REVIEW ARTICLE

The multitude of reactive oxygen species on periodontal health and disease

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Abstract

As soon as oxygen was used as the terminal electron acceptor in aerobic respiration, then came the curse in the form of reactive oxygen species (ROS). So as to overcome this problem the evolving organism had developed elaborate defence machinery to escape from these reactive by-products of its own metabolism, and also developed a mechanism by which there is utilization of these species in physiological processes to gain a survival advantage. Thus it can be said that reactive oxygen species (ROS) exert a multitude of biological effects that ranges from physiological regulatory functions to damaging alterations participating in the pathogenesis of number of diseases.

Periodontitis, an inflammatory disease of the supporting tissues of the teeth, is initiated and perpetuated by a small group of predominantly gram-negative, anaerobic or microaerophilic bacteria that colonize the subgingival area. These bacterial species result in the production of various cytokines including interleukin-8 and TNF-α, further causing an increase in number and activity of polymorphonucleocytes (PMN) along with these cytokines, PMNs also produce reactive oxygen species (ROS) superoxide via the respiratory burst mechanism as the part of the defence response to infection. ROS, when produced in excess, have deleterious effects on tissue cells. Human body has its own defence mechanisms to eliminate them as soon as they are formed so as to counter the harmful effects.

Recently, as the medical and dental research regarding ROS, free radicals antioxidant defence mechanisms has expanded tremendously, this review paper focuses on the key roles of ROS in both health and periodontal disease.

Introduction

Periodontal disease is an inflammatory disorder of the supporting tissues of the teeth that causes tissue damage through the complex interactions between host defence systems and periodontopathic bacteria. The role of reactive oxygen species (ROS) is likely to be common to both the host and bacterial-mediated pathways of tissue damage.[1]Many normal biologic processes need reactive oxygen species (ROS) and Free Radicals.[2]Priestley and Scheele who were the discoverers of oxygen, and Lavoisier, the discoverer of the oxidation process, realized that oxygen exhibit a dual role, acting either as a sustainers or/and a destroyer of life.[3] In Priestley's words 'for, as a candle burns out much faster in oxygenated than in common air, so we might, as may be said, live out too fast, and the animal powers be too soon exhausted in this pure kind of air'. Gerschman's work in 1959 gave an idea leading to the understanding of molecular mechanism of oxygen toxicity.[4]These free radicals, at low concentrations, play a beneficial role in stimulating the growth of fibroblasts and epithelial cells in culture, but at higher concentrations they may be injurious to health.

Bacterial pathogens in dental plaque stimulate host cells to release various pro-inflammatory cytokines such as interleukins and TNF-α which attract polymorphonucleocytes (PMNs) to the site of infection. PMNs confront this bacterial challenge by producing proteolytic enzymes and $O_2$by oxidative burst. An anti-oxidant defence system of human body includes endogenous anti-oxidants such as Vitamin A, C, E, and B, carotene, and enzymatic oxidants such as superoxide dismutase, catalase, and myeloperoxidase. This antioxidant

system detoxifies ROS and modifies them to form less reactive species.

This paper reviews current knowledge of role of reactive oxygen species and antioxidant defence mechanisms in inflammatory diseases, and to illustrate how such processes may play a role in the pathogenesis of periodontal disease, and indeed in future therapeutic strategies.

Reactive Oxygen Species - The Free Radicals

A free radical is defined as any atom or group of atoms that has an unpaired electron in its outer orbit. The reactive oxygen species includes hydrogen peroxide and lipid peroxide with no unpaired electron, and superoxide (O_2^-), hydroxyl (^-OH), peroxyl (ROO), alkoxyl (RO) radicals, radicals of nitric oxide (^-NO), nitrogen dioxide (NO_2), peroxynitrite ($ONOO^-$), ozone (O_3) and possibly singlet oxygen. Though hydrogen peroxide and lipid peroxide are not free radicals they are capable of radical formation in the extra and intracellular environments. Exogenous sources include heat, trauma, ultrasound, ultraviolet light, ozone, smoking, exhaust fumes, radiation, infection, excessive exercise, and therapeutic drugs. Endogenous sources include by-products of metabolic pathways, electron leakage from mitochondrial electron transport systems forming superoxide; functional generation by host defence cells (phagocytes) and cells of the connective tissues. These oxidants whether they are free radicals or ROS are known to play an important role in periodontal tissue destruction.[2]

