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## Review Article

# Proinflammatory Cytokines and Periodontal Disease

## Cytokine expression in periodontal health

Tissue homeostasis denotes 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. There is abundant evidence that cytokines, which are secreted by fibroblasts endothelial cells, and epithelial cells, have a key role in tissue homeostasis [9].

There are at least two major pathways that control the balance of gingival tissue and bone remodeling and the subsequent control of periodontal bone loss. The first encompasses the interactions with osteoblasts and stroma that couple between bone formation and resorption during physiological bone remodeling processes. Through the network of autocrine and paracrine regulations, a range of growth factors, such as platelet derived growth factor, basic fibroblast growth factor and insulin-like growth factor, exert their activities through their receptors on osteoblasts to stimulate the formation of new bone [10].

The second pathway deals with the inflammatory or / and osteoclastogenic cytokines / mediators that are produced during local tissue inflammation and trauma or systemic assaults and are thus responsible for bone loss under pathological conditions where bone remodeling becomes imbalanced or dysregulated as a result of increased osteoclast number and activity, resulting in irreversible bone loss [11].

## Gingival epithelium

The epithelium in the gingiva consists mainly of keratinocytes, but other cells are also present, including Langerhans cells, T-cells, Merckel cells and melanocytes keratinocytes in the gingival epithelium are continuously proliferating and gingival epithelium is well differentiated in morphologically distinguishable cell layers.

Although the epithelium was originally considered to be a physical barrier that protected the host from bacterial invasion, we now know that it plays a much more active role in the pathogenesis of inflammation [12].

Keratinocytes can produce alpha- and beta-defensins, which are antimicrobial peptides that are involved in the host response against infection. Additionally, keratinocytes, when challenged with bacterial infection, express a large variety of cytokines and growth factors, including interleukin-1alpha, interleukin-1beta, interleukin-8, tumor necrosis factor-alpha and platelet-derived growth factor. Physiologically, keratinocytes have a high turnover rate and, during inflammation the induction of epidermal growth factor enhances

## Review

Numerous biological procedures are strictly controlled by cell-cell interactions, which are categorized into two forms: cognate (adhesive) interactions, attained by mutual recognition between membrane-bound cell-surface molecules; and cytokine-mediated interactions [1].

Cytokines (Greek cyto-, cell; and -kinos, movement) are a category of signaling molecules that are used extensively in cellular communication.

The responses caused by these substances are diverse and interrelated. Generally, cytokines control growth, mobility and differentiation of lymphocytes, but they also exert a similar effect on other leukocytes and some non-immune cells [2].

Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cells. They used to have different names depending either on their origin, such as lymphokines (produced by lymphocytes), monokines (monocytes) or on their activity: chemokines, interleukins, interferon. The term "cytokine" has been used to refer to the immunomodulating agents, such as interleukins and interferons [3-5].

After binding with high affinity to specific receptors on target cells cytokines are capable of regulating pluripotent activities such as: cellular growth, differentiation, proliferation, migration, angiogenesis and fibrosis as well as apoptosis of the multiple cell types. Furthermore they are able to regulate the specific immune responses [6].

Some cytokines enhance or stop the action of other cytokines in complex ways, while others are chemical switches that turn certain immune cell types on and off. They include a diverse assortment of interleukins, interferons, and growth factors. They are important in health and disease, specifically in host responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction [7].

Pro-inflammatory cytokines and chemokines, comprising IL-1, IL-6, IL-8, and TNF-alpha create an environment that helps disease progression. These cytokines and chemo attractants are secreted by immune regulatory cells, tumor cells, tumor-associated macrophages, and stromal cells [8].

further proliferation. Together with cytokines and growth factors keratinocytes are able to express several adhesion molecules and integrins that serve as guidance receptors for leukocyte trafficking [11].

### Connective tissue of gingiva and periodontal ligament

The extracellular matrix in the subepithelial gingiva and periodontal ligament is composed predominantly of type-I collagen fibers, with type-III, -IV, -V and -VI collagen fibers being present in lesser amounts [13].

Large and small proteoglycans, such as aggrecan, decorin, biglycan, syndecan, perlecan and versican, have been revealed in the gingiva. Additionally, fibronectin, osteonectin and vitronectin are part of the extracellular matrix. The principal cell types are fibroblasts in the gingiva and fibroblast-like cells in the periodontal ligament. These cells express a variety of membrane and intracellular receptors, making the cells sensitive to regulation by many physiological and pathological, paracrine and endocrine signaling molecules [14].

