



REVIEW

Cytokines in Periodontal Health & Disease

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ABSTRACT: Destruction of gingival and periodontal tissue is mediated by a very large degree of host cells following stimulation by locally produced cytokines. These cytokines act as the initial mediators of the cellular component of inflammation. It has now been shown that a range of bacterial molecules is able to induce human cells to produce a variety of pro and anti-inflammatory cytokines. It is clear that cytokines play a key role in the immune system, in hematopoiesis, and in immunoregulation. They also play a role in the pathophysiology, both in producing tissue destruction as well as in healing. Host cells such as keratinocytes fibroblasts, endothelial cells and tissue monocytes respond to certain bacterial proteins and lipopolysaccharides by generating primary proinflammatory cytokines. Their excessive production in chronic inflammation may have pathologic consequences in diseases such as periodontitis.

Cytokines are a significant and integral part of the host response to periodontal infection. Additionally, these molecules are important as physiologic mediators in the periodontium, serving in both normal processes and as pathogenic mediators. A therapeutic goal in clinical periodontics can be aimed at maintaining a physiological role for the cytokines while recognizing that their overproduction results in pathologic changes.

Key words: Cytokines, periodontal disease, interleukins, chemokines, growth factors, cytokine therapy.

Multi cellular organisms use a wide variety of chemical signals to control and coordinate cellular activities for normal life sustaining operations as well as for mounting defenses against foreign organisms. The complex interaction among lymphocytes, inflammatory cells and other cellular elements in the connective tissues are mediated by a series of low molecular weight proteins called "CYTOKINES".^[1] Cytokines are signaling molecules that are also involved in the regulation of growth and development, activation of immune system cells and in the mediation of inflammatory responses.

Periodontal diseases are infectious diseases. The pathology of periodontitis lesions is characteristic of, and consistent with, a subversion of host defenses against bacterial pathogens. Locally-induced host-mediated periodontal tissues.

Periodontal tissue is mediated by host cells following stimulation by cytokines. Some cytokines signal and activate the body's defense system

against offending microorganism, molecules of bacterial origin act as the signaling molecules. Host cells such as keratinocytes, fibroblasts, endothelial cells and tissue monocytes respond to certain bacterial proteins and lipopolysaccharides by generating primary proinflammatory cytokines. These cytokines act as the initial mediators of the cellular component of inflammation. Primary proinflammatory cytokines activate resident cells such as fibroblasts and endothelial cells to generate secondary proinflammatory cytokines that have a chemoattractant effect on leukocytes. These chemoattractant cytokines amplify the inflammatory reaction and render specificity to the cellular response.

Included in the cytokine molecule group are interleukins, interferon, growth factors, cytotoxic factors, activating and inhibiting factors, colony stimulating factors, and intercrines. Cytokines are responsible for the maintenance of an intricate communication network between the host cells. Thus, cytokines play an important role in numerous biological activities including differentiation,

	Monocytes,macrophages Epithelium endothelium fibroblasts	Monocytes,macrophages, T-cells,epithelium, Hypothalamus endothelium	Activation, t TNF-a & IL- 2,fever

		T & B cells	Activation & t
	T cells & thymocytes	Many leukocytes differentiation	t proliferation
	Th2 cells mast cells basophils	T & B cells mast cells	Promotes IgE production & Th2 cells, CMI
	Th2 cells mast cells	Eosinophils, B cells, thymocytes	Activates eosinophils, t B cell growth
	Th2cells,monocytes, macrophages epithelium endothelium	Ilepatocytes, B cells	t acute phase reactants t IgM, IgA production
	Monocytes,macrophages epithelium	Neutrophils, eosinophils, monocytes,basophils,CDS+T	Activation, chemotaxis
	Th2cells,monocytes, macrophages eprthellum	Monocytes,macrophages Th2 cells B cells	production of IL- 1,TNF-u & IL-2, t IgA production
	Monocytes, macrophages	NK cells, T cells	Activates NK &Th1 cells
Interferon	Fibroblast dendrrtrc cells	Many cells, NK cells	Antiviral, t MHC class 1, proliferation, t cytolysis
Interferon	Thi cells, NK cells,macrophages	Many cells, NK cells	Antiviral,fever, proliferati tMHC class 1 & 11 & sc
	Macrophages, NK cells, eplthellum mast cells	Monocytes, macrophages, hypothalamus	Activates monocytes & PMNs, fever,anti-tumor
		Paracrme effects	
	Many cell types Many cell types Many cell types	Neutrophil precursors Monocyte precursors Both	Growth & maturation
	Tcells,monocytes, macrophages	Monocytes, B cells,T cells. Macrophages epithelium	t IgA & IgE production, inflammation

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Cytokines in periodontal health and disease

homeostasis, regeneration, repair and inflamm

ation.

