However, few studies have investigated the anti-inflammatory effects of ALA against periodontal tissue.

In this study, ALA was pre-administered against LPS-stimulated HGFs to investigate the anti-inflammatory effect of ALA against periodontal tissue-derived HGFs.

**Materials and Methods**

**Cell culture**

Gingival tissues were surgically excised during third molar extraction from patients who were clinically free of periodontal disease (mean age, 19.4 years; age range, 15-23; 2 males and 3 females) at the Department of Oral and Maxillofacial Surgery of Nippon Dental University Hospital (Tokyo, Japan). After washing with Hank’s Balanced Salt Solution (Gibco, Carlsbad, CA, USA), the extracted tissues were minced to a diameter of 2 mm and cultured in F12/Dulbecco’s Modified Eagle Medium (DMEM; Gibco), supplemented with 20% fetal bovine serum (FBS; Molegate, Australia), 100 U/mL of penicillin and streptomycin (Gibco), 0.25 μg/mL amphotericin B (Fungizone; Gibco), and 0.25 μg/mL of MEM non-essential amino acids (Gibco). Once the cells surrounding the tissues reached confluence, they were subcultured with 0.25% trypsin-EDTA (Gibco) and then incubated with DMEM containing 10% FBS. Cells used in this study were from passage 4 to 7. The study protocol as approved by the Ethics Committee of Nippon Dental University, School of Life Dentistry (approval no. NDU-T2013-45).

**Western blot analysis**

The inhibitory effect of ALA was assessed against NF-κB signal transduction of LPS-stimulated HGFs. The cells were seeded on a 10-cm dish and grown to confluence. Then, the DMEM containing 10% FBS was removed and the cells were cultured in DMEM containing 10% FBS only (control group), various concentrations (0.01, 0.1, or 1.0 mmol/L) of ALA (R(+)-α-lipoic acid; Sigma-Aldrich Corporation, St. Louis, MO, USA) with DMEM containing 10% FBS, or 0.1 mmol/L of the NF-κB signal blocker BAY 11-7082 (Sigma-Aldrich Corporation) with DMEM containing 10% FBS for 2 h. After the culture media was removed, the HGFs were stimulated with 0.1 μg/mL of LPS (Escherichia coli 0111: B4; Sigma-Aldrich Corporation) for...
30 min. Then, the HGFs were washed with phosphate-buffered saline (PBS) three times and the protein samples were collected from cell lysates using sample buffer (0.5 mol/L of Tris-HCl, pH 6.8, 10% sodium dodecyl sulfate, 143 mol/L of β-mercaptoethanol, and 137 mol/L of glycerol). An equal quantity of each sample was fractionated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis and then transferred onto polyvinylidene fluoride membranes (Millipore, Billerica, MA, USA). The membranes were blotted with polyclonal antibodies against phosphorylated IκBα (p-IκBα; R & D Systems, Inc., Minneapolis, MN, USA), IκBα, and phosphorylated NF-κB p65 (NF-κB p-p65; Cell Signaling Technology, Inc., Beverly, MA, USA) at a dilution of 1:1000 at room temperature (RT) for 1 h, and then incubated with anti-rabbit IgG horse-radish peroxidase (HRP)-conjugated species-specific whole antibody and ECL™ Anti-Mouse IgG, Horseradish Peroxidase-Linked Species-Specific Whole Antibody (Amersham Biosciences Corporation, Ams-ersham, UK) at a dilution of 1:1000 at RT for 1 h. The protein blots on the membranes were visualized using Amersham™ ECL™ Western Blotting Detection Reagents (Amersham Biosciences Corporation) and the band densities were calculated as a ratio to the internal control using CS Analyzer Image Analysis Software (Atto Corporation, Tokyo, Japan).