GENERATION OF ROS

Generation of ROS in cells can occur by two ways - either deliberately or accidentally. ROS are generated deliberately by cells in certain circumstances because they are useful, e.g. activated phagocytic cells generate ROS to exert a bactericidal action. Under normal circumstances, however, the major source of ROS in the cell is electron leakage from the electron transport chain in the mitochondria and endoplasmic reticulum.[5,6]

ANTIOXIDANT DEFENCE SYSTEM

Halliwell suggested that "an antioxidant is any substance that when present at low concentration compared to those of an oxidisable substrate significantly delays or prevents oxidation of that substrate".Anti-oxidants can be classified depending on their mode of function, their location of action, solubility, and their origin/source. A functional classification of antioxidant on the way they act appears to be more useful. (Table 1).[7]

ROLE OF REACTIVE OXYGEN SPECIES IN NORMAL PHYSIOLOGICAL PROCESSES

It would have been surprising if the evolving life form had not developed some mechanism to utilize these rather harmful radicals to its physiological advantage.

1. Role of ROS in Oxygen Sensing

Oxygen sensing has a crucial role in maintaining cellular health. It allows cells to initiate adaptive responses increasing the likelihood of survival in anticipation for restricted oxygen availability. In hypoxic condition, the Electron Transport Chain releases O_2, thus acting as an oxygen sensor. The hypoxia induced release of ROS act as signalling molecules that trigger diverse functional responses, among which is the increased production and stabilization of the hypoxia-inducible factor- 1 (HIF-1). A mutual regulation has been found for both HIF-1 and ROS.[9]

2. Role of ROS in normal vascular diameter regulation

ROS, most commonly superoxide anion and hydrogen peroxide which are present in mitochondria, have been identified to play a crucial role in normal vascular physiology in response to factors as shear-stress. In vascular system ROS originate mainly from mitochondria and this was confirmed using electro biophysical methods that assessed the ROS generation and the response of vessel diameter to the presence of antioxidants and the inhibitors of mitochondrial complexes.[10]

3. Role of ROS in signal transduction

ROS act as signalling messengers in a pathway from cytokine-receptor interactions to activation of transcription factors. H_2O_2 play a role in inducing Ca^{2+} mobilization, thus modulating the intracellular signalling pathway.[11]

4. Role of ROS in immune system

ROS deeply take part in both arms of the immunological defense system, the innate and the acquired responses. Exaggerated ROS production as a part of the oxidative burst in activated phagocytes upon exposure to environmental pathogens present in the local inflammatory milieu represents one of the first line of defense mounted against the invading pathogens. Due to activation of the membrane bound NADPH oxidase enzyme, O_2 consumption in polymorphonuclear leucocytes increases by at least 100-fold during phagocytosis. This leads to generation of ROS which act on the cell membrane of invading organisms.ROS are involved in the acquired immune response because excess ROS continue to be locally produced by the activated phagocytes and consequently enhance the intracellular signal transduction cascades within the

T lymphocytes and thereby decrease their activation threshold. Phagocytic cells kill bacteria by a mechanism known as respiratory burst resulting in the generation of bactericidal ROS.[12]

5. Reactive oxygen species in ageing

ROS also has an impact on the process of biological ageing such as, increased lipid peroxidation, damage to mitochondrial function such as membrane alteration, mitochondrial DNA damage especially the region coding for NADH dehydrogenase subunit; accumulation of oxidized products of cellular protein and DNA and their detection in body fluids; and altered antioxidant defence.[13]

DAMAGE CAUSED BY REACTIVE OXYGEN SPECIES TO BIOMOLECULES

ROS are highly toxic to all types of biological molecules including DNA, lipids, and proteins.

