Published in final edited form as:

Mol Oral Microbiol. 2018 February ; 33(1): 13–21. doi:10.1111/omi.12195.

The function of dendritic cells in modulating the host response

Liang Song^{1,2,*}, Guangyu Dong^{1,*}, Lijia Guo^{1,3,*}, and Dana T. Graves¹

¹Department of Periodontics, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

²Department of Stomatology, The Fifth People's Hospital of Shanghai, Fudan University, Shanghai 200240, China

³Molecular Laboratory for Gene Therapy and Tooth Regeneration and Department of Orthodontics, Beijing Key Laboratory of Tooth Regeneration and Function Reconstruction, Capital Medical University School of Stomatology, Beijing 100050, China

SUMMARY

Dendritic cells (DCs) are antigen-presenting cells that capture, process and present antigens to lymphocytes to initiate and regulate the adaptive immune response. DCs detect bacteria in skin and mucosa and migrate into regional lymph nodes, where they stimulate antigen-specific T and B lymphocyte activation and proliferation. DCs direct CD4 T cells to differentiate to T cell subsets such as Th1, Th2, Th17 and Treg cells. The periodontium is chronically exposed to oral bacteria that stimulate an inflammatory response to induce gingivitis or periodontitis. DCs play both a protective and destructive role through activation of the acquired immune response and are also reported to be a source of osteoclast precursors that promote bone resorption. FOXO1, a member of the forkhead box O family of transcription factors, plays a significant role in the activation of DCs. The function of DCs in periodontal inflammation has been investigated in a mouse model by lineage specific deletion of FOXO1 in these cells. Deletion of FOXO1 reduces DC protective function and enhances susceptibility to periodontitis. The kinase Akt, phosphorylates FOXO1 to inhibit FOXO activity. Thus the Akt-FOXO1 axis may play a key role in regulating DCs to have a significant impact on periodontal disease.

Keywords

Immune response; Forkhead; FOXO; Gingiva; Lymphocyte; Periodontal

INTRODUCTION

Dendritic cells (DCs) are antigen-presenting cells (APCs), which capture, process and present antigens to lymphocytes to initiate and regulate the adaptive immune response¹. Based on function and phenotype, DCs can be divided into plasmacytoid dendritic cells

Correspondence: Dr. Dana T. Graves, University of Pennsylvania School of Dental Medicine, 240 S. 40th Street, Evans F1B, Philadelphia, PA 19104, USA. Tel: +1 215 898 9068; dtgraves@upenn.edu.

*These authors contribute equally.

DR DANA GRAVES (Orcid ID : 0000-0002-4664-8529)

(pDCs) and conventional dendritic cells (cDCs). Langerhans cells are another member of the DC family found in oral mucosal epithelium and the skin epidermis². DCs play a key role in immune defense; when immune homeostasis mediated by DCs is disrupted, inflammatory destruction may occur³. There is ample evidence that DCs are activated in experimental periodontitis in animals and in humans with periodontitis. Interestingly, dendritic cells have the potential to play protective or destructive roles or both. Due to the limited number of studies examining cause and effect relationships this issue is not entirely clear. However there are reports in which deletion of Langerhans cells or reduced DC function through lineage specific FOXO1 deletion have been shown to increase susceptibility to periodontitis⁴⁻⁶, suggesting that in animal models DCs have an overall effect in the periodontium which is protective.

DCs and subsets—DCs are derived from CD34⁺ hematopoietic stem cells (HSCs) in the bone marrow⁷. These progenitor cells initially differentiate to immature DCs, which have high endocytic activity and low T cell activation potential^{8,9}. Immature DCs express various pattern recognition receptors (PRRs) that constantly sample the surrounding environment for pathogens such as viruses and bacteria¹⁰. Maturation of dendritic cells is induced by captured microbes or their components^{11,12}, inflammatory cytokines and ligation of select cell surface receptors.¹¹⁻¹³ Once DCs take-up antigen they become activated into mature dendritic cells and present pathogen fragments at their cell surface using MHC molecules. DCs initiate the acquired immune response by interacting with lymphocytes after migrating to lymph nodes¹⁴.