Fibroblasts are the mesenchymal cells that secrete the extracellular matrix molecules. On the other hand, fibroblasts are also important for the remodeling of these molecules. To retain tissue homeostasis physiologically, the degradation and the synthesis of these molecules have to be well controlled [15].

Platelet derived growth factor, released from platelets, macrophages or gingival epithelium, is strong stimulators of fibroblast proliferation and are proposed to be important in inflammation-induced fibroblast proliferation.

Regulation of matrix molecules may occur either through increased or decreased biosynthesis, or enhanced or decreased enzymatic breakdown.

Transforming growth factor-beta, released from platelets or macrophages, activates the transcription of a number of the collagen genes for collagen synthesis besides inhibits the synthesis of matrix metalloproteinases. By contrast, prostaglandin E2, interfeon-gamma and tumor necrosis factor-alpha inhibit collagen synthesis. Interleukin-1 is a most effective regulator of extracellular matrix turnover by increasing the expression of several matrix metalloproteinases [11].

### Alveolar bone tissue

The jaw bones are constituted of cortical bone in the periphery, including the tooth socket. In the central part of the mandible and maxilla, a relatively large amount of trabecular (spongy) bone is present, and bone marrow is distributed in between the trabecular bone. Histologically, there are large differences between cortical and trabecular bone, since the former is built up by lamellar bone surrounding Haversian canals harbouring blood vessels and nerves.

In addition to osteoblasts, bone tissue contains osteocytes. These cells are present within the mineralized bone and were originally osteoblasts, which were incorporated into the extracellular matrix and ultimately into the mineralized bone tissue. A third main cell is the osteoclast, the only cell that is capable of degrading bone, a process important for the remodeling and modeling of bone [11].

Bone tissue contains large amounts of growth factors, including transforming growth factor-beta, insulin-like growth factors I and II, basic fibroblast growth factor and bone morphogenetic proteins. These matrix molecules are mitogenic for osteoblasts and can also stimulate the bone-forming activity of osteoblasts. It is believed that these growth factors function during bone remodeling (when they are released during the resorptive process) and then act locally on osteoblasts. It is obvious that the amount of bone in the skeleton, including jaw bones, is regulated by many different signals. The number of osteoblasts present is dependent on osteoblast precursors differentiated from Mesenchymal stem cells, in a program where there is competition with differentiation along other pathways to adipocytes and related mesenchymal cells. The number of osteoblasts is then also dependent on signals controlling proliferation and apoptosis [11,16].

### Pathogenesis of periodontal disease

Periodontal disease is one of the most prevalent diseases worldwide and includes two major conditions, gingivitis and periodontitis. The milder, reversible form of the disease, gingivitis, involves inflammation of the gingival tissue. In disease-susceptible individuals, gingivitis may progress to periodontitis, which is a chronic infectious disease of the supporting tissues of the teeth [17].

Although periodontal diseases are initiated by bacteria, the host response is believed to play an essential role in the breakdown of connective tissue and bone. Microbial antigens and virulence factors elicit an inflammatory and immune reaction, in which both innate and adaptive immune responses are, involved [18].

The response differs among individuals, depending on potential variations in cytokine and other antimicrobial responses, environmental factors, and the subjects' genetics make up.

The host response to the bacterial challenge includes the action and stimulation of various inflammatory cell types as well as of resident cells of the tissue [19,20]. Antigens and products, such as LPS and peptidoglycans, released by bacteria are recognized by toll-like receptors (TLRs) on the surface of host cells, which initiates an inflammatory response [21].

Through a cascade of events, mast cells are stimulated to release vasoactive amines and preformed tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), which increases vascular permeability and the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and P-selection on endothelial cell surfaces. This process recruits PMNs into the tissue, where they release lysosomal enzymes, which contribute to tissue degradation [22]. In reaction, lymphocytes and macrophages further invade the tissue. 60–70% of the collagen in the gingival connective tissue is degraded at the site of the lesion at this point, however the bone is still intact [23].

At this stage, the gingival tissues damage is still reversible and it is possible to repair and remodel the damaged tissue after removal of the insult. However, in some individuals, due to innate susceptibility and/or environmental factors, the inflammation fails to resolve, with subsequent connective tissue breakdown and irreversible bone loss. In this situation, macrophages form pre-osteoclasts which, after maturing into osteoclasts, are capable of degrading alveolar bone [24].

Without active resolution of inflammation, the bacterial antigens ultimately encounter antigen presenting cells for instance dendritic cells, macrophages and B cells. Upon interaction of naïve CD4 T helper cells (Th0) with antigen presenting cells, naïve T cells differentiate into various subsets of cells including Th1, Th2, Th17 and regulatory T cells (Tregs), and this differentiation depends on the cytokines that they produce **Figure 1**.

