Review Article

Role of interleukin 10 as an anti-inflammatory cytokine in periodontal infection

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ABSTRACT

Periodontal diseases comprise a wide range of inflammatory conditions that affect the supporting structures of the teeth (the gingiva, bone, and periodontal ligament), which could lead to tooth loss and contribute to systemic inflammation. A complex network of pro- and anti-inflammatory cytokines acts in inflamed periodontal tissues. Among other cytokines, interleukin-10 (IL-10) is an important multifunctional cytokine. Periodontal inflammation may involve both an increase in inflammatory stimulators such as IL-1 and a decrease in inflammatory inhibitors like IL-10. IL-10 has been also regarded as an important regulator of bone homeostasis, in homeostatic, and inflammatory conditions. Hence, IL-10 given the role of IL-10 in bone remodeling, the use of IL-10 for inhibiting bone resorption and reducing inflammation may be beneficial for the treatments of periodontitis.

KEY WORDS: Cytokines, Inflammation, Interleukin, Periodontitis

INTRODUCTION

The destruction of periodontal tissues occurs by a complex interaction of the bacterial biofilm and host response.[1] Periodontitis is mainly caused by Gram-negative bacterial microorganisms present in the plaque adjacent to the gingiva in the mouth. This leads to the stimulation of host cells to produce molecules important in the immunoinflammatory response. There is a complex network of pro- and anti-inflammatory cytokines acting in the inflamed periodontal tissues.[2] An example being interleukins (IL) that are chemical substances which function primarily as growth and differentiating factors. IL have a wide array of biological effects that play a crucial role balancing the pro- and anti-inflammatory effects of other cytokines during chronic infections as in the case of periodontal disease. IL-10 is a key immunoregulatory cytokine that may be of significance in the immunopathogenesis of chronic inflammatory diseases such as periodontal disease.

IL

IL are group of cytokines, and they were first identified to be expressed by white blood cells.[3] The majority of interleukins are synthesised by CD4 helper T lymphocytes, as well as through monocytes, macrophages, and endothelial cell.[4] There are large group of interleukin, from interleukin 1 to interleukin 35 with various function but most are involved in directing immune cells to divide and differentiate. Each IL have their own functions that include induction of inflammatory response, growth of leukocytes,proliferation,differentiation,upregulation and downregulation by Interleukins 1 to Interleukin 10. Induction of IFN-γ by IL 12, production of macrophage inflammatory cytokines by IL 13, enhances NK cell cytotoxicity by IL 15, induction of production of inflammatory cytokines by IL 17, Induction of interferon gamma production by IL 18, and expansion of pathogenic CD4 T cells by IL 23. This review says about the role of IL 10 as an anti-inflammatory cytokines in periodontal infection.

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IL-10

About IL-10

The IL-10 gene is located on chromosome 1 at 1q31-32, spans about 4.7 kb and contains four introns and five exons.[5] IL-10 is a homodimer with a molecular mass of 37 kDa. Each monomer consists of 160 amino acids with a molecular mass of 18.5 kDa. IL-10 is an anti-inflammatory cytokine. IL-10 is encoded by

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the IL-10 gene in humans.[6] It has potent suppressive effects in preventing autoimmune disease.[7] IL-10 is produced by monocytes, macrophages, and T cells.[8] It is capable of inhibiting several functions of dendritic cells (DC), monocytes, and T cells including their cytokine production while stimulating B cell immunoglobulin (Ig) production and cytotoxic T lymphocyte generation.[9] During infection IL-10 inhibits the activity of Th1 cells, NK cells, and macrophages.[10] Studies says that IL-10 may play a role in maintaining persistence and pathogenicity in chronic infections.[11] It is also said to be a coregulator of mast cell growth.

Structure of IL-10

IL-10 is an intercalated dimer of two subunits (39–41) consisting of six amphipathic helices. The polypeptide chains of each subunit contribute to both parts of the dimer consisting of 160 amino acids. Initially, IL-10 binds to the IL-10 R1 (receptor), which contains a long cytoplasmic domain; as a result, the binding site for the second receptor chain, IL-10 R2, is formed and its binding completes the creation of the signaling complex.[12] The structure of human IL-10 was studied by X-ray crystal structure analysis.[13] It is 18.5 kDa acid-sensitive protein that lacks detectable carbohydrate moieties.

