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Inflammatory Cytokines and the Pathogenesis of Periodontal Disease

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Introduction

Inflammatory periodontal disease is a consequence of the interaction of environmental, genetic, host and microbial factors. Destruction of tooth supporting tissues in susceptible subjects results from the shifting balance of preventive and destructive immune mechanisms against microbial pathogens [1,2].

Periodontal inflammation which begins as an acute inflammatory response after host-bacterial interaction, progresses into a chronic stage dominated by B lymphocytes and macrophages, following intense T lymphocytes stage [3]. Transition between these stages, accumulation and differentiation of immune cells in the inflammatory site are mediated by "cytokines." Cytokines are soluble mediators contributing many biologic processes such as hematopoiesis, wound healing, systemic and local inflammatory responses [4] Many cell types other than immune cells like epithelial cells, gingival and periodontal ligament fibroblasts, and keratinocytes are shown to produce cytokines upon stimulation [5,6]. Cytokines show pleiotropic effects on different target cells by regulating cell activation, proliferation and function [4]. Therefore the net effect of cytokines is directing the intensity and duration of immune response which may serve as a critical determinant of tissue destruction in many inflammatory chronic diseases like rheumatoid arthritis, inflammatory osteoarthritis and periodontitis. A considerable number of studies demonstrated that the persistent host inflammatory response against bacterially derived factors results in the destruction of soft and mineralized periodontal tissues [7-10].

The complex cytokine network that mediates the immune response includes pro-inflammatory cytokines, anti-inflammatory cytokines and specific cytokine receptors [11]. As the other chronic inflammatory diseases inflammatory cytokines are considered to play an important role in the initiation, progression and the host modulation of periodontal disease [12,13] Current knowledge supports that the immunoregulatory properties of T cell derived cytokines can improve or attenuate the progression of periodontal disease [14]. There is evidence that failure to resolve inflammatory periodontal disease may be the result of an imbalance in T helper (Th) 1, Th2 and Th17 response and pro- and anti-inflammatory cytokines [14-17]. Therefore, in this mini-review, the Th cell subsets and their cytokines which are involved in the host inflammatory response and the destruction of periodontal tissues are summarized.

The Role of Th1/Th2/Th17 Cytokines in Periodontal Disease

Histopathological studies indicate that T cells which are the source of many cytokines are the dominant cell type in periodontitis lesions [18,19]. Th cells can be subdivided into lineages on the basis of cytokine profiles, expression of transcription factors and homing receptors which are named as Th1and Th2 lymphocytes. Recently additional subsets have been identified (Th17, Th9, Th22, Tregs) the most extensively studied being the Th17 one [20].

Because Th1, Th2, Th17 and monocyte-derived cytokines in periodontal tissues and gingival crevicular fluid (GCF) are involved in periodontal inflammation, even a minimal imbalance of cytokine production may affect induction of bone and collagen destruction in periodontal disease [14-16]. As a general rule, immune responses mediated by T cells polarized into a Th1-type phenotype are characteristically cellular and pro-inflammatory; while Th2 cells are associated with humoral immunity and present anti-inflammatory properties [14].

Th1 cytokines

Th1 cells activate cellular immunity against intracellular pathogens by producing interleukin [IL]-1, IL-12, IL-2, interferon (IFN)-γ, *and* tumor necrosis factor (TNF)-α.

IL-12, is the major cytokine which induces naive T cells in a Th1-specific manner. In humans, the major effect of IL-12 is to stimulate IFN-γ production by Th1 cells and regulate the transition from an early innate immune response to an adaptive immune response [21]. IL-12 also stimulates natural killer cells to synthesize multiple pro-inflammatory cytokines (IL-1, IFN-γ,TNF-α, IL-8) [21,22]. IL-12 was shown to mediate bone loss after *P. gingivalis* challenge [23]. Several other studies have attempted to determine the IL-12 profile in periodontal disease [24-26]. Although the results are contradictory, there is evidence that IL-12 plays a potential role in the progression of periodontal inflammation by inducing a Th1 response [26,27].

IL-1 is a multifactorial cytokine which is able to activate many cell types with potent inflammatory features. The wide biological effects of IL-1 result from its central role in regulation of many different genes. IL-1 affects approximately 90 genes that occur during inflammation. These include the genes which regulate cytokines, cytokine receptors, acute phase reactants, growth factors, extracellular matrix components and adhesion molecules [28]. Clinical studies have illustrated that the amount of IL-1β is much higher in GCF in periodontal pockets or in the underlying inflamed gingival tissue than at healthy sites. Furthermore, IL-1β levels are higher in active periodontitis sites than in stable sites [16,26,29] It is known that TNF-α induces bone and extracellular matrix resorption by activating the osteoclasts in a similar way with IL-1 [30]. Monocytes and macrophages are the potent cell types producing TNF-α. The local cellular effects of TNF-α include the adhesion of polymorph nuclear leukocytes (PMNs) to endothelial cells, degranulation of PMNs, activation of phagocytosis and intercellular adhesion molecule (ICAM) -1 expression. The amount of TNF-α was demonstrated at high levels in gingival crevicular fluid and diseased periodontal tissues [8,16] and experimental studies have shown a central role for TNF-α in alveolar bone resorption [31,32].

