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Inflammatory Cytokines and Periodontal Disease: a Reveiw

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ABSTRACT *Cytokines are soluble proteins that serve as mediators of cell function and are produced by various cell types, such as structural and inflammatory cells. Cytokines play important roles not only in tissue homeostasis but also in the pathogenesis of many infectious diseases. Cytokines play crucial roles in the maintenance of tissue homeostasis, which requires a delicate balance between anabolic and catabolic activities. Continuous or excessive production of cytokines in inflamed periodontal tissues is responsible for the progress of periodontitis and periodontal tissue destruction. Particularly, inflammatory cytokines such as IL-l, IL-13, IL-6 and IL-8 are present in the diseased periodontal tissues, and their excessive production seems to play a role in chronic leukocyte recruitment and tissue destruction. It can be concluded that monitoring cytokine production or its profile may allow us to diagnose an individual's periodontal disease status and/or susceptibility to the disease.*

INTRODUCTION

Cytokines are peptides or small proteins which act as intercellular messengers between tissues and the immune system. They are soluble proteins that serve as mediators of cell function and are produced by various cell types, such as structural and inflammatory cells. Cytokines are secreted by immune cells and act on other cells to exchange signals regulating appropriate immune responses. They are multifunctional molecules that mediate a wide range of physiological responses, primarily host defence which include immunity and inflammation. In addition to their role in immunity and inflammation, cytokines are also involved in a wide range of pathophysiological conditions in the central nervous system and the peripheral nervous system, and thus serve as neuro-immuno modulators. The immune system also utilizes cytokine-like messengers, referred as **chemokines**[1], to recruit and activate specific white blood cell subtypes. In short, cytokines play an important role in various biological activities including development, proliferation, differentiation, homeostasis, regeneration, repair, and inflammation.

Cytokines are generally classified by their ability promote or inhibit inflammatory responses .

- Pro inflammatory cytokines
- Anti inflammatory cytokines
- Chemokines

Pro-inflammatory cytokines include - IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17, IFN-γ, TNF-α

Anti inflammatory cytokines include - IL-4, IL-5, IL-10, IL-13, TGF-β

Chemokines include- IL-8, MCP-1, MIP-1β

Cytokines are also grouped based on the type of T-lymphocytes with which they are associated .These profiles are termed Th1, Th2, and Th17

Th1 cytokine profile -IL-2, IL-12, IFN- γ, TNF-α

Th2 cytokine profile - IL-4, IL-5, IL-10, IL-13
Th17 cytokine profile -IL-6, IL-17, TNF-α, TGF-β

Pathophysiological Significance

Cytokine levels differ tremendously from baseline in acute and chronic pathological conditions. In many disease conditions, marked local inflammatory responses can trigger cytokines to get released into general circulation, resulting in detectable levels in biological fluids, such as serum and plasma. Changes in the circulating levels of these proteins are linked to many disease conditions, making them valuable functional biomarkers. Excessive or diminished cytokine levels are associated with many clinical conditions and diseases, like tumors, diabetes, hypersensitivity reactions, bacterial and viral infections and cardiac disorders.

CYTOKINE EXPRESSION IN PERIODONTAL HEALTH

Tissue homeostasis is maintained by a delicate balance between anabolic and catabolic activities. Studies suggest that cytokines are secreted by fibroblasts (Moscatelli et al., 1986)[2], endothelial cells, and epithelial cells, which play a crucial role in tissue homeostasis. Polymerase chain reaction examination of clinically healthy gingival tissues showed, mRNA expression of a various of growth factors-such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and transforming growth factor-β(TGF-β).Inflammatory cytokines such as interleukin 1(IL-1), interleukin-6 (IL-6), TNF –α was also detected in healthy gingiva but their concentrations were relatively low compared to that of inflamed tissues. These evidence suggests that cytokines may be involved in the maintenance of periodontal tissue turnover or integrity.