Dendritic cells can be subdivided into plasmacytoid (pDC) and conventional (cDC). pDCs are derived from lymphoid progenitors and have characteristics that resemble a cross between B cells and cDCs¹⁵. pDCs predominantly recognize viral antigens¹⁶, specializing in the production and secretion of type I interferons, IL-12, IL-6, TNF- α and pro-inflammatory chemokines¹⁷. pDCs enter the lymphoid nodes directly via the bloodstream¹⁸. Murine pDCs express B220, SiglecH, Ly6c and low amounts of CD11c. Human pDCs express CD4, CD123, HLA-DR, and blood derived cell antigen-2 (BDCA-2), as well as toll-like receptor (TLR)-7 and -9 but do not express the cDC-marker CD11c^{17,19}. pDCs can act as antigen presenting cells, but are much less efficient than cDCs.

cDCs also called classical dendritic cells or myeloid dendritic cells, express high levels of CD11c and display a characteristic morphology of long dendrite extensions²⁰. There are two primary cDCs subpopulations in mice: CD11b⁻ and CD11b⁺. CD103⁺CD11b⁻ cDCs populate most connective tissues and share their origin and function with lymphoid tissue CD8⁺ cDCs²¹. The CD11b⁺ cDC subset most often lacks the integrin CD103²². In human, cDCs express CD11b, CD11c, CD1a, CD1c, CD14, CD45, CD141, CD172a, CD206, Clec9a/DNGR1, XCR1, HLA-DR, Fc ϵ RI. cDCs present antigens and produce the stimulatory mediators TNF, NO and IL-12²³. cDCs recognize both bacterial and viral antigens^{24,25}. Immature cDCs patrol various tissues to sample foreign antigens. During maturation cDCs migrate to draining lymph nodes to present pathogen-derived peptides to T cells²⁶.

Langerhans cells are a special member of the DC family that is usually situated in the oral mucosal epithelium and the skin epidermis² and can be distinguished by expression of langerin/CD207²⁷. Langerhans cells play an important role in immune surveillance by promoting immunity or tolerance through activation of antigen specific T cells²⁷.

DCs modulate specific lymphocyte responses—The interaction between DCs and pathogens contributes to different types of adaptive immunity. The specific cytokines expressed by DCs are dependent on stimulation by pathogen-associated molecular patterns (PAMPS). As a result under certain circumstances DCs can stimulate an immune response along a particular direction such as Th1, Th2, Th17, or Treg. DCs promote Th1 polarization by expressing IL-12²⁸. IL-12 secretion from DCs is induced by CD40 engagement²⁹. DCs primed with antigen stimulate naïve T cells to differentiate to Th1 cells³⁰. Interferon regulatory factor 4 plays an important role in DC initiation of Th2 cell responses³¹. High-mobility group nucleosome-binding protein 1 (HMGN1) modulates DCs to induce Th2 responses in a TLR4-dependent manner³². DCs primed with antigens of *Streptococcus mitis* increase differentiation of Th2 cells³⁰. DCs promote B cells through release of B-cell activating factor (BAFF)³³ and a proliferation-inducing ligand (APRIL)³⁴. They also promote B cell differentiation to plasma cells both via the secretion of IFN- α and IL-6³⁵ and via direct cell-cell contact³⁶. DCs promote Th17 cell differentiation through secretion of the cytokines TGF- β , IL-23 and IL-1 β ³⁷. DCs can induce the differentiation of Treg cells via TGF- β and IL-10³⁸. For example, DCs incubated with *Propionibacterium acnes* antigens induce differentiation of lymphocytes to Tregs³⁰. DCs also regulate the recruitment and activation of NK cells through secretion of IL-27³⁹.

Evidence of DCs in periodontal disease

DC stimulated by oral pathogens can contribute to different types of adaptive immunity and can lead to reduced proteolytic or osteolytic activity through Th2 or Treg responses or an increase through induction of Th1 or Th17 lymphocytes (Fig. 1). Although it is well recognized that dendritic cells play a key role in initiating an adaptive immune response there are relatively few studies which provide a causal link between dendritic cells and periodontal breakdown, particularly in animal models where specific hypotheses can be tested⁴⁰.

