Review Article

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CYTOKINES- A CRUCIAL AND PROTECTIVE ROLE IN PERIODONTAL DISEASE

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ABSTRACT:

Cytokines are low molecular weight proteins involved in the initiation and effector stages of immunity and inflammation, in which they regulate the amplitude and duration of the response they are usually produced transiently, are extremely potent, generally acting at picomolar concentrations and interact with specific cell surface receptors, which are usually expressed in relatively low numbers.

Keywords: Cytokine, Interleukins, periodontium

INTRODUCTION:

Cytokines are low molecular weight proteins involved in the initiation and effector stages of immunity and inflammation, in which they regulate the amplitude and duration of the response they are usually produced transiently, are extremely potent, generally acting at picomolar concentrations and interact with specific cell surface receptors, which are usually expressed in relatively low numbers.[1]

Cytokines play an important role in numerous biological activities including development, differentiation, homeostasis, regeneration, repair and inflammation.[2]

For tissue homeostasis, a primary role can be ascribed to cytokines which are constitutively secreted by resident cells composing of tissue. On the other hand, in diseased states cytokines may be secreted by not only by resident cells but also by locally infiltrated immunocompetent cells.

In chronic inflammatory periodontal disease, the predominant lymphocyte in the stable lesion is the T-cell, while increased proportions of B-cells and plasma cells can be demonstrated in the progressive lesion, indicating a role for Th2 cells in the progressive lesion. B-cells appear to be activated locally in the gingival lesion.

By acting as intercellular communicators between cells of the immune system, cytokines are central to the way in which helper T cells regulate the immune response.

Cell-mediated immune responses involve the activation of macrophages and induction of different CD8+ and CD4+ T cells, whereas humoral immunity is characterized by antibody production.

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The production of appropriate cytokines in response to infection is necessary for the development of protective immunity.

Main biological activities of cytokines, which may be important in the pathogenesis of periodontal Disease

Activation of bone resorbing processes:- TNF-α, IL-1 α/β, IL-6
Inhibition of bone resorption: - IL-4, IFN-γ.
Inhibition of bone formation: - TNF-α, IL-1 α/β
Mitogenic activity for fibroblasts: - TNF-α, IL-1 α/β
Stimulation of protease and PGE2 produced by fibroblasts: - TNF-α, IL-1 α/β
Fibroblast proliferation: - IL-1 α/β, IL-4, IFN-γ
Stimulation of neutrophils: - TNF-α, IL-1 α/β, IL-4, IL-6, IL-8
T cell proliferation: - TNF-α, IL-1 α/β, IL-2, IL-4, IL-8
B cell proliferation: - IL-1 α/β, IL-2, IL-4, IL-6, IFN-γ
NK cell proliferation: - TNF-α, IL-1 α/β, IL-2
Activation of eosinophils: - TNF-α, IL-4, IL-5
MHC expression on monocytes:- IFN-γ
Augmentation of IL-1 production:- IFN-γ, TNF-α, IL-1 α/β
Augmentation of IL-2production:- IL-1 α/β
Augmentation of TNF production:- IL-1 α/β,IL-2, IFN-γ

Cytokines identified in periodontal tissues are:-TNF-α, IL-1 α/β, IL-6, in patients with chronic adult periodontitis
Cytokines identified in crevicular fluid:- TNF-α, IL-1 α/β, IL-6, IL-1 inhibitor

INTERLEUKIN-1

Interleukin-1 is mainly a proinflammatory cytokine that stimulates the expression of many genes associated with inflammation and autoimmune diseases.