INFLAMMATORY CYTOKINES AND PERIODONTAL DISEASE

Periodontal disease is an inflammatory condition which occurs as a result of the interaction between environmental, genetic, host and microbial factors. Destruction of tooth supporting tissues in susceptible individuals occurs as a result of shift in the balance of preventive and destructive immune mechanisms against microbial pathogens[3] . Periodontal inflammation begins as an acute inflammatory response after host-bacterial interaction, later progresses to a chronic stage which is dominated predominantly by B lymphocytes and macrophages, following an intense T lymphocytes stage [4]. Most of the periodontopathic bacteria resides in periodontal pockets and do not invade the peri-

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odontal tissues and the immune system can never efficiently eliminate the microorganisms from the periodontal pockets. This unique situation leads to development of chronic inflammation and the excessive host responses will further results in tissue destruction. The local host response to the putative pathogens includes the recruitment of leukocytes to the inflamed area and subsequently will lead to release of inflammatory mediators and cytokines. The inflammatory mediators and cytokines appears to play crucial roles in the pathogenesis of periodontal diseases.

Thus, an imbalance between the plaque biofilm and the host immune system results in the over expression of an array of pro inflammatory cytokines, which leads to propagation of inflammation through the gingival tissues and the subsequent destruction of alveolar bone[5]. This inflammatory process further leads to destruction of connective tissue and alveolar bone, which is considered as the hallmarks of periodontal disease.

There are two important factors, which determines whether bone loss occurs as a response to inflammatory reaction.

1. The concentration of pro-inflammatory cytokines and mediators present in the gingival tissue must be sufficient to activate the pathways leading to bone resorption.

2. The inflammatory mediators must penetrate the gingival tissue to reach within a critical distance to alveolar bone [6]. Page and Schroeder demonstrated that bone resorption ceases when a 2.5 mm zone is created between the site of bacteria and bone[7] .

An inflammatory cytokine is defined as a cytokine which is induced during the course of an inflammatory response and is closely associated with its onset and/or progression. IL-l α, IL- 1β, IL-6, IL-8, and TNF-α are generally classified as inflammatory cytokines. These inflammatory cytokines plays an important role in pathogenesis of periodontal disease due to their enhancement of bone resorption.

ROLE OF INFLAMMATORY CYTOKINES IN PATHOGENESIS OF PERIODONTAL DISEASE [8]

Cytokine	Functions
IL-l	Enhancement of bone resorption Stimulation of metalloproteinase production Stimulation of plasminogen activator Stimulation of prostaglandin synthesis
IL-6	B-cell activation, resulting in non-specific antibody production and IL-1 production Enhancement of bone resorption
IL-8	Stimulation to attract and activate neutrophils
TNFα	Enhancement of bone resorption, showing synergistic effects with IL-1

Table 1: Role of Cytokines in pathogenesis of periodontal disease

INTERLEUKIN -1

IL-1 is a polypeptide with a wide array of diverse activities and plays important roles in immunity, inflammation, tissue breakdown, and tissue homeostasis. IL-1 is synthesized by various cell types, including macrophages, monocytes, lymphocytes, vascular cells, brain cells, skin cells, and fibroblasts. IL-1α and IL-1β share only 27% homology at the amino acid level, but they have similar biological functions. It has been demonstrated that IL-l α remains largely cell-associated, whereas IL-1β is released from the cell[9].

IL-1 is known to stimulate the proliferation of keratinocytes, fibroblasts, and endothelial cells and also enhances fibroblast synthesis of type I procollagen, collagenase, hyaluronate and fibronectin. IL-I is, thus considered, a critical component in the homeostasis of periodontal tissues.

Both IL-1α and IL-1β can also trigger prostaglandin E2 (PGE2) synthesis by the vascular endothelium of the hypothalamus and can also stimulate T cell proliferation. Furthermore, IL-1 also elicits the release of histamine from mast cells at the site of inflammation. Histamine then triggers early vasodilation and increase in vascular permeability.