DCs may promote periodontal disease through induction of Th1- or Th17-lymphocytes—DCs can potentially enhance periodontal bone loss through up regulation of Th1 or Th17 response. Th1 activity is correlated with the number of mature DCs in gingiva in periodontitis⁴¹. *Porphyromonas gingivalis* stimulates mature cDCs derived from individuals with chronic periodontitis to secrete IL-12 and IFN- γ ⁴². Both IL-12 and IFN- γ can promote Th1 responses and sustain inflammation⁴³. IFN- γ is the signature cytokine of Th1-type responses⁴⁴ associated with activating phagocytosis and the production of inflammatory cytokines and chemokines⁴⁵. Th1 responses have also been linked to increased RANKL expression⁴⁶, promotion of osteoclast formation and alveolar bone loss *in vivo*⁴⁷. Moreover, IFN- γ is present at high levels in periodontal lesions and is associated with progressive lesions or more severe periodontal disease⁴⁸.

Oral infection with *P. gingivalis* in mice increases the number of cDCs, which is positively correlated with the generation of a Th17 response^{47,49}. Oral infection with *P. gingivalis* and *Fusobacterium nucleatum* stimulate migration of cDCs to the lymph nodes and gingiva and is associated with increased IL-17 levels, as well as other pro-inflammatory factors such as TNF, IL-6 and IL-1 β , which contribute to alveolar bone loss^{4,50}. In humans IL-17 levels are correlated with more mature cDCs and increased periodontal bone loss⁴¹. IL-17 induces pro-inflammatory and osteoclastogenic mediators such as RANKL or TNF^{51,52}. Thus, cDCs are upregulated in response to periodontal infection and are associated with increased inflammation and bone loss. However, a cause and effect relationship has not been established.

Although Th17 and Th1 responses that are typically thought to promote periodontal bone loss, there is some indication that these responses may be protective. For example IFN- γ produced during a Th1 response can inhibit RANKL induced osteoclastogenesis⁵³. Th1 leukocytes also have the ability of enhance recruitment and the killing activity of neutrophils and macrophages, which promote bacterial clearance^{54,55}.

DCs may induce a protective response through induction of Th2-lymphocytes

—DCs triggered by *P. gingivalis* LPS induce a Th2 response through the TLR pathway^{56,57}. IL-4, the major Th2 type cytokine^{58–60} inhibits the production of MMPs and RANKL and up-regulates the MMP inhibitor TIMP and the RANKL inhibitor OPG^{61,62}. Inhibition of MMPs and RANKL leads to reduced severity of experimental periodontitis⁶³. IL-4 levels are reduced in patients with chronic periodontitis compared to healthy persons⁶⁴. IL-4 levels increase after non-surgical periodontal therapy, suggesting a protective role of Th2 cells⁶⁵. Although Th2 responses are generally thought of as being protective, there is also evidence that Th2 lymphocytes can play destructive role in periodontal disease. Mice infected with *Tannerella forsythia* causes a pronounced Th2 bias and induce alveolar bone loss⁶⁶.

DCs have the ability to stimulate naïve B cells^{67,68}. In a murine model, oral infection stimulated cDCs to migrate to lymph nodes, inducing formation of plasma cells and the production of bacteria-specific antibodies. When DC function is reduced there is less DC migration to the lymph nodes, reduced numbers of plasma cells and less bacteria-specific IgG1 production, leading to more alveolar bone loss compared to control mice⁴. This supports the contention that DCs activate a protective antibody response that leads to less bone loss.

DCs protective role in periodontal disease through Treg response—

Treg cells limit excessive inflammation and bone loss⁵⁴. In active periodontal lesions, Treg-related cytokine levels are inversely related to RANKL levels^{69,70}. Inhibition of Treg function leads to higher levels of IFN- γ , TNF- α and RANKL and more alveolar bone loss⁷¹. Oral DCs have the capacity to induce a Treg response through the secretion of IL-10 and TGF- β ⁷². The importance of IL-10 is illustrated by the finding that in IL-10 knockout mice, susceptibility to *P. gingivalis*-induced alveolar bone loss is greatly increased⁷³. Moreover, after periodontal treatment, inflammation is reduced and IL-10 expression is increased⁷⁴.