**Immunofluorescence assay**

To detect nuclear translocation of NF-κB p65, cells were seeded on a chamber and incubated until sub-confluent. After removal of the DMEM containing 10% FBS, the cells were incubated with DMEM containing 10% FBS only (control group), 0.1 mmol/L of ALA with DMEM containing 10% FBS, or 0.1 mmol/L of BAY 11-7082 with DMEM containing 10% FBS for 2 h. After the culture media was removed, the HGFs were stimulated with 0.1 μg/mL LPS for 1 h, then fixed in 4% paraformaldehyde for 30 min, washed with PBS three times, and permeabilized with ~20°C 100% methanol for 5 min. Next, the cells were blocked with 5% (w/v) skim milk for 30 min, then incubated with anti-NF-κB p65 antibody (Cell Signaling Technology) at a dilution of 1:200 at RT for 2 h followed by Donkey anti-Rabbit IgG Secondary Antibody, Alexa Fluor® 488 conjugate (Molecular Probes, Carlsbad, CA, USA) at a dilution of 1:1000 at RT for 1 h. The nuclei were stained with VECTASHIELD® Mounting Medium with DAPI (Vector Laboratories, Burlingame, CA, USA) and viewed using a confocal laser scanning mi-

**Enzyme-linked immunosorbent assay (ELISA)**

The inhibitory effect of inflammatory cytokine secretion by ALA was assessed as follows. Once cells seeded on 10-cm dishes were grown to confluence, the DMEM with 10% FBS was removed. Then, the cells were incubated with DMEM containing 10% FBS only (control group) or 0.1 mmol/L of ALA with DMEM containing 10% FBS for 2 h. After the culture media was removed, the HGFs were stimulated with 0.1 μg/mL LPS and then the culture supernatant was collected at various time points to assess secretion levels of TNF-α, IL-1β, IL-6, and IL-8 using an ELISA (Quanti-kin ELISA Human TNF-α, Human IL-1β, Human IL-6, Human CXCL8/IL-8; R & D Systems, Inc.). A spectrophotometer (SH-9000, Corona Electric, Hitachinaka, Japan) was used to measure the sample at an absorption wavelength of 450 nm and a reference wavelength of 570 nm. The concentration of each inflammatory cytokine was calculated according to a pre-made standard curve. Further, the secretion level ratio of the groups were calculated in relation with the control group.

**Statistical analysis**

Differences between the control group and the experimental groups were evaluated by analysis of variance followed by Dunnet’s test using SPSS ver. 15.0 J software (IBM-SPSS, Inc., Chicago, IL, USA). A probability (p) value of <0.05 was considered statistically significant.

**Results**

**Assessment of the inhibitory effect of NF-κB signaling by ALA**

The 0.1 μg/mL LPS group, the 0.01 mmol/L ALA + 0.1 μg/mL LPS group, and the 1.0 mmol/L ALA + 0.1 μg/mL LPS group showed a significant increase in p-IκBα expression, as compared with the control group (p <0.01). However, the 0.1 mmol/L ALA + 0.1 μg/mL LPS group and the 0.1 mmol/L BAY11-1072 + 0.1 μg/mL LPS group did not show a significant increase in p-IκBα expression, as compared with the control group (Fig. 1 (a), (b)). The 0.1 μg/mL LPS group, the 0.01 mmol/L ALA + 0.1 μg/mL LPS group, and the 1.0 mmol/L ALA + 0.1 μg/mL LPS showed a significant decrease in IκBα expression, as compared with the
control group (p < 0.01). However, the 0.1 mmol/L ALA + 0.1 μg/mL LPS group and the 0.1 mmol/L BAY11-1072 + 0.1 μg/mL LPS group did not show a significant decrease in IκBα expression, as compared with the control group (Fig. 1 (a), (c)). The 0.1 μg/mL LPS group, the 0.01 mmol/L ALA + 0.1 μg/mL LPS group, and the 1.0 mmol/L ALA + 0.1 μg/mL LPS group showed a significant increase in NF-κB p-p65 expression, as compared with the control group (p < 0.05). However, the 0.1 mmol/L ALA + 0.1 μg/mL LPS group and the 0.1 mmol/L BAY11-1072 + 0.1 μg/mL LPS group did not show a significant increase in NF-κB p-p65 expression, as compared with the control group (Fig. 1 (a), (d)).