Research on the pathogenesis of the periodontal disease have clarified that cytokines play an imp ortant role.

Hence, this review reviews the cyokine expression in periodontal tissues and its importance in tissue homeostasis and in particular in the pathogenesis of periodontal diseases (Table-1).

CYTOKINES IDENTIFIED IN SERA FROM PATIENTS WITH PERIODONTITIS

It has recently been demonstrated that sera of patients with untreated, severe periodontitis, diagnosed on the basis of clinical and radiographical registrations, contained higher levels of IL-2, IL-2 receptors and IL-4 than did sera of healthy individuals.¹⁵¹ Thus, IL-2 was detected in 10% of sera from the healthy controls, but in 88% of sera from periodontitis patients. Despite a

wide variation in the xxIL-2 levels, there was no correlation between the degree of bone loss or pocket formation and the amounts of IL-2 in serum. IL-4 in sera from individuals of the periodontitis group was also significantly increased as compared to sera from the control group. Future studies are needed to elucidate a possible use of IL-2 and/or IL-2 receptor and IL-4 levels in serum as markers of periodontitis activity.

CYTOKINES IDENTIFIED IN PERIODONTAL TISSUES

Different techniques have been used to demonstrate the presence of cytokines in gingival tissue. Thus immunohistochemical techniques have been used as well as ELISA and bioassays on supernatants from homogenized gingival tissue.

In a study of gingival tissue from periodontitis patients with reduced inflammation after scaling, the localization of IL- 113 was demonstrated by an immunohistochemical technique. [⁶¹ IL- 1 β was located at or in individual lamina propria cells, which showed intense surface and cytoplasmatic

staining. There was a three-fold increase in staining intensity between

The presence of IL-1 β has been detected in extracts from inflamed gingival tissue of periodontitis patients.¹⁷ The

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cytokine was found in increased amounts in supernatants from periodontitis lesions, and there was no IL-1 β in non-inflamed gingival tissue. Recent homogenized biopsies from patients with active or inactive disease as defined by the tolerance method,¹⁸ as well as from healthy gingival sites of adult periodontitis patients, showed an increased IL-1 β level in inflamed sites.

IL-1 α , IL-1 β , and TNF α were identified by ELISA in tissue from patients with chronic adult periodontitis.¹⁰ The presence of the cytokines in frozen tissue specimens was also shown by indirect immunofluorescence. The IL-1 β and TNF α levels in diseased tissue were significantly higher than in healthy tissue. IL-1 α was only revealed in a few diseased and healthy gingival sites. The IL-1 β containing cells were present in much higher numbers than IL-1 α and TNF α containing cells.¹⁰ The authors therefore suggested that an important mediator in the pathogenesis of periodontitis.

Another study demonstrated both IL-1 α and IL-1 β mRNA in all examined gingival biopsies from untreated patients with periodontitis. IL-1 β mRNA dominated in almost all biopsies. TNF α -like activity has been found in supernatants of homogenized inflamed periodontal tissue using bioassay.

Recently, it was also suggested that IL-6 may participate in the pathogenesis of periodontitis, since IL-6 was identified in inflamed human gingival tissue using an immunohistochemical technique.¹³ The foci of inflammation showed intense staining for IL-6 in the MNC, and staining was also associated with resident fibroblasts. However, non-inflamed areas also showed a positive staining reaction.

CYTOKINES IDENTIFIED IN CREVICULAR FLUID

The first studies of cytokines in crevicular fluid demonstrated the presence of a thymocyte-activating factor.^{14,15} which was indistinguishable from IL-1 with respect to biological activities and biochemical properties appeared that crevicular fluid from inflamed sites contained more thymocyte-activating factor than non-inflamed sites.

