Chapter

"Interleukin" - An Essential Mediator of the Pathophysiology of Periodontitis

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Abstract

Chronic periodontitis is a multifactorial polymicrobial disease caused by a complex interaction between periodontal pathogens and host immune response. This interaction is largely regulalated by a group of signaling molecules called Interleukins. Initially, investigators believed that interleukins were made chiefly by leukocytes to act primarily on other leukocytes, and for this reason they named them interleukins, meaning "between leukocytes". The majority of interleukins are synthesized by helper CD4+ T lymphocytes, as well as through monocytes, macrophages, and endothelial cells. Interleukins provide information to various inflammatory cells to produce essential proteins which exert pro inflammatory as well as anti inflammatory responses. This chapter will emphasize the role of interleukins in the pathophysiology of periodontitis.

Keywords: periodontitis, interleukins, genetic polymorphism, transcription factors, modulation of signaling, mRNA stability

1. Introduction

Interleukins are a group of cytokines (secreted proteins/signaling molecules) that are expressed by white blood cells. Initially, investigators believed that interleukins were made chiefly by leukocytes to act primarily on other leukocytes, and for this reason they named them interleukins, meaning "between leukocytes". The majority of interleukins are synthesized by helper CD4+ T lymphocytes, as well as through monocytes, macrophages, and endothelial cells. In 1977, **Steve Gillis & Kendal A. Smith** found that *T cell Growth Factor (TCGF)* is needed by Cytotoxic T Lymphocyte Lines to kill leukemia cells [1]. In 1979, it was found that *Lymphocyte Activating Factor (LAF)* produced by macrophages could enhance the production of TCGF. So LAF name was changed to *Interleukin-1* because it functioned first in the sequence and TCGF became *IL-2* because it came second though it was the first interleukin to be discovered. Interleukins are broadly classified as pro- inflammatory (IL -1, IL-6, IL-8, IL-17) and anti-inflammatory (IL-4, IL-6, IL-10, IL-11, IL-13, IL- 16). Though there are many interleukins, which exerts dual action.

2. Pro-inflammatory interleukins

2.1 Interleukin-1

The original members of the IL-1 superfamily are IL-1α, IL-1β and the IL-1 Receptor antagonist (IL-1RA). IL-1α and -1β are pro-inflammatory cytokines. The receptors for interleukin 1 are Interleukin 1 receptor, type I (IL-1RI) and Interleukin 1 receptor, type II (IL-1RII). IL-1R1 found in astrocytes, chondrocytes, keratinocytes, oocytes, fibroblasts etc. IL-1α binds preferentially to IL-1RI. IL-1RII found in B cells, T cells, keratinocytes, monocytes and neutrophils. IL-1β binds to IL-1RII. Besides the above two there is *IL-1RI accessory protein (IL-1RAcP)* which is a transmembrane glycoprotein. It interacts with *IL-1RI* only, but shows no affinity for IL-1α, IL-1β or IL-1receptor antagonist. IL-1α ligation of the type 1 IL-1 receptor (IL-1R1) leads to multiple pro inflammatory effects [2], including cytokine secretion, neutrophil recruitment, and upregulation of major histocompatibility complex (MHC) and co stimulatory molecules on antigen presenting cells. Pro-IL-1α (p33) is processed to mature IL-1α (p17) by calpain [3] and it increases its affinity for IL-1 Receptor I. IL-1 receptor 2 (IL-1R2) whose binding to pro-IL-1α inhibited its cytokine activity. IL-1α also has powerful effects on adaptive immunity by enhancing expansion and survival of T cells, differentiation of **T helper 17 (Th17) cells**, and effector T cell proliferation in the presence of **regulatory T cells** [4]. IL-1β is a pro-inflammatory cytokine. Although little or no IL-1ß is normally detected in human plasma or serum obtained from healthy, rested human subjects, elevated levels have been reported in the circulation of febrile or septic patients, in patients with inflammatory disease like chronic periodontitis. IL-1RA is a molecule that competes for receptor binding with IL-1α and IL-1β thus blocking their role in immune activation. Interleukin 1 receptor antagonist is used in the treatment of rheumatoid arthritis and diabetes mellitus. Its commercial variety ANAKINRA blocks Interleukin-1 (which causes impaired insulin secretion, decreased cell proliferation and apoptosis in patients with type 2 diabetes mellitus) and thus improves glycemic and pancreatic beta cell secretory function.