The local unrestricted production of IL- 1 by the cells of periodontium appears to be capable of stimulating gingival and periodontal ligament fibroblasts, in an autocrine or paracrine fashion, to induce the production of other cytokines, matrix-degrading enzymes, and prostaglandin E2. These mediators may be responsible for causing connective tissue destruction, leading to loss of attachment. Thus, IL-1 has been suggested to play a key role in the pathogenesis of various bone diseases, including periodontitis. IL-α, IL-13, and tumor necrosis factor-alpha (TNFα) can stimulate bone resorption and inhibit bone formation. In addition, IL-1 synergizes the bone-resorptive actions of TNF-α .It was found that IL-1β is significantly more potent than either IL-1α or TNF-α in mediating effects on bone. IL- 1 can induce the production of matrix metalloproteinases (MMPs) and can also cause elevated level of procollagenase in both gingival fibroblasts and periodontal ligament (PDL) cells. In addition, IL-1 can stimulate plasminogen activator in gingival fibroblasts, which results in the generation of plasmin which is a putative, naturally occurring, activator of several matrix metalloproteinases. IL-1 has been found to be 500-fold more potent than TNF-α in mediating bone resorption[10] The pro-inflammatory effects of IL-1 can be inhibited by IL-1 receptor antagonist (IL-1Ra),also referred as IL-1 inhibitor[11].

INTERLEUKIN -6

IL-6 is a pleiotropic cytokine, synthesised mainly by stimulated monocytes, fibroblasts, and endothelial cells[12]. Macrophages, T- and B-cells, and keratinocytes also synthesise IL-6 after stimulation. Studies shows that IL-6 levels in inflamed gingival tissues were higher than those in healthy control tissues. One of the most important function of IL-6 is the induction of the final maturation of B-cells into immunoglobulin-secreting plasma cells. IL-6 acts as a growth factor for mature B cells and induces their final maturation into antibody producing plasma cells. It triggers the secretion of antibodies to such a degree that serum IgG I levels can rise 120-400-fold. In periodontal lesions, a number of cell types-such as T-cells, macrophages, endothelial cells, and fibrobalsts are shown to express IL-6 at both mRNA and protein levels. It is believed that the expansion of B-cells/plasma cells s in periodontitis lesions may occur as a result from an increased production of IL-6 at diseased

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sites. Also, it is suggested that IL-6 plays an important role in the local regulation of bone turnover and appears to be essential for bone loss caused by estrogen deficiency . IL-6 may act as an autocrine and/or paracrine factor in bone resorption in pathologic states by stimulating the synthesis of osteoclasts and thus resulting in activation of osteoclastic bone resorption. IL-6 has been considered as a proinflammatory cytokine induced by lipopolysaccharide along with TNF-α and IL-1. IL-6 is often used as a marker for systemic activation of proinflammatorycytokines[13] . IL-6 has both proinflammatory and anti-inflammatory properties.

Eventhough, IL-6 is a potent inducer of the acute-phase protein response, it has anti-inflammatory properties also[14] IL-6 downregulates the synthesis of IL-1 and TNF [15,16] . IL-6 attenuates the synthesis of the proinflammatory cytokines while having little effect on the synthesis of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β).

INTERLEUKIN -8

IL-8, previously referred as neutrophil-activating peptide-1 (NAP-1) and neutrophil chemotactic factor (NCF)[17] . IL-8 is considered as a potent chemotactic factor for leukocytes. IL-8 is synthesised by monocytes, fibroblasts, lymphocytes, and endothelial cells. IL-8 is also expressed in epithelial cells and macrophages of inflamed gingival tissues.

IL-8 may play a significant role in the pathogenesis of periodontitis because of its pro-inflammatory and neutrophil chemotactic properties.IL-8 mediates the recruitment and activation of neutrophils in inflamed tissue[18] .Locally secreted IL-8 stimulates neutrophil extravasation at the site of inflammation and that the numerous neutrophils present in the lamina propria and the epithelium of inflamed gingiva may be migrating to the inflamed site by IL-8.