Later, an IL-1-like factor in crevicular fluid from patients with chronic periodontitis was characterized.¹⁷ A study revealed that the IL-1-like activity in crevicular fluid was completely neutralized by an antiserum to human recombinant IL-1 α , but not to IL-1 β . This result, however, is contrasted by another study which by using an ELISA-technique demonstrated IL-1 β more frequently than IL-1 α in crevicular fluid from untreated patients with periodontitis.¹¹ The discrepancy may be due to differences in assay techniques, and/or to differences between the groups of patients. The latter results are more compatible with the fact that IL-1 α is predominantly membrane-bound, whereas IL-1 β is readily secreted from the cells.^{18, 19}

TNF α has been detected in crevicular fluid but was not correlated with gingival index, plaque index, or probing depth.²⁰ It was suggested that TNF α may be a marker of early inflammatory activity because of the patternless distribution of TNF α within the individuals and the lack of correlation of clinical inflammation with the TNF α levels.

IL-6 has been demonstrated by ELISA in crevicular fluid of five periodontitis patients.²¹ A significant correlation between bleeding index, probing depth, and the IL-6 levels of the crevicular fluids was also demonstrated.²¹ Further research is needed to evaluate IL-6 as a possible marker of periodontal breakdown.

CYTOKINE EXPRESSION IN PERIODONTAL HEALTH

The type of immune response that occurs on exposure to a pathogen is vital in determining resistance or susceptibility to disease. The importance of the cytokines induced locally is paramount due to their different effects on the function of cells in the immediate neighborhood, which then determines the course of the response and hence the resistance or susceptibility to the particular pathogen.²² Once the

epithelial barriers is breached and the immune system comes into play. Cytokines are central response, production of "appropriate" cytokines protective immunity and the production of inappropriate cytokines leads to tissue destruction progression. [23] Just how the immune system chooses and regulates the right cytokines is unclear, although genetic factors are most likely involved.[24]

Tissue homeostasis represents a delicate balance between anabolic and catabolic activities. The regulations of migration, proliferation and differentiation of resident cells and of the production of tissue matrix in a healthy state are major aspects of periodontal tissue homeostasis.[25] There is abundant evidence that cytokines, which are secreted by fibroblasts, endothelial cells and epithelial cells, play a crucial role in tissue homeostasis. [25]

Cytokines interact in a network: first by inducing each other; second by transmodulating cell surface receptors; and third by synergistic, additive or antagonistic interactions on the cell function. [26]

The mRNA expression of cytokines in clinically healthy gingival tissues was examined by reverse transcription/polymerase chain-reaction (RT-PCR), mRNA expression of a variety of growth factors-such as Epidermal growth factor (EGF), Platelet-derived growth factor (PDGF), and Transforming growth factor- β (TGF β)-was observed.[27]

Interestingly, mRNA of so-called inflammatory cytokines (such as IL-1, IL-6, and TNF- α) was also detected in the clinically healthy gingival tissues, although their density was relatively low compared with that in the inflamed sites. This suggests that myriad cytokines may be involved in the maintenance of periodontal tissue turnover or integrity.

The biological activity of certain cytokines have been relatively well-characterized through the research of periodontal regeneration such as Insulin like growth factor (IGF), TGF- β and cementum derived growth factor (CDGF).

CYTOKINE GENE POLYMORPHISMS

The inter-individual differences in the inflammatory response (and the differences in periodontal disease susceptibility as well as the interaction between

background may affect human inflammation periodontal

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Figure 1

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Mechanism by which IL-1 or TNF could contribute to the net loss of periodontal tissues