**Assessment of the inhibitory effect of NF-κB p65 nuclear translocation by ALA**

NF-κB p65 was expressed in all groups showed. However, NF-κB p65 was expressed in the cytoplasm, but not in the nucleus, of the control group, while the 0.1 μg/mL LPS group showed NF-κB p65 expression in the nucleus. NF-κB p65 was expressed in the nucleus, but not in the cytosol, of the 0.1 mmol/L ALA + 0.1 μg/mL LPS group and the 0.1 mmol/L BAY11-1072 + 0.1 μg/mL LPS group.
1072 + 0.1 μg/mL LPS group (Fig. 2).

**Assessment of the inhibitory effect of inflammatory cytokine secretion by ALA**

TNF-α secretion was clearly detected at 2 h after stimulation and increased up to 6 h. However, from 6 to 12 h after stimulation, the secretion level sharply decreased. After 12 h, the secretion level decreased to the same level as the control group (Fig. 3 (a)). At 6 h, the 0.1 μg/mL LPS group showed a significant increase in TNF-α secretion, as compared with the control group (p<0.01). However, the 0.1 mmol/L ALA + 0.1 μg/mL LPS group did not show a significant increase in TNF-α secretion, as compared with the control group (Fig. 3 (b)). IL-1β secretion was clearly detected at 2 h and increased up to 6 h after stimulation. However, from 6 to 12 h, the secretion level sharply decreased. After 12 h, the secretion level decreased to the same level as the control group (Fig. 3 (c)). At 6 h, the 0.1 μg/mL LPS group showed a significant increase in IL-1β secretion, as compared with the control group (p<0.01). However, the 0.1 mmol/L ALA +
0.1 μg/mL LPS group did not show a significant increase in IL-1β secretion, as compared with the control group (Fig. 3 (d)). IL-6 secretion continuously increased in every group (Fig. 3 (e)). At 12 h, the 0.1 μg/mL LPS group showed a significant increase in IL-6 secretion, as compared with the control group (p < 0.01). However, the 0.1 mmol/L ALA + 0.1 μg/mL LPS group did not show a significant increase in IL-6 secretion, as compared with the control group (p < 0.01).
tion, as compared with the control group (Fig. 3 (f)). IL-8 secretion continuously increased in every group (Fig. 3 (g)). At 6 h, the 0.1 μg/mL LPS group showed a significant increase in IL-8 secretion, as compared with the control group (p < 0.01). However, IL-8 secretion was not significantly increased in the 0.1 mmol/L ALA + 0.1 μg/mL LPS group, as compared with the control group (Fig. 3 (h)).

**Discussion**

After successful treatment of patients with periodontitis, local residual periodontal pockets may still be present. These residual pockets are a risk factor for recurrence of periodontitis. To inhibit inflammation in periodontitis, several types of adjunctive therapies have been studied. In this study, we focused on the anti-inflammatory agent ALA as a potential agent for adjunctive periodontal therapy. The aim of this study was to investigate the anti-inflammatory effects of ALA against LPS-stimulated HGFs, which are known to secrete inflammatory mediators during the immunological reaction in periodontitis34).

In many in-vitro studies, 0.1 μg/mL LPS has been used to investigate inflammation. Sipert al et al.35) and Suphasiriruj et al.36) added 0.01, 0.1, 1.0, and 10 μg/mL LPS to cultured cell including HGFs and found 0.1 μg/mL LPS stimulation induced the highest secretion of inflammatory cytokines, as compared with other LPS concentrations. For this reason, 0.1 μg/mL LPS was used in the present study.

In the mechanism of NF-κB signal transduction induced by LPS stimulation, LPS binds to cell-surface TLRs, which induces intracellular phosphorylation. On NF-κB signaling, the increase in p-1κBα expression leads to 1κBα degradation. As a result, NF-κB p-p65 expression increases and signal transduction continues to the inner nucleus. Ambili et al.37) studied gingival tissue derived from periodontitis patients and healthy patients and reported that gingival tissue derived from periodontitis patients had higher expression of inner-nucleus NF-κB compared with healthy patients. This implied NF-κB expression has a correlation to periodontitis-derived inflammation. Thus, in this study, the inhibitory effects of ALA on NF-κB signal transduction were investigated. BAY11-7082 was used as a positive control, as it is a well-known specific blocker of the NF-κB signaling pathway.38, 39)