TUMOR NECROSIS FACTOR α (TNF-α)

TNF-α is a pleiotropic / multifunctional pro-inflammatory cytokine that is secreted mainly by monocytes and macrophages. It stimulates the secretion of collagenase by fibroblasts, leading to resorption of cartilage and bone, and thus leading to periodontal tissue destruction. TNF-α induces the synthesis of IL-1 and prostaglandin E2. TNF-α also activates osteoclasts and thus stimulates bone resorption. TNF-α has synergistic effects with the bone-resorptive actions of IL-1. Lipopolysaccharide (LPS) of periodontal Gram-negative bacteria can stimulate the production of TNF-α by peripheral blood monocytes , which will leads not only to alveolar bone resorption but also to the enhanced synthesis of collagenase by human gingival fibroblasts. TNF-α also has an important inflammatory property with IL-6 and IL-11, *i.e.* they can cause induction of acute phase reactant protein production by the liver. TNF-α,is also known as lymphotoxin, since it is synthesised by activated T and B lymphocytes. TNF-α is responsible for cell migration process at multiple levels, induces the upregulation of adhesion molecules and helps in the production of chemokines, which are chemotactic cytokines involved in cell migration to infected and inflamed sites .TNF-α is present at high levels in gingival crevicular fluid (GCF), diseased periodontal tissues it is correlated with MMPs and RANKL expression[19]. TNF-α plays a pivotal role in the inflammatory reaction, alveolar bone resorption and in the connective tissue attachment loss .While the destructive roles of TNF-α in periodontal conditions lead to the proposal of anti-TNF therapies to control periodontal diseases it also showed a dual role for TNF-α in the pathogenesis of experimental periodontal disease, since this cytokine present an important role in the control of experimental *A.actinomycetemcomitans* infection, as demonstrated by the increased bacterial load and acute phase response presented by TNFp55-KO infected mice (Garlet et al., 2007) [20]. Besides its role in inflammatory cell migration TNF-α plays an important role in both innate and adaptive immune responses, upregulates antigen presentation and the bactericidal activity of phagocytes.

CONCLUSION

Inflammatory periodontal disease occurs as a consequence of the interaction of environmental, genetic, host and microbial factors. Destruction of tooth supporting tissues in susceptible individuals results from the shift in balance of preventive and destructive immune mechanisms against microbial pathogens. The development of inflammatory diseases like periodontal disease is characterized by the persistent release of inflammatory mediators, such as cytokines and chemokines and migration of inflammatory cells to infected sites. These responses, eventhough directed against bacteria, may perpetuate and mediate the destruction of connective and mineralized periodontal tissues, being the main responsible factor for periodontal breakdown. The effects of cytokines that promote osteoclast formation and bone resorption seem to be counteracted by other cytokines that are anti-inflammatory. It is possible that the balance between stimulatory and inhibitory cytokines, together with the regulation of their receptors and signaling cascades, determines the level of periodontal tissue loss. It is clear that in periodontal pathogenesis, cytokines have wide ranging and overlapping functions, as in any tissue compartment exposed to a chronic bacterial challenge and in which there is persistent chronic inflammation. In short, the balance between pro- and anti-inflammatory cytokines and regulation of their receptors and signaling pathways determines the extent of periodontal tissue destruction. It is becoming more evident that cytokines interact and function in some sort of a web system. Unfortunately despite the extensive researches still we do not yet fully understand intricacies of these networks. Recent studies suggest that the control of periodontal infection by "protective and destructive" mediators is an obviously simplified concept and several cytokines may demonstrate dual and apparently conflicting protective and destructive roles. Thus, researches to unravel the destructive and protective role of cytokines and chemokines from the tissue destruction viewpoint make the development of effective therapies a very interesting challenge.

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