Th1 cells initiate the cell-mediated immune response and secrete interferon- $\gamma$  (IFN- $\gamma$ ), transforming growth factor- $\beta$  (TGF- $\beta$ ), interleukin-2 (IL-2) and TNF $\alpha$  in the presence of IL-12. Whereas Th2 cells derive the humoral immune response and produce the cytokines IL-4, IL-5, IL-6, IL-10, IL-13 and TGF- $\beta$  in the presence of IL-4.

The remaining two CD4 T cells, Th17 and Tregs play a critical role in autoimmunity and in the maintenance of immune homeostasis. The TH17 subset of cells produce IL-17, IL-23, IL-22, IL-6 and TNF $\alpha$  in the presence of TGF- $\beta$ , IL-1 $\beta$  and IL-6 while Tregs arise in the presence of TGF- $\beta$  and secrete the immunosuppressive cytokines IL-10 and TGF- $\beta$ . Remarkably, IL-17 stimulates the production of various inflammatory mediators including TNF $\alpha$ , prostaglandin E2 (PGE2), IL-6 and IL-1 $\beta$ , mediating bone resorption via osteoclasts activation [22,24].

### Cytokines in periodontal inflammation

Cytokines are biologically active molecules released by specific cells that elicit a particular response from other cells on which they act [2]. They are effective in very low concentrations, are produced transiently, act locally in the tissue where they are produced [25].

An inflammatory cytokine is a cytokine which is induced during the course of an inflammatory response and is closely associated with its onset and/or progression. IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-8 and TNF- $\alpha$  are classified as proinflammatory cytokines [1].

Pro-inflammatory cytokines enhance the bactericidal capacity of phagocytes, recruit additional innate cell populations to sites of infection, induce dendritic cell maturation and direct the subsequent specific immune response to the invading microbes [26].

Anti-inflammatory cytokines block this process or at least suppress the intensity of the cascade. IL-4, IL-10, IL-13 and transforming growth factor (TGF) - $\beta$  suppress the production of IL-1, TNF, chemokines such as IL-8, and vascular adhesion molecules [27].

Cytokines play a key role in a number of different physiologic processes, but if secreted inappropriately, they also induce pathology. In periodontal disease, the balance between pro- and anti-inflammation is directed towards proinflammatory activity [28].

Three proinflammatory cytokines, interleukin-1 (IL-1), IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), appear to have a central role in periodontal tissue destruction [29].

They are secreted by a variety of cell types comprising monocytes, macrophages, dendritic cells, epithelial cells, keratinocytes and fibroblasts. IL-1 $\alpha$  is a regulator of intracellular events and a mediator of local inflammation, while IL-1 $\beta$  is primarily an extracellular protein released from cells [30].

IL-1 stimulates the proliferation of keratinocytes, fibroblasts and endothelial cells of the periodontal tissues. Additionally it enhances fibroblast synthesis of type I procollagen, collagenase, hyaluronate, fibronectin, and prostaglandin E2I. Therefore IL-1 is a critical component in the homeostasis of periodontal tissues and its unrestricted production may lead to tissue damage [1].

IL-1 $\beta$  upregulates matrix metalloproteinases and downregulates tissue inhibitors of metalloproteinase production [25] and it is also an effective stimulator of bone resorption [31].

There is enough evidence that PGE2 and IL-1 $\beta$  are important mediators in the periodontal inflammation and bone destruction and are involved in tissue response regulation. It is well known that IL-1 $\beta$  stimulate bone loss and have inhibitory effect to bone forming [32].