The 0.1 μg/mL LPS group, 0.01 mmol/L and 1.0 mmol/L ALA group showed significant increases in p-1κBα expression, significant decreases in 1κBα expression, and significant increases in NF-κB p-p65 expression, as compared with the control group, suggesting that the addition of 0.1 μg/mL LPS activated NF-κB signal transduction even pre-administered with 0.01 or 1.0 mmol/L of ALA. However, the 0.1 mmol/L ALA group did not show a significant increase in p-1κBα expression, a significant decrease in 1κBα expression, or a significant increase in NF-κB p-p65 expression, as compared with the control group, suggesting that pre-administration of 0.1 mmol/L of ALA inhibited LPS-induced NF-κB signal transduction. There have been no studies about 0.01 mmol/L of ALA administration to cultured cells. However, we estimated that a concentration of ALA of 0.01 mmol/L was insufficient to inhibit NF-κB signal transduction. Milward et al.40) studied ALA administration against an immortal cell line derived from an oral squamous cell carcinoma of the alveolar process and found that an ALA concentration of >1.0 mmol/L caused >50% of the cells to lose adherence to the dish. Loss of cell adhesion was dependent on ALA concentration. However, an ALA concentration of <0.5 mmol/L caused few cells to lose adherence to the dish. Kiemer et al.41) studied the effect of ALA pre-administration against LPS-stimulated NF-κB pathway activation in RAW 264.7 macrophages using a gel shift assay and found that 100 μg/mL (equivalent to approximately 0.5 mmol/L) of ALA did not inhibit NF-κB binding activity. We also investigated the cytotoxic effect of ALA against HGFs using a cell growth curve as a preliminary experiment and found that cell growth was continuously suppressed in the 1.0 mmol/L ALA group, as compared with ALA non-administered group. For this reason, we considered that an ALA concentration of less than 0.1 mmol/L was insufficient to fully inhibit NF-κB signal transduction. A high concentration of ALA induced cytotoxic effects, but failed to inhibit NF-κB signal transduction. Thus, we considered that an ALA concentration of 0.1 mmol/L was an optimal concentration to inhibit NF-κB signal transduction and used this concentration to investigate NF-κB p65 nuclear translocation and inflammatory cytokine secretion.

An immunofluorescence assay was used to assess the inhibitory effect of ALA on NF-κB p65 translocation to the nucleus. The LPS-stimulated group showed NF-κB p65 expression in the nucleus. However, administration of ALA and the NF-κB signal blocker BAY11-7082 resulted in NF-κB p65 expression in the cytosol. Herath et al.23) conducted an immunofluores-
cence assay of NF-κB p65 translocation to the nucleus and an ELISA of IL-6/IL-8 secretion by LPS-stimulated HGFs, and reported increased NF-κB p65 expression in the nucleus and IL-6/IL-8 secretion in the LPS-stimulated group. These results suggest that LPS stimulation activated NF-κB signal transduction, NF-κB p65 is translocated to the nucleus and binds to DNA, which leads to secretion of inflammatory cytokines. However, ALA pre-administration inhibited NF-κB p65 translocation to the nucleus and suppressed secretion of inflammatory cytokines.