In periodontal inflammation, IL-1β is mainly expressed by macrophages and dendritic cells, but gingival fibroblasts, periodontal ligament cells and osteoblasts in response to microorganisms, bacterial endotoxins and exotoxins , complement component, or tissue injury show increased levels of IL-1β, as well as of IL-1α and IL-1 receptor antagonist, in gingival crevicular fluid which has been reported.[5]

In pathological situations, such as during periodontal disease, the delicate balance between synthesis and degradation is disturbed. Microbial products may trigger a host response which induces the production and release of cytokines and proteolytic enzymes by both inflammatory and resident cells.[3,4]

On the other hand, TGF-β a cytokine known for its wound healing and repair-stimulating activities has a downregulating effect on MMP-1 expression, synthesis, and release, and moreover appears to neutralize the activity by stimulating the production of TIMP.[10]

INTERLEUKIN -2

The present investigation has shown that serum IL-2 and IL-4 are elevated in patients with periodontitis, but did not correlate with bone loss and with pocket formation observed clinically. Since IL-2 is a product of activated T-lymphocytes and is expressed by T-cells and B-cells, it acts a marker for immune cell function.[23]

INTERLEUKIN-4 ⁄ INTERLEUKIN-13/ INTERLEUKIN -17

The recent findings indicate that periodontitis is associated with increased levels of IL-4 [6,7] whereas conflicting reports are also available.[8,9] These differences in observations can be attributed to the population differences in the rates of production of IL-4.

The concentration of IL-4 in gingival crevicular fluid from periodontitis sites have been found to be significantly decreased [20], which supports the view that interleukin-4, has a protective role in alveolar breakdown.

IL-4 and IL-13 inhibit the formation of osteoclasts and bone resorption by two cellular mechanisms: one by decreasing the osteoclastogenic activity of osteoblasts and the other by directly targeting osteoclasts progenitors.[7,19]

IL-17 is a proinflammatory cytokine that stimulates a variety of cells to produce inflammatory mediators such as IL-1, IL-6, and TNF-α .[24] In gingival tissue samples, IL-17 mRNA was detected in gingivitis more frequently than in periodontitis. These results suggest that IL-17 but not RANKL may be involved in the pathogenesis of periodontal diseases. However, there may be negative regulatory mechanisms for IL-17 in gingivitis.[20] Elevated tissue concentrations of IL-17 could promote periodontitis progression by increasing concentrations of bone resorbing chemokines, which suggests that IL-17 may be a mediator of periodontal destruction.[25]

INTERLEUKIN 5.

A study was conducted to examine the production of cytokines of importance in B-cell responses, e.g., interleukin (IL)-2, IL-4, IL-5, and IL-6 by gingival mononuclear cells (GMC) isolated from patients in severe stages of adult periodontitis(AP). [4] These cytokines were assessed at the protein and messenger (m)RNA levels to understand their importance for increased B-cell responses present in these tissues. Results showed that GMC from localized inflammatory tissues in severe stages of AP possess a distinct cytokine profile represented by high levels of IL-5 and IL-6 mRNA expression and protein synthesis, whereas IL-2 and IL-4 were not detected. Further, this study supports the concept that AP is a localized inflammatory disease, because GMC from the inflamed tissue actively produce IL-5 and IL-6, whereas peripheral blood mononuclear cells from the same patients do not.[4]

INTERLEUKIN-6 FAMILY

In the periodontium, IL-6 is expressed by osteoblasts, [11] gingival fibroblasts [12] and periodontal ligament cells,[13,14] and its regulation is controlled by many cytokines and toll-like receptors. Increased amounts of IL-6 and oncostatin M have been detected in the gingival crevicular fluid. [15]

INTERLEUKIN-7

A study was conducted to understand the involvement of IL-6 and IL-7 in the T cell regulation of osteoclast (OC) formation, in an in vitro osteoclastogenesis model from periodontitis patients (Pp).The results showed that B cells, in fact, overexpressed IL-7 at mRNA and protein levels, and this production was up-regulated by IL-6. Moreover, the OC formation decreased in the presence of anti-IL-6 and IL-7 functional antibodies in Pp. These data suggest that B cells could be responsible for the T cell-dependent osteoclastogenesis in periodontitis through the involvement of IL-6 and IL-7.[8]

INTERLEUKIN-8

In inflamed gingival tissues, it was observed that IL-8 was expressed in epithelial cells and macrophages. It was also reported that IL-1- or TNF-α-stimulated gingival fibroblasts expressed IL-8 mRNA. Because of its pro-inflammatory and neutrophil chemotactic properties, IL-8 may play a significant role in the pathogenesis of periodontitis. It is likely that locally secreted IL-8 induces 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 directed there by IL-8 which may contribute to local tissue destruction of the periodontal tissues. IL-8 may also attract T-cells and induce motility in the $CD45RO^{+}$ γδ and αβ T-cells present in inflamed gingiva.[2]