Production and Sources of IL-10

Production of IL-10 is stimulated by various endogenous and exogenous factors, but certain allelic variants of IL-10 gene are also associated with differences in IL-10 expression.[14]

The main T cell sources of IL-10 are Th2 cells, subsets of regulatory T cells designated Tr1, Th1, and Th17 cells as well as CD8+ cells which also produce IL10. Other sources of production of IL-10 also include monocytes, macrophages, and some DC. The important sources of B cells are some granulocytes including eosinophils and mast cells. Nonimmune cells sources of IL-10 include epithelial cells, keratinocytes, and even tumor cells.[15] Innate immune effector cell types, primarily of myeloid and lymphoid origin, represent a primary and well-studied source of IL-10, other cell types, including γδT- cells, natural killer (NK) cells, mast cells, granulocytes, as well as epithelial cells, keratinocytes, hepatocytes, and even tumor cells have shown capacity for IL-10 expression.[16] In addition to this, many other cell types of the immune system are known to express IL-10. These include CD8+ T cells, T-cell receptors activation or interaction with CD40 ligand, stimulation of B cells with autoantigens, toll-like receptors (TLR4), TLR9 ligands, or Vitamin D3 can also lead to the production of IL-10. Neutrophils also produce IL-10 in response to TLR and C-type lectin coactivation through MyD88 and SYK, respectively. Moreover, NK cells are also an important source of production of IL-10.[16] Figure 1 shows Monocytes and lymphocytes of certain group of cells in order to produce Interleukin 10. Figure 2 shows During infection CD 4 cells present in the surface are stimulated and results in the production of IL 10.

Major Action of IL-10

IL-10 is a cytokine with immune regulation and inflammation. IL-10 was originally described as an inhibitor of T helper cells. Its major action is it inhibits interferon production[7] while having pleiotropic effect in immune regulation and inflammation. It downregulates the expression of Th1 cytokines, MHC class 2 antigens and costimulatory molecules of macrophages. It also enhances B cell survival, and proliferation as well as antibody production. It can even block NF- KB activity and is involved in the regulation of the JAK-STAT signaling pathway which is responsible for interferon resistance.[12] Elevated levels of IL-10 can hinder host response to microbial pathogenesis and prevent resolution of associated tissue damage and hemodynamic disturbances. In contrast, deficient levels of IL-10 can lead to the development of autoimmune disease and enhanced tumorigenicity.[17]

Initially, IL-10 inhibits the release of pro-inflammatory mediators which includes TNF-α, IL-1β, IL-6, and IL-8 from monocytes/macrophages and inhibits the proliferation and the cytokine synthesis of activated CD4+ T cells. IL-10 also constrains antigen presentation of monocytes and macrophages by reducing the cell surface expression of major histocompatibility complex class II (MHC II), costimulating, and adhesion molecules.[17] In addition, it also enhances the production of anti-inflammatory mediators such as IL-1 receptor antagonist. It is also said to have important actions on B-cells by preventing apoptosis, enhancing proliferation and differentiation, increasing MHC II expression, and facilitating Ig class switching.

Polymorphism

The human IL-10 gene is located on chromosome 1 and encodes for five exons (5.1 kb). The IL-10 promoter is highly polymorphic with two informative microsatellites, IL-10.G and IL-10.R.[10]

IL-10 gene polymorphism has been studied to elucidate their role in chronic inflammatory disease.

Table 1 shows Interleukin polymorphism and the author of the article who first mentioned or identified it.

Role of IL-10 on Other Cells

IL-10 was previously known as cytokines synthesis inhibitory factor. IL-10 antagonizes the expression of MHC class 2 and costimulatory molecules B7. 1/B7.2 (CD80/CD86) as well as the pro-inflammatory

Table 1: IL polymorphism and the author of the article who first mentioned or identified it

First author, year, journal	Polymorphism
Kinane *et al*.[12]	IL-10 promoter region (IL-10 R and IL-10 G)
Gonzales *et al*.[13]	IL-10-824 and IL-10-597. This is not associated with the periodontal disease
Reichert *et al*.[16]	IL-10-1082 G>A, - 819 C>T - 590 C>T
Soapoli *et al*.	IL-10-819, - 592, - 1082
Brett *et al*.[17]	IL-10 - (627), IL-10 - (1082)
Erciyas *et al*.[18]	IL=10 (−819, −1082, −592)
Mellati *et al*.	IL-10-1082
Uh *et al*.	IL-10-592 C>A, - 819 C>T, - 1082 G>A
Jaradat *et al*.[19]	IL-10-1087 (G/A), IL-10-597 (C/A)