DCs may affect periodontal disease through enhancement or attenuation of the innate immune response—

cDCs produce a number of mediators that can modulate the innate immune response. *P. gingivalis* and LPS stimulate DCs to produce TNF- α ⁷⁵ and IL-8¹². *P. gingivalis* binds to TLR-2 to activate complement receptor-3 (CR3), and subsequent binding to CR3 by *P. gingivalis* fimbriae contributes to the induction of inflammatory cytokines such as TNF⁷⁶. In addition, *P. gingivalis* may affect dendritic cells by affecting autophagy and intracellular killing^{77,78}. Chemokines produced by DC can attract neutrophils and monocytes to sites of inflammation⁷⁹ enhancing inflammation and the expression of factors that stimulate osteoclastogenesis⁸⁰ (Fig. 1). Meanwhile IL-10 and TGF- β from DCs can potentially have the opposite effect, reducing inflammation⁸¹.

The role of Langerhans cells in periodontal disease—Langerhans cells, a subset of DCs have been linked to periodontal disease. There is a positive correlation between the number of Langerhans cells in the gingival epithelium of chronic periodontitis patients versus healthy persons^{82,83} and increased numbers in individuals with chronic gingivitis compared to non-inflamed gingiva⁸⁴. There is increased migration of Langerhans cells to the gingival epithelium in response to the accumulation of bacterial plaque⁸⁵ and a decrease following periodontal treatment⁸⁶. In one of the few cause and effect studies, ablation of Langerhans cells in experimental periodontitis in mice results in reduced numbers of Tregs, elevated production of RANKL and enhanced alveolar bone loss⁶. Taken together these results suggest that Langerhans cells are increased by periodontal inflammation and have a protective effect through the generation of Treg cells. The results are also consistent with findings that reduction of cDC activity through deletion of FOXO1 increases periodontal disease susceptibility in both young and aged mice^{4,5}, suggesting that DCs have a protective function against increased periodontal inflammation.

Evidence of DC to osteoclast differentiation in periodontal disease

DCs as a source of osteoclast precursors—DCs are the professional antigen-presenting cells that also share several features with osteoclasts. Both DCs and osteoclasts are derived from a common hematopoietic precursor and exhibit phagocytic activities⁸⁷. *In vitro*, these precursors can be stimulated to differentiate to DCs by granulocyte monocyte colony stimulating factor (GM-CSF) and IL-4 or osteoclast precursors by M-CSF⁸⁸. There is increasing evidence that committed immature cDCs in some inflammatory conditions such as rheumatoid arthritis or periodontitis can transdifferentiate toward osteoclasts in the presence of RANKL⁸⁷. The co-culture of CD11c⁺ DCs with CD4⁺ T cells and *Aggregatibacter actinomycetemcomitans* produces osteoclasts that can induce bone resorption *in vitro* and *in vivo*⁸⁹. Moreover, the differentiation of DCs to osteoclasts could potentially be enhanced by bacteria induced inflammation. Thus, immature cDCs may be directly involved in osteoclastogenesis and contribute to bone loss in rheumatoid arthritis, histiocytosis, or periodontitis⁹⁰ (Fig. 2).

Immature cDCs either from bone marrow or from spleen are able to develop into osteoclasts, but mature cDCs do not have this ability. cDC-derived osteoclast formation is positively regulated by pro-inflammatory cytokines such as IL-1 β , TNF- α and negatively regulated by IFN- α , IFN- γ , IL-2 and IL-4⁹¹. *In vivo*, immature CD11c⁺ cDCs can form osteoclasts

when injected into osteopetrotic mice that normally lacked osteoclasts⁹². mRNA profiling compared DC-derived and monocyte-derived osteoclasts and showed that both formed molecularly indistinguishable mature osteoclasts. Interestingly, fewer genes need to be up- or down-regulated when osteoclasts are formed from cDCs compared to monocytic precursors⁹³.

In humans, cDCs are contributors to inflammatory bone destruction. Synovial fluid from arthritic patients increases the differentiation of osteoclasts from immature but committed cDCs⁹⁰. Moreover, the presence of Th17 cells is associated with the emergence of cDC-derived osteoclasts⁹². In myeloproliferative diseases, the participation of DC to osteoclast formation has also been suggested. Langerhans cell histiocytosis (LCH) is a rare disease caused by the clonal accumulation of dendritic Langerhans cells. LCH is frequently associated with osteolytic lesion and multinucleated giant cells expressing osteoclast markers (TRAP, cathepsin K, MMP9). Bone loss in this disease can be accounted for the transdifferentiation of cDCs to functional osteoclasts both *in vivo* and *in vitro*⁹⁴.