A. Lipids

Lipid biomolecule is the most susceptible to the damaging effects of ROS. Oxidative destruction of lipids, particularly of polyunsaturated fatty acids (PUFA) initiates a self-perpetuating chain reaction predisposing to atherosclerosis (Fig. 1)[8].Such a reaction is further helped by transition metals leading to generation of lipid peroxyl (ROO·) and lipid alkoxyl (RO·) radicals. Biomarkers commonly employed for lipid peroxidation are, conjugated dienes, thiobarbituric acid reactive substances (notably MDA), isoprostanes, ethane/pentane, and other volatile hydrocarbons. Another aldehyde formed by lipid peroxidation is acrolein, which is more cytotoxic than MDA and may be a better biomarker.[14] Isoprostanes form following peroxidation of PUFA side chains of lipids and are currently regarded as the best biomarkers of lipid peroxidation e.g., F2‐isoprostanes.[15]

B. DNA

The genetic material in a living organism is potentially vulnerable to ROS directly as well as indirectly. ROS can react with DNA in distinct ways (figure 2)[8]

1. The chemically predominant reaction is the breakage of double bonds in the DNA bases resulting in the loss of UV absorption at 260 nm.
2. After H_2O_2 treatment all the four DNA bases, altered as well as unaltered, are liberated and detected in the Free State.
3. A break in the sugar-phosphate backbone is mainly due to an indirect result of prior base alteration and removal.[16]

The detection of oxidized nucleobases such as 8-hydroxyguanosine in human urine has been taken as evidence for a continual oxidative attack on DNA.

C. Protein

Unless very extensive, a random attack of ROS on proteins is unlikely to be very damaging (unlike the situation for lipids and DNA). A useful indicator of oxidative damage to proteins is measurement of carbonyls.[17, 18]

POLYMORPHONEUTROPHILS PRODUCING ROS

The role of periodonto-pathogens and the "Priming" effect.

The product of some bacteria in dental plaque may lead to altered PMN function, modifying their response to a second stimulus. This action of preparing PMN for stimulation is referred to as "Priming". P. gingivalis lipopolysaccharide causes a dose dependent increase in O_2production by formylmethionyl-leucyl-phenylalanine (FMLP)-stimulated PMN derived from rapidly progressive periodontitis patients.P. gingivalis releases trypsin like protease enzyme which stimulates neutrophils thus producing O_2. An extract of A. Actinomycetemcomitans increases H_2O_2 production following stimulation with FMLP and zymosan. Oral treponemes possess factors which inhibit the O_2 production by PMN.[7]

How are reactive oxygen species responsible for causing periodontal tissue destruction?

Periodontal disease can be caused by immune reaction between pathogenic bacteria and host. Polymorphoneutrophil is the most abundant leukocyte within the periodontal environment. PMNLs constitute about 90% of leukocytes that enter GCF and 50% of those that infiltrate the junctional epithelium. Although, defense mechanism is their primary role, they are also capable of causing periodontal damage through the elaboration of the ROS's. They are also known to release lysosomal enzymes. The actions of the reactive oxygen species that may cause periodontal tissue damage include the following: (figure 3)[1].

1. Damage to the DNA.
2. Degradation of the Ground substance (including hyaluronic acid and proteoglycans),
protein damage.
3. Collagenolysis either directly or as a result of oxidation of important enzymes eg:
Antiproteases such as α_1-antitrypsin.
4. Release of excessive pro-inflammatory cytokine through NF-κBactivation.
5. PG-E_2 production via lipid peroxidation (through activation of cyclooxygenases and
lipo-oxygenases) and superoxide release, both of which causes bone resorption.
6. It is a known fact that IL-1 and TNF-α positively regulate their own production.

Through the NF-κBsystem, thus it is possible that the additive effects of endotoxin mediated

cytokine production and that arising from the respiratory burst of PMNL's in response to the same organisms, could lead to periodontal inflammation and subsequent attachmentloss.[19]

EVIDENCE OF TISSUE DESTRUCTION BY ROS IN PERIODONTITIS

Periodontal tissue destruction is considered to be caused by aberrant inflammatory /immune response to microbial plaque surrounding the gingival margin and due to the prolong release of neutrophil enzyme and ROS. Thiobarbituric acid reactive substances have been found in periodontal disease. In a study conducted on chronic periodontitis patients by Wei et al, he measured the total oxidant status (TOS), lipid peroxidation levels and superoxidase dismutase (SOD) in saliva serum and GCF before and after periodontal therapy. They concluded that the levels of TOS and SOD values were significantly higher in chronic periodontitis patients as compared to healthy individuals. However after periodontal therapy, the levels significantly decreased as compared to baseline values.

A Japanese group has investigated 8-hydroxydeoxyguanosine levels in saliva by ELISA test and found that levels were higher in samples from subjects with chronic periodontitis as compared with periodontally healthy controls.[20]

How can the antioxidant status be measured?