IL: Interleukin

Table 2: The association of polymorphism and autoimmune disease

Disease	Positive association reported number of studies (total affected studies)
SLE	6 (455 Cauc; 200 Af-Am; 230 Mex)
RA	1 (251 Cauc; 61 Af-Am)
MS	2 (463 Cauc)
Psoriasis	2 (352 Cauc)
AS	-
GBS	1 (87 Cauc)

SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, MS: Multiple sclerosis, AS: Ankylosing spondylitis, GBS: Guillain-Barre syndrome

cytokines IL-1 beta, IL-6, IL-8, TNF-α, and notably IL-12. It regulates antigen-specific Th-cell population. It also enhances B cells, granulocytes, mast cells, and keratinocytes growth/differentiation, as well as NK cell and CD8+ cytotoxic cell activation.[20] IL-10 has no impact on DN T-cell function or proliferation but greatly accelerates apoptosis.[15] IL-10 can exert immunosuppressive effects in the presence of bacterial product stimulated myeloid cells. Some IL-10 responses are on antigen presenting cells which result in decreased expression of MHC class 2 molecules accompanied by a decrease in antigen presenting cells and B7 costimulatory molecules on macrophages.[21] In B cells, IL-10 promotes B cells proliferation and plasma cell development, whereas In T cells, IL-10 stimulates a shift toward Th2. IL-10 in NK cells increase proliferative response to IL10 and increases the level of major histocompatibility.[22]

Roles of IL-10 on Autoimmune Disease

Autoimmunity can be defined as the breakdown of the mechanism responsible for self-tolerance and induction of an immune response against components of the self. Such an immune response not usually harmful.[23] IL 10 is a candidate gene in pathophysiologic mechanism of autoimmune disease.[24]

In numerous autoimmune diseases, it is well recognized that the products of the immune system cause damage to self. Autoimmune disorders are generally associated with a decrease in IL-10.[23] An increased level of IL-10 can result in a severe immune response.[25]

Some studies show that administration of IL-10 could result in improvement of the disease phenotype while other studies have shown that IL-10-deficient mice fail to develop an autoimmune syndrome. High serum levels of IL-10 have been documented in human autoimmune disease.[26] Production of high levels of IL-10 has also been demonstrated in synovial T-lymphocytes of rheumatoid arthritis patients, in the serum of systemic sclerosis, Kawasaki disease, and autoimmune lymphoproliferative syndrome (ALPS) patients, as well as in the cultured cells of polymyositis and dermatomyositis patients. High level of IL-10 mRNA is seen in the early stages of Grave's disease, Hashimoto's thyroiditis, Sjögren's syndrome, myasthenia gravis, psoriasis, and ALPS.[27] Whether through direct injection of IL-10 or IL-10 gene delivery methods, the use of recombinant IL-10 (rIL-10) supplementation in autoimmune and hypersensitive disorders has been beneficial for minimizing these disorders. IL-10 augmentation has been explored in many types of disorders: Transplant infectious disease, rheumatoid arthritis, inflammatory bowel disease, asthma models, and others.[22]

In systemic lupus erythematosus abnormalities production of autoantibodies by b lymphocytes is IL-10 dependent and there is a positive correlation between serum IL-10 levels with disease activity.[28,29]

Synovial fluid from patients with RA also contains detectable levels of anti-inflammatory cytokine IL-10.[30] RA patients showed significantly reduced IL-10 levels in serum in comparison to healthy donors; this suggests that in RA patients IL-10 synthesis is suppressed.[31]

In psoriasis patients, the level of expression of anti-inflammatory cytokines (IL-10) is low and insufficient to counterbalance pro-inflammatory effects.[32]

In allergic asthma, IL-10 was shown to be capable of inhibiting allergen-induced airway inflammation and non-specific responsiveness.