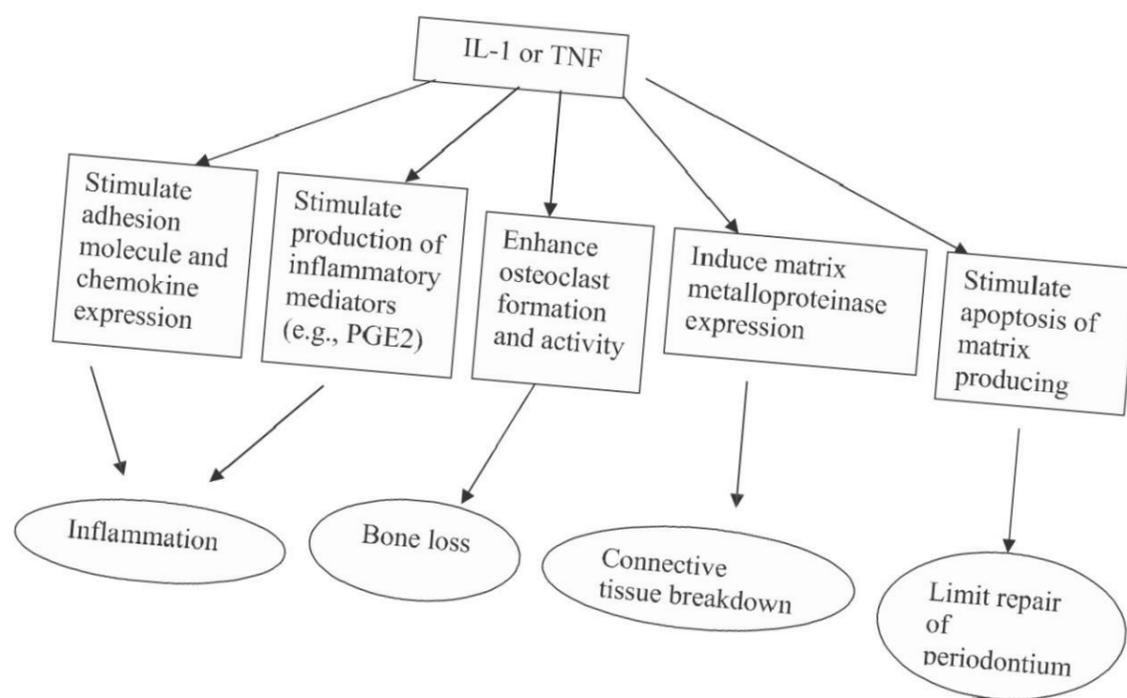


Table 2: Pathophysiological roles of inflammatory cytokines in periodontal tissue destruction

Cytokine	Functions
	Enhancement of bone resorption Stimulation of metalloproteinase production
	B-cell activation, resulting in non-specific antibody production and IL-1 production
	Stimulation to attract and activate neutrophils

expression. This includes the inflammatory response, innate and adaptive immunity, bacterial colonization and other modifying factors (i.e. stress effect of smoking, etc.). The periodontal diseases, chronic periodontitis and aggressive periodontitis, are not considered as "simple genetic diseases", in which a mutation in a single gene causes some disruption of a specific protein, but as a "complex disease" in which many genes as well as other

environmental factors contribute⁽¹⁾ to the onset and severity of the disease. The genetic variants (polymorphisms) that contribute to complex diseases are prevalent in any population and are often reported to differ between diseased and healthy individuals. Because of the inflammatory nature of periodontal destruction, researchers are searching a connection between periodontal diseases and variants in genes that are

involved in the inflammatory and immune responses. Wide ranges of genes exist and the search is on for variation in genes whose products have been associated with periodontal destruction.

As the immune system plays a crucial role in the pathogenesis of periodontitis, researchers have concentrated on the identification of genetic polymorphisms in several aspects of host immunity. Differences in the expression of cytokines, especially proinflammatory cytokines, are of great interest in periodontal research. [29]

CYTOKINES AND ALVEOLAR BONE LOSS 1301

The innate and acquired immune responses are both thought to play a role in periodontal bone resorption. When activated, cell types produce cytokines that are potent inducers of bone resorption. PMNs and monocytes of the innate immune response produce IL-1 and TNF that can stimulate bone resorption. Studies suggest that overproduction of IL-1, TNF- α by the innate host defense is a major contributor to periodontal bone

of the adaptive immune response (osteoblasts) produce RANKL, which is a member that is one of the most potent inducers of osteoclast formation and activity. Evidence response plays a significant role in periodontal disease was demonstrated by alis-induced bone

absence of functional lymphocytes and that greater bone loss occurs when lymphocytes are activated by antigenic stimulation. Thus, both the innate and adaptive arms of the immune response are capable of stimulating events that lead to destruction of periodontal tissues. Moreover, interactions between them are likely to amplify the osteolytic capacity of each. Based upon this concept; a goal of periodontal therapy that may be effective would be dampening the overreaction of the host response so that the inflammation front does not reach concentration and a critical distance to the alveolar bone.

CYTOKINES AND THE LOSS OF GINGIVAL CONNECTIVE TISSUE 1301

Periodontopathic bacteria do not reside periodontal tissue in large numbers but chronic inflammation and

a continuous and sometimes excessive host response. It is generally believed that most periodontal destruction results from activating host proteases collectively known as matrix metalloproteinases.