2.2 Interleukin-6

IL-6 increases the synthesis of the two major acute-phase proteins, *C-reactive protein (CRP),* which increases the rate of phagocytosis of bacteria, and *serum amyloid A (SAA)* by regulating changes in the gene transcription rate of these proteins. It also increases the synthesis of fibrinogen. Interleukin-6 is especially important in the early stages of T-cell differentiation. In this phase, it reinforces the effect of IL-2 and promotes the differentiation of CD4 cells into T-helper2 cells [5]. IL-6 enhances the release of antibodies by acting as a growth factor for already differentiated plasma cells. It stimulates mostly the release of IgG from these cells [6].

2.3 Interleukin-8

Interleukin-8 (IL-8) is a chemokine produced by macrophages, epithelial cells and endothelial cell. IL-8 was renamed CXCL8 by the Chemokine Nomenclature Subcommittee of the International Union of Immunological Societies. IL-8's primary function is to recruit neutrophils to phagocytose the antigen which trigger the antigen pattern toll-like receptors. It serves as a chemical signal that attracts neutrophils at the site of inflammation, and therefore is also known as a *neutrophil chemotactic factor*.

2.4 Interleukin-17

It is also a pro inflammatory cytokine produced by T- helper cells. To elicit its function,IL-17 binds to type 1 cell surface receptor called IL-17R of which there are 3 variants IL-17RA, IL-17RB and IL-17RC. IL-17 inhibits the gingival endothelial cell expression of developmental endothelial locus-1(DEL-1) which is an endogenous inhibitor of neutrophil adhesion dependent on LFA-1 and ICAM-1 ligation [7].

2.5 Genetic polymorphism of pro-inflammatory interleukins

Kornman et al. first reported on polymorphism for IL-1 genes in relation to chronic periodontitis. IL-1β in GCF was 2.5 times higher in patients showing genetic polymorphism at IL-1α-889 and IL-1β + 3954 (IL-1 composite genotype). Even in these sites after treatment, IL-1β in GCF was still 2.2 times higher for IL-1 composite genotype patients [8]. *N Sharma et al in 2014* demonstrated the association of genetic polymorphism of IL-6 [−597/−174] with chronic periodontitis [9]. *Zacarias et al in 2015* showed that IL-17A G197A rs 2,275,913 polymorphism, AA genotype and A allele could be associated with the susceptibility to chronic periodontitis [10]. Das et al. 2021 suggested a strong association of polymorphism of IL-12β (rs7709212) in both chronic and aggressive periodontitis in a group of the Bengali population [11].

3. Anti-inflammatory interleukins

Pro-inflammatory interleukins induce a Th1, pro-inflammatory phenotype in lymphocytes, while anti-inflammatory interleukins induce a shift to a Th2 profile, with attenuation of pro-inflammatory cytokine expression and concomitant increase in anti-inflammatory cytokine expression.

3.1 Interleukin-10 [IL-10]

is considered a prototype anti-inflammatory cytokine. Its effector functions include a shift of T cell cytokine expression from a Th1 to a Th2 profile, and attenuation of the production of pro-inflammatory cytokines.

3.2 Interleukin-4 (IL-4)

Promotes a Th2 response in lymphocytes and it also negatively regulates the production of pro-inflammatory cytokines [12].

3.3 Interleukin-19

Has been recently described [2000] IL-10 family member and shares 20% amino acid identity to IL-10. It decreases the expression of IFNγ and increases the expression of IL-4 in T lymphocytes [13].