In intestinal bowel disease which is manifested as ulcerative colitis, elevated IL-10 has also been detected in the serum of some human UC patients.[14]

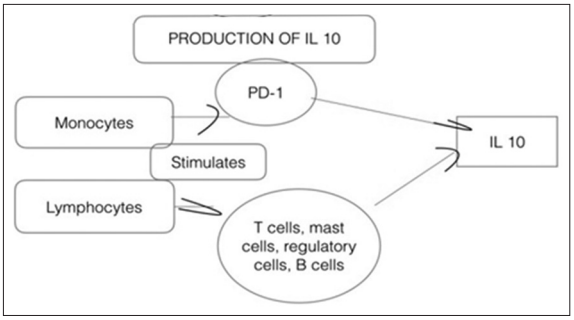

Figure 1: Monocytes and lymphocytes of certain group of cells to produce

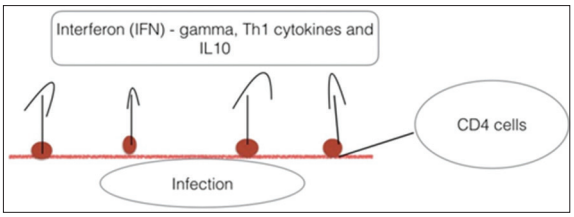

Figure 2: During infection CD 4 cells present in the surface are stimulated and results in the production

Table 2 shows the association of polymorphism and autoimmune disease.

Association of IL-10 polymorphism and autoimmune disease.

Periodontal Disease

Periodontitis is an inflammatory disease affecting periodontium. It is characterized by localized infections and inflammatory conditions where anaerobic Gram-negative bacteria are mainly involved and directly affect the teeth-supporting structure.[33]

This leads to the loss of alveolar bone and even usually to loss of tooth if left untreated researches shows that IL-10 has some role in periodontitis. Current views on periodontitis are that it affects severely a high-risk group representing around 15% population in whom the disease progresses from chronic gingivitis to chronic periodontitis.[34] Risk factors associated with periodontal disease is smoking, hormonal changes in girls/women, diabetes, diseases such as cancer or AIDS and medications that reduce the flow of saliva and genetic susceptibility.[35]

Role of Autoimmune Responses in Periodontal Disease

Many investigations had been done based on the role of autoimmune responses in periodontal disease. Majority of reports deal with the detection of antibodies to host components, in particular, collagen, although antibodies to DNA and aggregated IgG have also been reported.

In periodontal disease, there is a reduction in the T cell population of lymphocytes which leads to an increase in B cell components. In periodontal disease, there is so far no evidence for the existence of anti-idiotype antibodies. The antibodies to Ig detected in humans and experimental animal periodontal disease are directed to the Fc end of the molecule not the idiotype region. Studies says that microorganisms present in the periodontal pocket stimulates the production of antibody and also produces autoantibody to serum components or generated host periodontal tissues.[2] In aggressive periodontitis, self-antigens may be altered in the course of infection.

Diabetic patients are at a higher risk of developing periodontitis; however, the mechanism is not fully understood. An autoimmune component cannot be fully ruled out as per the timings of Mahamed *et al*. The study indicated that the autoimmune environment and CD4+ T cells display an unusual hyperactive response when mounting an antibacterial immune response to oral microbial assaults in experimental diabetic non-obese diabetic mice, which is similar to human type 1 diabetes.[24]

Role of IL-10 in Periodontal Disease

The –819 and –592 SNPs in the promoter of IL-10 gene and specific haplotypes have been shown to be associated with CP in Brazilian patients.[22] However, evidence from other data suggests that a significant difference is seen between diseased and control populations, demonstrating that IL-10 loci are unlikely to be involved as a genetic factor in generalized early-onset periodontitis suspect.[34] Periodontal inflammation may involve both an increase in inflammatory stimulators such as IL-1 and a decrease in inflammatory inhibitors like IL-10, and such a double impact may be the underlying factor in severe progressive changes inherent to periodontitis.[36] Studies suggest that IL-10 levels are higher in patients with gingivitis than whose condition progressed to periodontitis. This shows the protective role of the anti-inflammatory cytokine, IL-10 in limiting progression of gingivitis to periodontitis.[2] Some studies say that IL-10 seems to result in accelerating alveolar bone absorption and decreasing bone formation. As said above, some studies says that the specific genotypes (−819TT/−592AA) with low IL-10 expression may aggravate the inflammation response and cause the overgrowth of gingiva. IL-10 has been also regarded as an important regulator of bone homeostasis, in homeostatic and inflammatory conditions. A study says that IL10 inhibits osteoclast formation and promotes osteoblasts differentiation overall.[37]

CONCLUSION

IL-10 seems to have a major role in periodontal disease and due to the factor that IL-10 can inhibit osteoclast formation; it can be used to accelerate the

healing process of fracture. It also can be used as a treatment option for inflammation-related bone loss, such as periodontal diseases, periapical lesions, and inflammatory bowel disease.

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