An early event in the pathogenesis of periodontal disease is dissolution of approximately 70% of the gingival connective tissue. The presence of proinflammatory cytokines (IL-1) inhibits the intracellular route of collagen breakdown while stimulating the extracellular route by activating MMPs to degrade collagen. TGF- β has the opposite effect. Activation of proinflammatory cytokines and other mediators result in an altered matrix, which, in turn, may affect cell function and subsequent tissue remodeling.

However, recognition that MMPs have multiple functions raises the possibility that blocking MMP activity can have unanticipated consequences. Thus, future therapeutic efforts in periodontics will likely focus on specific MMP inhibitors targeted to well-defined MMP molecules.

CYTOKINES AND APOPTOSIS OF MATRIXPRODUCING CELLS

The breakdown of gingival connective tissue would not be problematic if there were adequate repair mechanisms. Therefore factors that limit repair may be as important as those that initiate tissue loss. One mechanism by which this may occur is the stimulation of

apoptosis, programmed cell death, in critical periodontal cells such as fibroblasts or osteoblasts. One of the most striking features of periodontal tissue destruction is the loss of fibroblasts. This may occur through apoptosis of fibroblasts that are present in areas of the gingiva associated with inflammation.

One study indicated that *P.gingivalis* infection stimulates TNF production and TNF causes most of the programmed cell death of fibroblasts. Thus, the host response has a more prominent role in apoptosis of fibroblasts than the direct effect of bacterial products.

Regardless of the mechanisms, the loss of fibroblasts and osteoblasts is likely to be a significant event and

may limit the natural repair process that would be expected to occur. Loss of attachment may occur not just because matrix is destroyed, but also because the potential to repair damage induced by bacterial-stimulated cytokine production is limited by apoptosis of matrix-producing cells. (Table-2, Fig-1)

CYTOKINE THERAPY 1221

The use of cytokines to change the course of the disease or to alleviate symptoms or side effects of other therapies is becoming important in clinical medicine. Cytokines can theoretically be used as therapeutic modalities in two forms. One is over production of cytokines may be inhibited by the cytokines suppressing anti inflammatory drugs. Alternatively, missing, defective or reduced cytokines and /or their receptors can be replaced directly to reconstitute a reduced immune system or used to stimulate further the immune system in cases of overwhelming infection neoplasias. These therapies can be achieved using recombinant cytokines or gene encoding for them.

Initially, cytokine therapy was used for hematopoiesis. Recombinant cytokines and or their inhibitors can be used in the control Of rheumatoid-term clinical trails have variety of cytokine-blocking mechanisms.

In different clinical situations, cytokines, antibodies to cytokines and agonists could a ment. Two major problems r he need to achieve the cytokine levels

or blockade in the long term, and the second is to overcome the adverse outcomes that may result from systemically blocking or increasing cytokines that are normally involved in homeostasis.

IMPLICATION OF ANTI-CYTOKINE THERAPY FOR PERIODONTITIS

There are 3 basic therapeutic strategies, including neutralization of cytokines, blockage of cytokine receptors, and activation of anti-inflammatory pathways such as immunosuppressive cytokines.

TNF- α is especially a target molecule for its neutralizing therapeutics. Anti-TNF- α antibodies can effectively attenuate or prevent inflammation of arthritis in experimental models. TNF- α can also be neutralized with genetically engineered sTNF-RII. Two therapeutics, Infliximab and Etanercept have been

available commercially and proven in the treatment of rheumatoid arthritis.

Although there are drawbacks to reducing inflammation using anti-cytokine therapeutics, there are several studies that show the potential of using IL-13 and TNF- α antagonist to reduce tissue destruction in periodontal diseases. These researchers applied exogenous sIL-1RI and sTNF-RII to the gingival tissue of non-human primates with experimental periodontitis, inhibition of inflammatory cell infiltration, alveolar bone loss, and loss of tissue attachment. These are quite exciting results relating to the regulation of the immune reaction in connective tissue, although future studies should assess microbial infection. [34]

CONSIDERATION OF ANTIMICROBIAL THERAPY FOR ANTI-CYTOKINE THERAPY IN PERIODONTAL TREATMENT

With antimicrobials, caution must be taken to prevent inapparent infection without inflammatory symptoms when anti-cytokine therapy is performed. If anti-cytokine therapy is applied to periodontal treatment we may use chemical plaque control reagents chlorhexidine gluconate in addition mechanical control. For a future antimicrobial responses antimicrobial therapeutics. Host-derived antimicrobial peptides have received much attention. Defensins,

especially, have been detected in periodontal tissue by immunohistochemistry.