Anti‑oxidants status, ROS and free radicals, can be measured in serum, gingival crevicular fluid (GCF) and saliva. But their levels in saliva and GCF provide a more accurate status of periodontal disease activity.

Plasma Antioxidant Status in Periodontal Diseases

Pussinen et al in 2003 observed an inverse relationship between serum vitamin C concentrations and antibody levels to Porphyromonas gingivalis.[21] It was noticed by Panjamurthy et al that lower plasma vitamin C, vitamin E and reduced Glutathione levels are seen in periodontitis subjects. In contrast to this antioxidant enzyme levels were raised and this can be due to a protective response to oxidative stress.[22] Total antioxidant capacity (TAOC) concentration is reduced in serum and plasma of periodontitis patients.[23] Tamaki et al found a positive correlation between plasma oxidative status and clinical attachment loss in patients in the maintenance phase of periodontal treatment. Systemic increase in oxidative stress influences the rate of progression of periodontal disease.[24]

Salivary Antioxidant Status in Periodontal Diseases

The total antioxidant concentration in the saliva of periodontitis patients is lower when compared to periodontally healthy controls.[25] Markers of oxidative damage (malondialdehyde 8-hydroxy-deoxy-guanosine) were found to be higher in saliva of periodontitis patients which decreased following initial treatment.[20]

GCF Antioxidant Status in Periodontal Diseases

The most important antioxidant in GCF is reduced GSH (Glutathione)and is significantly lower in periodontitis subjects relative to matched control subjects. A positive correlation between GCF lipid peroxidation and periodontopathogens and a negative correlation between GCF GPX and periodontopathogens was reported by Tsai et al. They came to a decision that the increased levels of lipid peroxidation with decreased level of antioxidants proved that oxidative stress, after the stimulation of periodontopathogens might play a role in the pathogenesis of periodontitis. [26]

Periodontal Tissue Antioxidant Status in Periodontal Diseases

According to Giorgi et al subjects with gingivitis experienced higher levels of GSH in gingival tissue samples when compared to controls.[20]It was found that with increasing pocket depth in subjects with periodontitis, the tissue levels of Catalase and Super Oxide Dimutase (SOD) decreased. On the contrary, increased levels of SOD activity was observed in the GCF and gingival tissue samples of periodontitis subjects.[27] Higher levels of thiobarbituric acid reactive substances (TBARS), a marker of oxidative stress was found in the gingival tissue obtained from unresolved pockets following Phase I therapy in patients with chronicperiodontitis.[28]It was noticed by Panjamurthy et al that there is increased levels of TBARS and enzyme antioxidants with lower levels of scavenging antioxidants in the gingival tissue of subjects with periodontal disease when compared to controls.[21] Also, Borges et al reported increased activities of myeloperoxidase, glutathione-S-transferase, Glutatione Peroxidase (GPX), oxidized GSH and higher levels of TBARS in gingival tissue of chronic periodontitis patients when compared to controls, which suggests that there exists a correlation between oxidative stress biomarkers and periodontal diseases.[29]

Conclusion

Physiological alterations and pathological status, directly or indirectly produced by free radicals/reactive oxygen (FR/ROS) species actions, depend on disequilibrium between increased FR/ROS production and decreased (or insufficiently increased) anti-oxidant levels or activities. Such conditions usually lead to impairment of part or all of the anti-oxidant defence system and to the appearance of biological damage.

The key messages that we can get from the above review is

a) Infection, smoking UV light etc can result in generation free radicals , so exposure to these should be avoided.
b) Consumption of few nutrients such as vitamin C and E, β-carotene, manganese and selenium should be advised as they contain anti-oxidant ability which helps to fight oxidative insults to the periodontal tissues.

The above concept led to emergence of a need for appropriate "anti-oxidant therapy" in inflammatory disease. The successful therapeutic manipulation of the cellular response by antioxidant molecule might necessitate the maintenance of the critical balance between FR/ROS and antioxidant defence systems. The antioxidants should be delivered selectively to specific cell types. Also it is essential to define the concentrations suitable for blocking inappropriate cell responses but leaving the unimpaired physiological levels of FR/ROS activity necessary for normal cell function.