PI3K/Akt-FOXO1 signaling pathway in DCs

FOXO1 promotes DC activity and Akt enhances DC survival and proliferation

—FOXO1, a member of forkhead transcription factor family, plays an important role in the regulation of many cellular and biological processes that include protection against oxidative stress, apoptosis and progression through the cell cycle⁹⁵. Surprisingly FOXO1 can have opposite effects depending upon the microenvironment and the specific cell type⁹⁶. FOXO1 affects immune responses by controlling cytokine production⁹⁷, protecting hematopoietic stem cells from oxidative stress⁹⁵ and by promoting lymphocyte homeostasis through development of T regulatory lymphocytes and maintenance of naïve T cells⁹⁸. Lineage specific deletion of FOXO1 in cDCs reduces their capacity for bacterial phagocytosis, migration and binding to lymphocytes⁹⁹. FOXO1 is needed for efficient DC homing to lymph nodes and regulates CCR7, a key receptor needed for the DC homing⁹⁹. FOXO1 participates in cDC activation of both T and B lymphocytes and regulates expression of ICAM-1, which is needed to form an immune synapse. FOXO1 regulates these key molecules by binding to their promoters to transactivate transcription⁹⁹. In DCs, FOXO1 mediates LPS induced IL-6 and IL-12 expression, but reduces IL-10 production¹⁰⁰. In keratinocytes, *P. gingivalis* induces loss of barrier function and apoptosis by reducing expression of genes associated with epithelial barriers (integrin beta-1, -3 and -6) and increasing those that stimulate apoptosis¹⁰¹. In addition *P. gingivalis* induces reactive oxygen species (ROS) that activate FOXO transcription factors through Jun-N-terminal kinase (JNK) signaling, which may modulate oxidative stress responses in gingival keratinocytes¹⁰².

Forkhead box O (FOXO) transcription factors are downstream targets of the serine/threonine protein kinase B (PKB)/Akt¹⁰³. Akt is a kinase, which regulates processes of cellular proliferation and survival. The PI3K-Akt pathway has been reported to regulate cDC proliferation and survival¹⁰⁴. Phosphorylation of FOXOs by Akt inhibits the transcriptional function of FOXOs and contributes to cell survival, growth and proliferation¹⁰³. FOXO signaling is regulated by interactions with other intracellular proteins as well as post-

translational modifications such as phosphorylation¹⁰³. In addition to FOXOs, Akt phosphorylates and inhibits glycogen synthase kinase-3 β (GSK-3 β)¹⁰⁵. GSK3 is a serine protein kinase involved in regulation of DCs¹⁰⁶. PI3K reduces GSK3 activity via Akt phosphorylation^{107,108,109}. In plasmacytoid dendritic cells, PI3K-Akt pathway is an important regulator of type I interferon production via activation of the interferon-regulatory factor 7^{110,111}.

PI3K/Akt-FOXO1 signaling pathway in DCs in periodontal disease—It has been shown that FOXO1 activation promotes the expression of inflammatory cytokines in a number of cell types including dendritic cells⁴, macrophages¹¹² and epithelial cells¹¹³. This result suggests that deletion of FOXO1 in DC could reduce periodontal bone loss through reduced inflammatory cytokine expression. However experimental evidence is the opposite; deletion of FOXO1 in DC increases susceptibility to periodontitis.

P. gingivalis increases FOXO1 gene expression in cDCs through TLR signaling^{99,114}. Oral infection stimulates recruitment of cDCs to oral mucosal epithelium and connective tissue⁴. Deletion of FOXO1 specifically in cDCs blocks enhanced recruitment of cDCs and increases susceptibility to periodontitis⁴. Oral infection stimulates migration of cDCs to the cervical lymph nodes, the formation of plasma cells and bacteria-specific antibody production⁴. Each of these is significantly blocked with lineage specific FOXO1 deletion in cDCs by CD11c driven Cre recombinase⁴. When FOXO1-deleted cDCs exhibited a compensatory increase in IL-1 β and IL-17 in response to oral infection *in vivo*, which likely occurred from a reduced protective antibody response⁴. This hypothesis is supported by a failure to upregulate APRIL and BAFF mRNA when FOXO1 in DC is ablated whereas both mediators are increased by wild type cDCs in response to bacterial stimulation⁹⁹. This is significant since cDCs regulate B cells through production of BAFF and APRIL. Moreover, deletion of FOXO1 in DC leads to reduced antibody production⁴ and reduced lymphocyte activity. Thus, the principal effect of FOXO1 may be due to a reduced ability of DC to stimulate a protective acquired immune response.