One study found oral epithelium to be a major source of these peptides, suggesting that defensins may be secreted into the oral cavity and act as an innate defense on the gingival surface. Thus, their clinical application has been proposed. [35] These peptides kill bacteria by making holes in the bacterial cell wall. Synthetic human β -defensin 2 (hBD-2) has bactericidal activity in saliva but not in serum. It may be possible to add host-derived antimicrobial peptides into future practice.

FUTURE ANTI-CYTOKINE THERAPY FOR PERIODONTAL TREATMENT BASED ON FIBROBLAST BIOLOGY

Human gingival fibroblasts (HGF) are involved in immune and inflammatory responses. Furthermore, HGFs are the major cell population in periodontal tissue. If we could modify HGF activities, these cells could serve as therapeutics by secreting anti-cytokine and antimicrobial molecules. Transfer of exogenous genes such as sTNF-RII and hBD-2 genes to HGF would modify the conditions of inflammation and infection in periodontal tissue.

The TNF-RII gene modified not to have a cytoplasmic domain is introduced to gingival fibroblasts to overexpress sTNF-R11. Produced sTNF-R11 binds TNF α around gingival fibroblasts to block binding of TNF- α to mTNF-Rs. At the same time, the hBD-2 gene is also introduced to gingival fibroblasts, resulting in overexpression of hBD-2 peptide in the gingival tissue. Produced hBD-2 may be inactive in the tissue because of serum components, but could turn active when it exudes into periodontal pockets or is dissolved in saliva. The transfer of the hBD-2 gene into gingival fibroblasts is complementary to its native production by gingival epithelium. Active regulation of gingival fibroblast functions may have great potential for periodontal therapy.

PLATELET-RICH PLASMA (PRP): A SOURCE OF MULTIPLE AUTOLOGOUS GROWTH FACTORS FOR BONE GRAFTS

The use of platelet-rich plasma (PRP) is one strategy available today that can modulate and enhance wound healing.

The processing of PRP fundamentally involves the sequestration and concentration of platelets and, therefore, the many growth factors they contain. The oversimplified strategy is to amplify and accelerate the effects of growth factors contained in platelets, which are the universal initiators of almost all wound healing.

By taking advantage of all of the natural regeneration pathways, and using all the known and as yet to be identified growth factors in platelets, autologous platelet-rich plasma, which is nontoxic and nonimmunoreactive, accelerates existing wound-healing pathways. [36]

PRP also modulates and upregulates one growth factor's function in the presence of second or third growth factor. It is this specific feature that separates PRP growth factors from recombinant growth factors, which are single growth factors that focus only on a single regeneration pathway.

Specific studies of PRP have identified at least three important growth factors in the alpha granules sequestered platelets: PDGF, TGF- β 1, and TGF- β 2. In addition, other studies have documented the presence of IGF-I in platelets from peripheral human blood tests. [37]

PRP represents an advance over standard grafting techniques. It offers the surgeon access to growth factors with a simple and available technology.

CONCLUSION AND FUTURE CONSIDERATION

The conversion of gingivitis to periodontitis is likely to involve the progression of an inflammatory front to deeper areas of connective tissue. The reasons why this occurs have not been established. One mechanism may be that bacteria acquire the ability to penetrate deeper into the connective tissue, or the host defense is perturbed, allowing deeper penetration, or, more likely, their product expression of pro-inflammation play an important role in the upregulation of the inflammatory response. This one of secondary mediators cyclooxygenase products, whose degree of inflammation be induced that destroy connective

tissue, Simultaneously, cytokines may reduce the capacity to repair the damaged tissue through apoptosis of resident cells such as fibroblasts. And finally, the induction of an inflammatory cascade stimulates osteoclastogenesis that results in destruction of bone.

Thus, cytokines are a significant and integral part of the host response to periodontal infection. Additionally,

these molecules are important as physiologic mediators in the periodontium, serving in both normal processes and as pathogenic mediators. A therapeutic goal in clinical periodontics can be aimed at maintaining a physiological role for the cytokines while recognizing that their overproduction results in pathologic changes. Further studies in this exciting field are awaited.

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