3.4 Molecular mechanism of anti-inflammatory interleukins

The molecular mechanism of anti-inflammatory interleukins can be categorized into the following categories:

3.4.1 Modulation of signaling

The specificity of signaling between different interleukins often lies with different, specific usage of "cytokine-specific" STAT(signal transducer and activator of transcription) proteins. The IL-10 activity requires STAT3, which transactivates multiple genes germane to regulation of the inflammatory response, and STAT3 is required for IL-10 attenuation of TNFα induced inflammatory events. IL-10 binding to IL-10 receptor activates the IL-10/JAK1/STAT3 cascade, where phosphorylated STAT3 homodimers translocate to the nucleus within seconds to activate the expression of target genes. Upon entering the nucleus, STAT3 activates specific target genes among which the ultimate effectors of the ANTI-INFLAMMATORY RESPONSE (the 'AIR factors') are found. STAT3's role is to stimulate the expression of specific genes (AIR factors), which in turn suppress the expression of pro-inflammatory genes. STAT6 is an IL-4–induced transcription factor, and it was reasoned that this factor might block NF-κB activation by binding it directly and/or by preventing its DNA binding activity. STAT6 is required for IL-4 inhibition of osteoclastogenesis [14]. Anti-inflammatory cytokines have also evolved the capacity to diminish Mitogen Activated Protein Kinase [MAPK] signaling.

3.4.2 Modulation of transcription factors

A second mechanism whereby anti-inflammatory interleukins exert their effects is by modulation of NF-κB activity. The NF-κB complex is a cytoplasmic transcription factor consisting of 2 subunits (p50 and p65). NF-κB is present in the cytoplasm, where it exists in an inactive form. Upon stimulation with inflammatory factors, an inhibitory protein termed IκB disassociates from this complex and is proteolyticaly degraded, allowing the p50/p65 complex to translocate into the nucleus and act as a transcriptional activator. NF-κB is considered to be a "**master switch**" in transactivation of multiple genes involved in the inflammatory response.IL-4 can negatively regulate NF-κB by increasing **IκB** transcription, leading to increased binding and inhibition of NF-κB nuclear translocation [14]. Correspondingly, both IL-10 and IL-13 can also reduce or prevent IκB degradation. IL-10 can target other transcription factors as well like Early growth response factor-1 (Egr-1). It has been found that IL-10 can significantly decrease Lipopolysaccharide (LPS) stimulated Egr-1 activation in macrophages, indicating a more direct link to inhibition of proliferation [15].

3.4.3 Regulation of gene expression and mRNA stability

Anti-inflammatory interleukins can also prevent inflammatory response by destabilization of mRNA transcripts mediated by mRNA-binding stability factors [16]. The 3′ untranslated region (UTR) of many transcripts associated with inflammation contain an AU-rich elements (AREs) which are target sites for these mRNAs-binding stability factors. Up regulation of one of these mRNAs stability factors, **HuR** (a ubiquitously expressed member of the Hu family of RNA-binding proteins), can support hyper activation of inflammatory mediators. One manuscript describes the down-regulation of HuR by IL-10 in monocytes and attributes this as a major mechanism whereby IL-10 exerts systemic anti-Inflammatory effects [17].

3.5 Relationship between anti-inflammatory interleukins and statins

Several studies demonstrate that Statins can inhibit MAPKs, including p44/42 and p38, and can directly modulate inflammatory gene expression by diminishing activity of NF-κB [18]. In T cells, statins can also induce the release of Th2 promoting cytokines, including IL-10, and diminish secretion of Th1 cytokines such as IL-2 [19].

3.6 Genetic polymorphism of anti-inflammatory interleukins

Dong CHEN et al. in 2016 did one study aimed to evaluate whether three single nucleotide polymorphisms (SNPs), rs2070874 and rs2243248 from *IL4* and rs1800925 from *IL13*, are associated with chronic periodontitis in a Han Chinese population consisting of 440 moderate or severe CP patients and 324 healthy controls [20]. Zahra Armingohar et al. in 2015 studied seventy-two patients with vascular disease(VD)of whom 35 had Chronic Periodontitis were genotyped for single nucleotide polymorphisms (SNPs) in the IL10 − 592 (rs1800872), −819 (rs1800871), and − 1082 (rs1800896) gene by Taqman rtPCR method and by DNA sequencing [21]. The C alleles and C/C genotypes of IL10 − 592 and IL10 − 819 frequencies were significantly higher, while the frequencies of the IL10 − 592 (C/A) and IL10 − 819 (C/T) heterozygote genotypes were significantly lower in the VD group with CP compared to those without chronic periodontitis. The IL10 haplotype ATA frequency (−1082, −819, −592) showed a trend to a significant difference between the two groups indicating protection against chronic periodontitis.