Analysis of IL-1, TNF-alpha, IL-2, IFN-gamma and IL-10 mRNA levels by RT-PCR in healthy and inflamed periodontal tissues demonstrated that IL-1, TNF-alpha, IL-2, IFN-gamma levels are increased in periodontitis lesions supporting the hypothesis that Th1 cytokines are associated with periodontal tissue destruction [16].

Th17 cytokines

Recent studies indicate that both Th1 and Th17 can be involved in inflammatory disorders and these two cell subsets can develop concurrently [33,34]. It has been suggested that IL-1beta was essential for inducing IL-17/IFN-γ cells, the so called Th17/Th1 subset [33]. Th17 cells differentiate from $CD61^+$ cells and $CD4^+$ T cell precursors in the presence of IL-1beta and IL-23 [35]. The prototypical Th17 cytokine is IL-17; Th17 cells can also produce other effector cytokines with osteoclastogenic properties, such as IL-6 and IL-23. IL-17 is involved in osteoclastogenesis by inducing RANKL expression on osteoblastic cells [36]. The main function of IL-17 is to mediate inflammation by stimulating resident cells to secrete potent pro-inflammatory cytokines like IL-1, IL-6- IL-8 and prostaglandin E2 (PGE2) that exacerbate the inflammatory reaction and tissue destruction. Several studies demonstrated the presence of Th17 cells in chronic periodontitis lesions [37-39]. Cytokines produced and induced by Th17 cells like IL-6, IL-23 and IL-1 beta mRNA levels were reported to be elevated in lesions with periodontitis [37]. Recently, increased GCF IL-17 levels were reported in aggressive periodontitis patients [40]. Taken together, in addition to Th1/Th2 paradigm, Th17 subset has a major impact on immunoregulation of host response in periodontal tissue destruction.

Th2 cytokines

Th2 lymphocytes play a crucial role in humoral immunity against extracellular pathogens by producing IL-3, IL-4, IL-5, IL-6, IL-10, IL-11 and IL-13 [41].

Th2 polarization from naïve CD4 T cells is achieved by production of IL-4 [42]. Several studies have demonstrated that anti-inflammatory cytokines such as IL-4 and IL-10 can down regulate pro-inflammatory cytokine production from effector cells such as macrophages [43]. IL-10, the major anti-inflammatory cytokine demonstrates wide immunoregulatory effects by reducing IFN-gamma and IL-17 from T cells and also inhibiting bone resorption via preventing RANK-RANKL connection [44,45]. It is widely expressed in periodontal tissues and is associated with lower disease severity. Besides IL-10, another Th2 cytokine, IL-11 is supposed to have anti-inflammatory properties due to its inhibition of pro-inflammatory cytokines [46]. It has been shown that IL-11 can inhibit the production of IL-1β, TNF-α, IL-6, IL-12 p40 and nitric oxide and down regulates LPS-induced cytokines through inhibition of NF-κB expression in vitro [47,48]. In animal models, IL-11 appears to be important in controlling the development of an inflammatory response in periodontal tissues [49,50]. It was reported that the twice-weekly administration of recombinant human IL-11 in the developing periodontal disease model acted by blocking the cytokines most associated with inflammation, leaded to a reduction in both attachment loss and bone resorption [50]. In a study which we aimed to determine the possible role of IL-11 in periodontal pathogenesis, together with the pro-inflammatory cytokines IL-1β and IL-12, lower levels of IL-11 were detected in GCF of chronic periodontitis patients in comparison with gingivitis and healthy subjects [26]. Moreover, IL-11: IL-1β ratio became progressively lower with increasing probing depth. We suggested that IL-11 may be acting as a key mediator in preventing the progressive inflammation leading to periodontal tissue breakdown. Although a destructive role for Th2 subset via B-cell differentiation in periodontal lesions is indicated [51], Th2 cells are capable of producing multiple anti-inflammatory cytokines like IL-11, IL-10 and IL-4, which attenuate the destructive host response mediated by mostly Th1/Th17 cytokines [11].

Concluding Remarks

Multiple host defense mechanisms including neutrophil migration, complement activation and antibody production take action to eradicate the infection caused by periodontopathogens. T helper cytokines have a potent impact on periodontal pathogenesis by both destructive and protective perspectives. Besides their destructive effects, Th1/Th17 mediated cytokines play crucial role to generate an efficient immune response to protect the host against periodontal infection. Th2 cytokines seem to control or attenuate the up-regulation of pro-inflammatory cytokines. Further studies are required to clarify the mechanisms of Th1, Th17 and Th2 regulation in order to improve host–modulatory interventions for resolution of inflammation in periodontal diseases.

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