TNF-α, IL-1β, IL-6, and IL-8 are reported to be the main inflammatory cytokines secreted by HGFs. Fujita et al. reported that GCF derived from periodontal pockets from patients with periodontitis contained significantly greater levels of inflammatory cytokines, as compared with sulcus-derived GCF from healthy subjects without periodontal disease. Based on these results, we expected a correlation between the levels of cytokine secretion and destruction of periodontal tissue. Thus, pre-administration with ALA was expected to inhibit inflammatory cytokine secretion and subsequently inhibit periodontal disease progression. TNF-α and IL-1β showed remarkable increases from 2 to 6 h after LPS stimulation. Agarwal et al. investigated LPS-induced inflammatory cytokine secretion by HGFs and reported an increase in TNF-α and IL-1β expression levels until 8 h after LPS stimulation. After 8 h, the secretion levels decreased. These results are similar to those of the present study. Ohe et al. reported that IL-1Ra expression in HGFs was induced after stimulation with IL-1β or IL-6. Sawada et al. reported that the binding ability of cell surface TNF-α receptors was decreased after inflammatory stimulation. Based on these reports, we postulated that secreted TNF-α and IL-1β act on their own receptors on HGFs, and negative feedback caused a decrease in TNF-α and IL-1β secretion at 6 h after LPS stimulation. Secreted TNF-α and IL-1β might be diminished because of decomposition or reuptake by HGFs. However, ALA pre-administration inhibited TNF-α and IL-1β secretion from 2 to 6 h after LPS stimulation, as compared with the control group. IL-6 and IL-8 secretion continuously increased in all groups, including the non-LPS-stimulated group. Tabeta et al. reported that even without LPS stimulation and inflammation, HGFs continuously secrete IL-6. However, stimulation of inflamed HGFs with LPS or other stimulants caused an even larger increase in IL-6 secretion, which resulted in destruction of periodontal tissue. Oido-Mori et al. reported the HGFs also continuously secreted IL-8 even without inflammatory stimulation. The LPS-stimulated group showed a sharp increase in expression of IL-6 and IL-8 at 12 h after LPS stimulation. However, ALA pre-administration down-regulated IL-6 and IL-8 secretion to the same level as the control group. TNF-α and IL-1β are known to induce secretion of IL-6 and IL-8. We postulated that an increase in IL-6 and IL-8 secretion levels after an increase in TNF-α and IL-1β secretion is due to earlier secreted TNF-α and IL-1β, which stimulates HGFs to increase the secretion of IL-6 and IL-8. On the other hand, ALA pre-administration down-regulated IL-6 and IL-8 secretion to the same level as the control group because ALA pre-administration down-regulated secretion of TNF-α and IL-1β. There is also the possibility that ALA directly inhibited IL-6 and IL-8 secretion. Thus, further mechanisms need to be studied.

In conclusion, this study elucidated the following effect by ALA pre-administration: LPS stimulation of HGFs activated the NF-κB signaling pathway, resulting in secretion of inflammatory cytokines. ALA pre-administration inhibited IκBα phosphorylation in the NF-κB signaling pathway, even with stimulation by LPS, IκBα degradation and NF-κB p65 phosphorylation were also inhibited, which lead to the down-regulation of inflammatory cytokine secretion. This suggests that ALA pre-administration has the potential to inhibit inflammation of periodontal tissue and may become a candidate agent for adjunctive therapy. This is the first report about ALA administration against LPS-stimulated NF-κB signaling pathway activation in HGFs, which is a well-studied pathway in the inflammation process. Lee et al. reported that ALA pre-administration against TNF-α-stimulated rheumatoid arthritis fibroblast-like synovial cells inhibited activation of IκB kinase (IKK)-α and IKK-β, which was known as the upper cascade of the NF-κB signaling pathway. However, there are few reports regarding about the relationship between periodontitis induced inflammation and IKKs and the effect of ALA against IKKs. In the future, the effects of ALA administration on the upper cascade of the NF-κB signaling pathway and other inflammatory signaling pathways, for example, the MAPK pathway, should be investigated. Furthermore, the anti-inflammatory effects of ALA against LPS stimulation from periodontal pathogens, such as P. gingivalis, and the effect of ALA against secretion of other inflammatory mediators should also
be investigated.

Conclusion

Pre-administration of 0.1 mmol/L ALA to HGFs stimulated with 0.1 μg/mL of LPS inhibited activation of the NF-κB signaling pathway, nuclear translocation of NF-κB p65, and secretion of inflammatory cytokines, as compared with the control group. For this reason, ALA pre-administration has the potential to inhibit inflammation of periodontal tissue.

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The authors report no conflicts of interest related to this study.

References


LPS 刺激下ヒト歯肉線維芽細胞に対する α-リポ酸事前添加による
炎症性サイトカイン産生抑制効果の検討

石井マイケル大宜*1，村 櫻 悦 子*1，五十嵐（武内）寛子*1，
杉 司 洋 文*2，沼 部 幸 博*1

*1日本歯科大学生命歯学部歯周病学講座
*2日本歯科大学病院口腔外科

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連絡先：村桜悦子
〒102-0071 東京都千代田区富士見1-9-20
日本歯科大学生命歯学部歯周病学講座