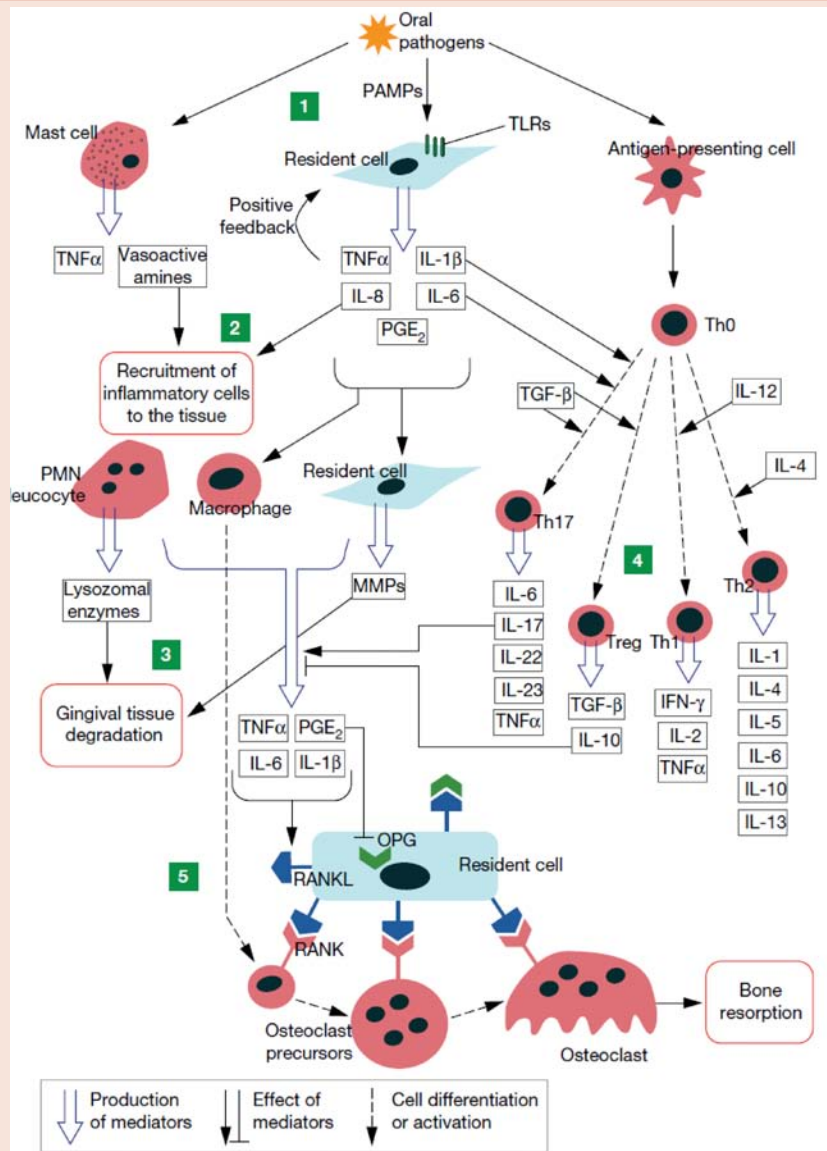
Prostaglandin E2 (PGE2) is one of the main mediators in the periodontal inflammation by stimulating the suppression of lymphocyte production, decreasing the collagen synthesis by fibroblasts and influencing osteoclastic bone resorption the rates of proinflammatory cytokines PGE2 and IL-1 $\beta$  in crevicular fluid and gingival tissue in patients with chronic periodontitis are increasing proportionally to severity of periodontal disease [33].

IL-6 was originally recognized as a B-cell stimulatory and differentiation factor, but at this time it is known as a regulator of the immune response, hematopoiesis, acute phase response and inflammation [34].

IL-6 is secreted by a number of cells comprising monocytes/macrophages, activated T-cells, endothelial cells, adipocytes and fibroblasts [34]. IL-6 synthesis and secretion are stimulated by two major proinflammatory cytokines, IL-1 $\beta$  and TNF- $\alpha$ , but the fact that IL-6 remains considerably longer in the plasma makes this molecule a good marker of inflammation [35]. Additionally IL-6 plays a role in the transition between acute and chronic inflammation. A lately described effector T-cell subset, Th17, will only differentiate from naïve T cells in the presence of IL-6 and TGF- $\beta$  [36]. Other biological activities of IL-6 include the enhancement of T-cell proliferation and acceleration of bone resorption by increasing osteoclast formation [37]. Furthermore IL-6 has non-immunological effects, such as the regulation of tumorigenesis by enhancing proliferation of tumor-initiating cells and protecting cells from apoptosis [38].

IL-6 is produced locally in the inflamed tissues following cellular activation by bacterial lipopolysaccharide (LPS) or other cytokines such as IL-1 $\beta$  or TNF- $\alpha$  [39]. Local production of IL-6 also occurs in inflamed periodontal tissues [40], and significant correlations have been found between periodontal pocket depth and IL-6 -content in gingival crevicular fluid [41]. Correspondingly IL-6 has been found in elevated levels in gingival connective tissue adjacent to intrabony pockets demonstrating poor response to non-surgical periodontal treatment [42].

Tumor necrosis factor is a pro-inflammatory cytokines that possesses a wide range of immunoregulatory functions. Tumor necrosis factor has the potential to stimulate the production of secondary mediators, including chemokines or cyclooxygenase products, which consequently amplifies the degree of inflammation [43].



**Figure 1:** Inflammatory mediators in the pathogenesis of periodontitis (24).

Two forms of TNF have been found, TNF- $\alpha$  and TNF- $\beta$  [28].