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Table 1 - Classification of antioxidant (7)

Type of defence System	**Mode of action**	**Examples**
Preventive antioxidants	The formation of free radicals is supressed: a) Non radical decomposition of LOOH and H_2O_2 b) quenching of active O_2 c) sequestrationof metal by chelation	a) catalase, glutathione peroxidase , and S-transferase. b) Superoxide dismutase, carotenoids. c) Transferrin, ceruloplasmin, albumin, haptaglobin
Radical scavenging (chain breaking) anti-oxidants	Chain initiation and chain propogation is inhibited by radical scavenger.	Hydrophilic (water attracting): uric acid, ascorbic acid, albumin, bilirubin. Lipophilic (lipid attracting): ubiquinol, vit A, vit E, carotenoids.
Repair and *de novo* enzymes	The damage is repaired and there is reconstitution of membranes.	DNA repair enzymes,lipase, protease, transferase.

Table 2 - Defence against Reactive Oxygen Species (8)

Free radical generation is prevented by:	
1. Coupling of ROS generating systems. 2. Metal chelators ferritin, transferrin, ceruloplasmin and other metallothioneins. 3. Melanin. 4. Target modification, e.g. stable modification of LDL by dehydroascorbate.	To prevent leakage of O_2 radicals to the environment. Sequestering of metals to prevent generation of hydroxyl radical. Prevents UV radiation damage. Imparts resistance to metal ioninduced Oxidation.

Interception of free radicals generated ***Non-enzymatic*** 1. α-tocophercl (vitamin E) 2. Ascorbate (vitamin C) 3. Plasma proteins 4.Bilirubin 5. Glutathione(GSH) 6. β-carotene 7. Chemicals, e.g. food additives ***Enzymatic*** 1. Superoxide dismutase (SOD) $O_2 + O_2 + 2H^+ \rightarrow H_2O_2 + O_2$ 2. Catalase $2H_2O_2 \rightarrow 2H_2O + O_2$ 3. Glutathione peroxidase $H_2O_2 + AH_2 \rightarrow 2H_2O + A$	Before free radicals can cause cellular damage, they are intercepted to harmless end products. Converts superoxide to hydrogen peroxide. Breaks down $H_2O_2$to H_2O and oxygen(O_2). Uses a secondmolecule of H_2O_2as electron acceptor. Removes $H_2O_2$and other hydroperoxide using an organic substrate as electron acceptor.
Repair mechanisms of damage caused by free radicals	DNA repair systems

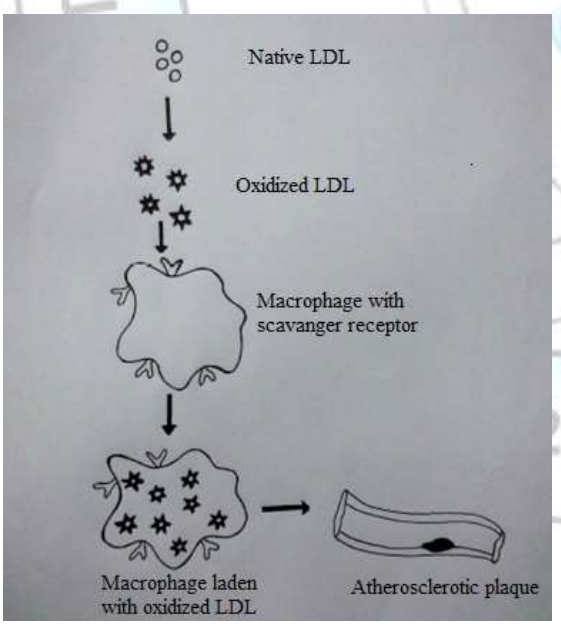

Figure 1 - Scavenger receptors of macrophage internalize oxidized LDL (low density lipoprotein). Macrophages are loaded with lipid droplets called foam cells as internalized cholesterol does not downregulate this route of uptake. There is deposition of cholesterol