INTERLEUKIN-10

The prevalence of IL-10 in periodontitis lesions may have an important bearing on microbial killing because of its potential role in diminishing TNF-α- and IFN-γ- mediated responses.[16] To clarify the role of serum IL-10 and TNF-α in periodontal inflammation, author examined whether any association exists between the extent of bleeding on probing (BOP), probing pocket depth (PD) ≥4mm and attachment level (AL) ≥4mm and the serum levels of IL-10 and TNF-α. The significantly higher serum TNF-α/IL-10 ratio in the subjects with chronic periodontitis when compared with the ratio in the controls is indicative of a stronger systemic pro-inflammatory state in chronic periodontitis. [16]

INTERLEUKIN-11

In another study, concentration of IL-11 was compared within healthy and diseased human gingiva to determine their possible role in the initiation or progression of periodontal disease. It was found that IL-11 concentration was

highest within gingiva adjacent to 3mm diseased pocket and it was lower in gingiva adjacent to ≥6mm pocket.[17]

However, reduced concentration of IL-11 in deeper pockets as compared to shallow pocket suggests these protective effects could be minimized by lower concentration of IL-11 in tissue. Reduced concentration of IL-11 could also result from increased degradation of cytokine within those tissues. Thus, addition of IL-11 to gingival microenvironment could compensate for reduced concentration during late gingivitis period. [17]

INTERLEUKIN-12

Number of studies showed that the mRNA expression and /or concentration of IL-12 and INF-γ in GCF, gingival tissues and serum were able to affect specific periodontal condition, such as gingivitis, probing depth, and alveolar bone loss. The total amount of IL-12 found in GCF was variable in different studies. It was lower in GCF samples from chronic periodontitis and gingivitis sites than from healthy sites.[18]The serum levels IL-12 was significantly higher in chronic periodontitis patients than in periodontally healthy subjects, suggesting an involvement of this molecule in the initiation and progression of chronic periodontitis.[19]

INTERLEUKIN-15

Upregulation of the IL-17,IL-15, and increased amounts of fibrosis were observed in sites of chronic periodontitis in subjects with type 2 DM. [7]

Another study was conducted to compare the expression of 22 chemokines and cytokines in gingival crevicular fluid (GCF) from smokers and non-smokers with periodontitis and periodontally healthy control subjects.[26] Compared with healthy control subjects, GCF in subjects with chronic periodontitis contained significantly higher amounts of pro-inflammatory cytokines; IL-8, IL-2, IFN-*γ*, IL-3, IL-4 ,IL-15 [regulator of T-cells and natural killer (NK) cells]. However, smokers displayed decreased amounts of pro-inflammatory cytokines [IL-1*α*, IL-6, IL-12], chemokines (IL-8, MCP-1, MIP-1, RANTES), and regulators of T-cells and NK cells (IL-7, IL-15).[26]

INTERLEUKIN-18

IL-18 is involved in the maturation of myeloid dendritic cells into mature dendritic cells (DCs), however, it has little effect on monocytes or the differentiation of monocytes to DCs, which means that IL-18 is involved in the activation of the adaptive immune response, specifically via the activation of the myeloid compartment.[21]

The level of IL-18 in GCF was increased with the severity of periodontal disease. In addition, the level of IL-18 was found to decrease significantly after periodontal therapy in chronic periodontitis patients. Thus, IL-18 can be considered an inflammatory biomarker of periodontal disease.[22]

CONCLUSION:

Our knowledge of the physiological, biochemical, and molecular biological properties and actions of interleukins and their receptors has grown tremendously over the last two decades. However, despite the progress that has been made, we do not fully understand the pathogenesis of periodontal diseases at the molecular level. Clarification of how various interleukins contribute to the problem and/or solution of pathological situations such as periodontal diseases may enable us to diagnose and treat the disease at the molecular and cellular levels to an extent previously thought to be impossible. Thus, great excitement awaits further studies in this field.

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