IL-1 and TNF are produced by the same cell types [28], they often affect together, and many of their pathways are shared including inflammatory bone resorption [44].

In the development of T Th17 response TNF- $\alpha$  and IL-1 $\beta$  are found to amplify the response induced by TGF- $\beta$  and IL-6, but are not able to substitute for either of these cytokines [45].

Furthermore, IL-1 and TNF can induce upregulation of adhesion molecules on leukocytes and endothelial cells and stimulate the production of chemokines and other inflammatory mediators, such as prostaglandins, and lytic enzymes, such as matrix metalloproteinases [28] and their inhibitors [46].

Cytokines may also reduce the capacity to repair the damaged

periodontal tissue through apoptosis of resident cells, such as fibroblasts [47].

In a complex network of pro- and anti-inflammatory cytokines acting in the inflamed periodontal tissues, interleukin-10 is an example of a cytokine with anti-inflammatory effects. Interleukin-10 is a regulatory cytokine, which on the one hand limits inflammatory responses by inhibiting the expression of proinflammatory cytokines (e.g. IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), but also upregulates the recruitment and activation of B cells [48]. It down regulates the T helper 1 response, and by controlling the B-cell lesion [48]. It is suggested to play a role in controlling the progression of periodontal disease.

**Diagnostic use of Cytokines in periodontal disease**

Inflammation involves the secretion, release and activities of



biochemical agents from the cells located around vascularized tissues that defend the host organisms against infection, tissue healing and repair.

Individuals with periodontal infections have elevated concentrations of circulating inflammatory markers and the severity of periodontal destruction directly correlates with serum concentrations of inflammatory markers [49].

Numerous cytokines and chemokines have been detected in the gingival crevicular fluid (GCF), exudates collected at the gingival margin, and in gingival tissue from patients with periodontitis. Enhanced levels of IL-6 have been demonstrated in the GCF of patients with periodontitis, compared with healthy controls, and higher expression of IL-6 was reported in diseased gingival tissues when compared with healthy tissue in periodontitis patients similarly, increased circulating systemic levels of IL-6 decreased after nonsurgical periodontal therapy resulting in clinical improvement of the periodontal status. TNF $\alpha$  and IL-1 $\beta$  have been found in increased concentrations in GCF and gingival tissue of periodontitis sites and levels are reported to decrease after treatment of periodontal disease [50,51].

From human and animal models, there is strong evidence of a role for IL-1 in mediating bone loss stimulated by periodontal pathogens. In humans, elevated level of IL-1 $\beta$  was detected in the gingival crevicular fluid at sites of recent bone and attachment loss in patients with PD [52].

It has been demonstrated that a significant correlation exists between the IL-1 $\beta$  levels of gingival crevicular fluid (GCF) and periodontal parameters such as probing pocket depth and attachment level [53,54].

### Therapeutic uses of cytokines in periodontal disease

The modification of destructive host response against Periodontopathogens by inhibition of pro-inflammatory cytokines has a potential therapeutic means in the treatment of periodontitis. Reduction in the levels of pro-inflammatory mediators by using NSAIDs may reduce host modulation bone resorption in chronic periodontitis [55].

Many studies exhibit improved treatment effect with additional use of non-steroidal anti-inflammatory drug (NSAID) in non-surgical periodontal therapy [56,57].

NSAIDs include a suppressing effect of prostaglandin synthesis via COX- 1 and COX- 2 and may act as inhibitor of gingival inflammation and bone destruction [55,58].

Detection of elevated levels of PGE2 and IL-1 $\beta$  in gingival tissue may be recognized as indicator for activity of periodontitis and may provide the evaluation of recurrence and progression of disease. Reducing the production of PGE2 and IL-1 $\beta$  after treatment may be indicator for successful periodontal therapy. Higher levels of this cytokines in crevicular fluid and gingival tissue of periodontal patients in supporting periodontal treatment can be capable predictor of further destruction [33].

### Conclusion

Periodontal diseases are chronic inflammatory disorders that affect the supporting structures of the teeth. It is widely accepted that bacteria initiate periodontal diseases. The host responds to this bacterial attack by eliciting an immuno-inflammatory response. The host response is essential to protect against the bacterial attack and prevent the systemic dissemination of infection. Nevertheless in the process, the inflammatory response can also cause tissue destruction and alveolar bone loss. Inflammation is now recognized as the essential component of periodontal disease. Better understanding of the disease process will facilitate the way for adopting novel treatment approaches and thereby improve clinical outcomes. Therapeutic agents antagonistic to the inflammatory mediators may be useful adjuncts to the conventional periodontal treatment procedures.

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