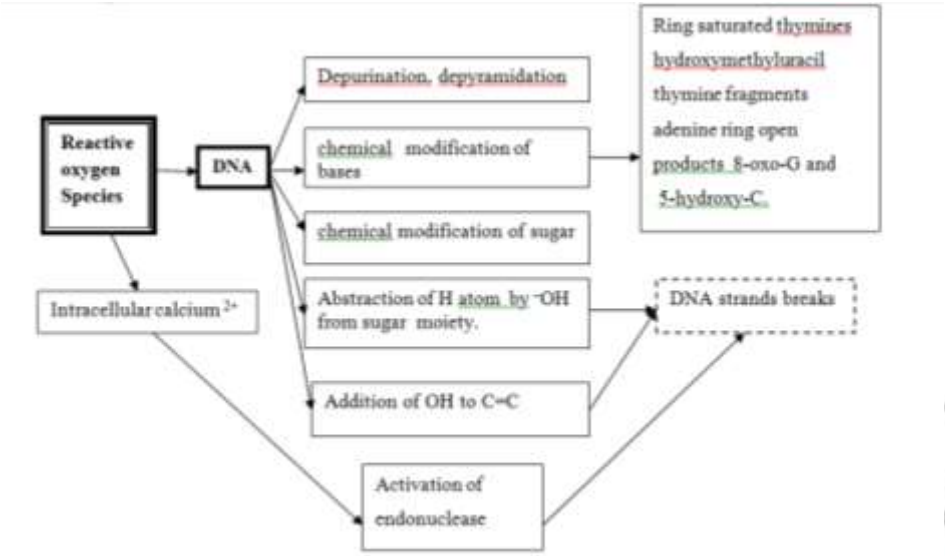

Figure 2 - Mechanism of oxidative damage to DNA (8)

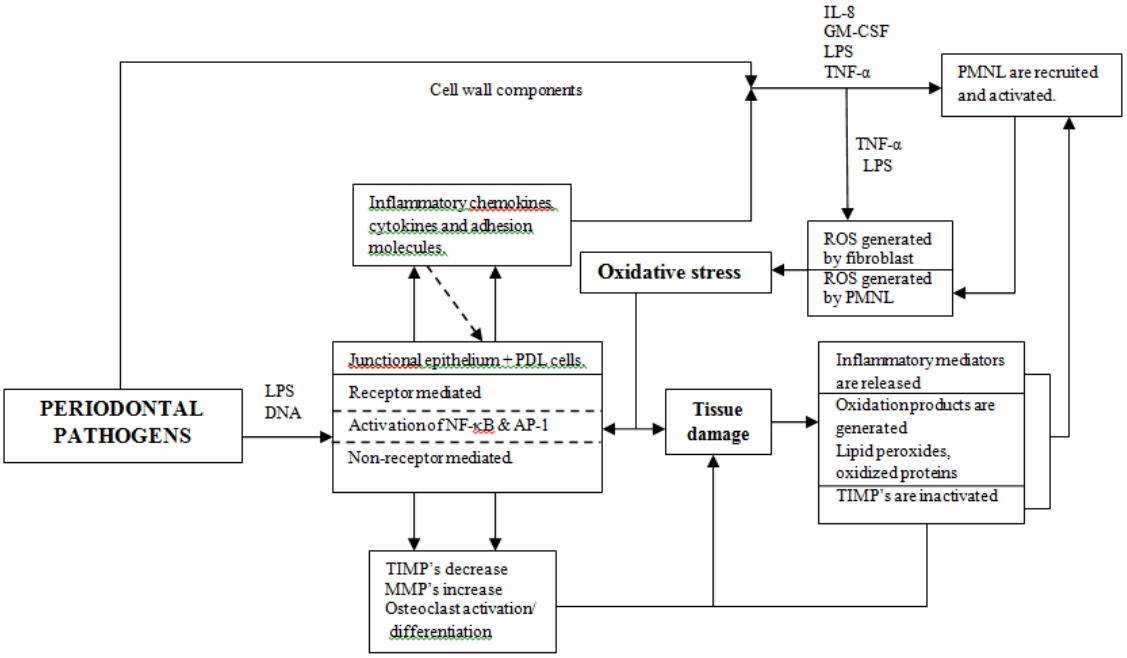

Figure 3 - A central role of ROS in producing chronic inflammation and tissue damage in response to periodontal pathogens (1)

ROS = Reactive oxygen species; LPS = Lipopolysaccharide; TIMP = Tissue inhibitor of matrix metalloproteinase; PDL = Periodontal ligament; NF-κB = Nuclear factor kappa B; AP-1 = Activating protein 1; MMP = Matrix metalloproteinase; TNF = Tumor necrosis factor; IL = Interleukin; GM-CSF = Granulocyte-macrophage colony-stimulating factor.