There have been few studies that have examined the Akt-FOXO1 pathway in dendritic cells. Those studies that have been reported have not used a lineage-specific approach, limiting interpretation of the data. For example, it has been shown that a global deletion of transforming growth factor beta-activated kinase 1 (TAK1) disrupts Akt-FOXO in DC and may disrupt generation of Tregs¹¹⁵. However, the direct linkage to the Akt FOXO1 axis in DC was not demonstrated due to the global nature of the gene deletion and since TAK1 has other substrates such as NF- κ B that may also be responsible for the effect. In another study the compound piperlongumine was shown to inhibit DC maturation and reduce the symptoms of rheumatoid arthritis. Although these changes were associated with an inhibition of Akt pathway in DC a cause and effect relationship was not established because piperlongumine affects several other pathways including NF- κ B¹¹⁶.

CONCLUSION

DCs are antigen-presenting cells, which capture, process and present antigens to lymphocytes to initiate and regulate the adaptive immune response¹. DCs play a critical role

in the adaptive immune response and can modulate lymphocyte polarization that is potentially destructive (Th1, Th17) or protective (Th2, Treg). DCs can transdifferentiate into osteoclasts and cause bone resorption during periodontal inflammation. However it is not clear whether immature DCs represent a significant source of osteoclast precursors in periodontal inflammation. Recent evidence makes it clear that the FOXO1 signaling plays an important role in DCs (Fig. 3). Our results are consistent with the hypothesis that FOXO1 deletion leads to loss of protection against bacterial challenge in the periodontium. We hypothesize that this may be due to a reduced capacity to upregulate the acquired immune response when FOXO1 is deleted. Alternatively, if DC are an important source of osteoclast precursors, deletion of FOXO1 could potentially increase DC to osteoclast differentiation to enhance bone loss. However, the precise mechanisms through which FOXO1 modulates periodontal disease susceptibility through altering DC function remains to be established. It is possible that FOXO1 enhances formation of Tregs to limit periodontal bone loss or increases formation of plasma cells to generate a protective antibody response. Moreover, the potential role of Akt in modulating FOXO1 may also be an important component of DC function that remains to be investigated in the context of periodontal disease.

Acknowledgments

This work was supported by National Institutes of Health funding from the DE019108 and DE021921. The authors declare no competing financial interests. We thank Daniel Feinberg for help in preparing this manuscript.

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Figure 1.

DCs activate T cells and innate immune response in periodontal disease. Immature DCs capture oral bacteria, which induces migration to lymph nodes and maturation. Mature DCs can attract neutrophils and macrophage to sites of inflammation through IL-8 or TNF- α and present bacterial antigen to lymphocytes. DCs in turn may stimulate naïve T cells to differentiate along several pathways including Th1, Th17, Th2 and Treg cells. Cytokines produced by Th1 and Th17 cells may up-regulate TNF- α and IL-1 β and cause greater MMP and RANKL expression, more osteoclast formation and more bone resorption. Th2 and Tregs have the opposite effect and may restrain inflammatory cytokine production to limit bone loss.

Figure 2.

The pathway of DCs transdifferentiating to osteoclast.

DCs and monocytes are derived from a common myeloid progenitor under the stimulation of GM-CSF and IL-4 (for DCs) or M-CSF (for monocytes). Immature cDCs can transdifferentiate to osteoclasts under the influence of M-CSF and RANKL. Thus, cDCs can transdifferentiate into osteoclasts and cause bone resorption in some inflammatory environments such as periodontitis and rheumatoid arthritis.

Figure 3.

The Akt-FOXO1 signaling pathway maintains DC's protective or destructive function to control periodontal inflammation. FOXO1 is essential for DCs to maintain their protective function and control periodontitis. Phosphorylation of FOXO1 by Akt inhibits FOXO1 activity and reduces the protective function of DCs enhancing susceptibilities to periodontitis.