4. Role of interleukins in the inflammatory process of periodontitis

The inflammatory process of periodontitis is initiated by the activation of specific protein structures called Toll-like receptors (TLRs) situated on the wall of the epithelial cells of the sulcular epithelium [22]. The function of these TLRs is to recognize the lipoproteins and peptidoglycans of gram positive bacteria (TLR-2) and lipopolysaccarides of gram negative bacteria (TLR-4) [23]. The recognition of bacterial substances through TLRs of epithelial cells leads to the activation of cell mediated immune response which is regulated by subsets of CD4 + T cells called T helper (Th) cells. The different subsets of T helper cells are characterized by releasing different cytokine profiles.Th-1 cells are mainly responsible for the secretion of pro-inflammatory interleukins (IL-1, IL-2, IL-12), while Th-2 cells induces the release of anti-inflammatory interleukins (IL-4, IL-5, IL-6, IL-10, IL-13) [24]. Apart from this Th-17 cells release IL-17 which helps in rapid neutrophil recruitment during early stage of the inflammatory process of periodontitis [25]. Interleukin-8 or CXCL8 establishes a chemotactic gradient for this neutrophil emigration.

The persistent presence virulent factors within the subgingival microenvironent leads to shift of the cellular profile from polymorphonuclear leukocyte to mononuclear leukocyte.IL-6 plays major role in shifting of this cellular profile. There are two types of IL-6 receptors, membrane bound receptors present on the wall of PMNLs(mIL-6R) and soluble receptors present freely in extravascular spaces (sIL-6R). Large number of neutrophils which are migrated during early stages of inflammatory process cleave their mIL-6R from cell membrane to inhibit further binding with IL-6. Thus the free receptors easily coupled with IL-6 and this complex further

attaches with gp-130 subunit situated on the endothelial cell membrane. This leads to release of monocyte chemoattractant protein –1 (MCP-1) which creates a chemotactic gradient for the transmigration of monocytes [5].

IL-1, IL-6 and TNF-α induces the differentiation of these recruited monocytes into preosteoclasts [26].

5. Therapeutic strategies for the potential use of interleukin blockage in periodontitis

The benefit of IL-1 blockage has been demonstrated in conditions, such as gout, diabetes mellitus and even myeloma [27]. Studies have discussed that blocking of IL-1 may reduce the periodontal bone loss and also suggesting future prospects [28].

Anakinra (Kineret) was the first interleukin-1 blocking agent to get the approval for the treatment of rheumatoid arthritis in the USA in 2001. It is a recombinant IL-1 receptor antagontist. However, due to short half-life (4–6 h) daily subcutaneous injections were required [29]. In comparison to Anakinra, other agents like **Rilonacept** (recombinant soluble receptor which prevents IL-1β to bind to membrane bound receptors presents on the cell membrane of inflammatory cells, thus inhibits further signal transduction) and **Canakinumab** (monoclonal antibody against IL-1β) have longer half life. Rilonacept has a half life of 6–8 days,while the half life of canakinumabis as long as 26 days [29, 30].

6. Inflammasome inhibitors

NLRP3 inflammasome helps in the maturation of IL-1β. Inflammasome inhibitors target caspas-1 and NLRP3,thus prevents the maturation of IL-1β. **Belnacasan** (VX-765, Vertex Pharmaceuticals) a caspas-1 inhibitor partly decreases bone resorption in the periapical lesion of rat experimental apical periodontitis [31].

7. Conclusion

Hence interleukins can be considered as the group of signaling molecules that provide information to various inflammatory cells to produce essential proteins which exerts pro inflammatory as well as anti inflammatory responses. They also play crucial role in shifting of polynuclear to mononuclear cellular profile and further differentiation of pro bone resorptive cells. Therapeutic strategies of blocking Interleukin functions through receptor antagonist, soluble receptors, monoclonal antibodies and inflammasome inhibitors showed beneficial outcomes. However, more investigation is necessary for interleukin blockage to be used as a treatment for periodontitis or as an adjunctive to periodontal therapy.

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