REVIEW

Interleukins in Periodontal Health and Disease

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ABSTRACT:

Periodontal diseases, a series of infections of the periodontal tissues which eventually can lead to loss of teeth, are form of aberrant inflammation. The release of inflammatory mediators and cytokines as local host response to the periodontopathic bacteria appears to play crucial role in the pathogenesis of periodontal diseases Interleukins are a large group of immunomodulatory proteins that elicit a wide variety of responses in cells and tissues . Interleukins function in a paracrine or autocrine fashion, rather than as an endocrine signal, which is more common with steroidal and amino acid-derived hormones. Thus, the investigation of interleukins responses to periodontal diseases is at the forefront of the translational research agenda in oral science. This review summarizes interleukin expression in periodontal tissues and its importance in tissue homeostasis and, in particular, in the pathogenesis of periodontal diseases.

Key words: Interleukins, Periodontitis, cytokines, mediators, pathogenesis

INTRODUCTION

Periodontal diseases, a series of infections of the periodontal tissues which eventually can lead to loss of teeth, are form of aberrant inflammation.[1] The release of inflammatory mediators and cytokines as local host response to the periodontopathic bacteria appears to play crucial roles in the pathogenesis of periodontal diseases.[1] Many biological events are strictly regulated by cell-cell interactions, which may be either cognate (adhesive) interactions, achieved by membrane-bound cell-surface molecules; or cytokine-mediated interactions. Cytokines are small soluble proteins produced by a cell that alter the behavior or properties of another cell locally or systemically in an autocrine or paracrine manner. They are pleiotropic molecules and most of them are multifunctional. Cytokines are involved in extensive networks that involve synergistic as well as antagonistic interactions and exhibit both negative and positive regulatory effects on various target cells.[1]These play an important role in numerous biological activities including proliferation, development, differentiation, homoeostasis, regeneration, repair and inflammation.[2]

Thus, the investigation of interleukins responses to periodontal diseases is at the forefront of the translational research agenda in oral science. This review summarizes interleukin expression in

periodontal tissues and its importance in tissue homeostasis and, in particular, in the pathogenesis of periodontal diseases.

Interleukins are a large group of immunomodulatory proteins that elicit a wide variety of responses in cells and tissues. Interleukins initiate a response by binding to high-affinity receptors located on the surface of cells; Interleukins function in a paracrine or autocrine fashion, rather than as an endocrine signal, which is more common with steroidal and amino acid-derived hormones. The response of a particular cell to these cytokines depends on the ligands involved, specific receptors expressed on the cell surface and the particular signalling cascades that are activated. ILs modulate growth, differentiation and activation during an immune response. This distinguishes them from chemokines - the main function of which is to direct immune cells to the site of inflammation via chemotaxis - and interferons (IFNs), which predominantly mediate cellular response to viral infection.

The Nomenclature of Interleukins

The term interleukin derives from (inter-) "as a means of communication", and (-leukin) "deriving from the fact that many of these proteins are produced by leukocytes and act on leukocytes". The term interleukin was coined by Dr. Paetkau, University of Victoria. Being non-structural proteins, biological properties were and still are the gold standards for defining a cytokine. The interleukin nomenclature was invented to deal with the issue of multiple biological properties of cytokines. At the time of naming these molecules with an interleukin number, primary amino acid sequences of the active molecules were not known. But the nomenclature did nothing to resolve the broader issue of multiple biological properties ascribed to a single molecule.[3]

Classification of Cytokines

The local host response to the oral pathogens capable of causing periodontal disease includes the recruitment of leukocytes and the subsequent release of inflammatory mediators and cytokines, which appear to play crucial roles in the pathogenesis of periodontal diseases.[2, 4] Cytokines are generally classified by their ability promote or inhibit inflammatory responses.[5] The classification of cytokines is shown in. 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. Thus far, IL-la, IL- 113, IL-6, 1L-8, and TNI-7-7 are generally classified as inflammatory cytokines.[5]

INTERLEUKINS INVOLVED IN INFLAMMATION
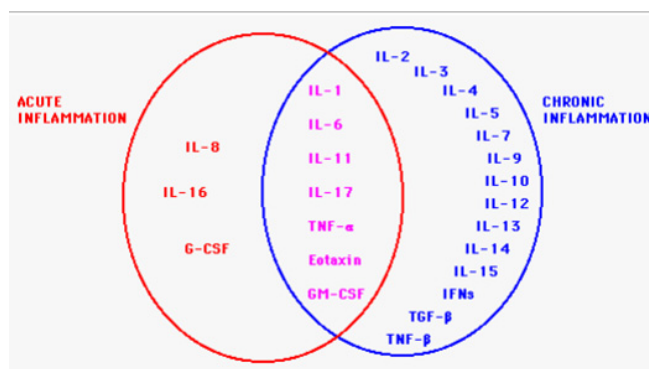
CYTOKINES V/S CHEMOKINES

The term chemokines, a short form of 'chemotactic cytokines', was coined in 1992. All the 50 or so human chemokines that were discovered over the years have chemo-tactic activity. They constitute a large family of mediators of inflammation and immunity with similarity to cytokines, but also some clear differences. Like cytokines the chemokines are secretory proteins produced by leucocytes and tissues cells either constitutively or after induction, and exert their effects locally in paracrine or autocrine fashion.

Interleukin Expression in Gingival and Periodontal Health

Tissue homeostasis represents a delicate balance between anabolic and catabolic activities. The regulations of migration, proliferation and differentiation of resident cells and of the production of tissue matrix in a healthy state are major aspects of periodontal tissue homeostasis. There is abundant evidence that myriad cytokines are involved in the maintenance of periodontal tissue turnover or integrity.[2]

Epithelium

The epithelium plays an active role in the pathogenesis of inflammation The gingival epithelium consists of keratinocytes, Langerhans

cells, T-cells, Merckel cells and melanocytes.[3] Keratinocytes, when challenged, with bacterial infection, express a large variety of cytokines and growth factors including interleukin-1 alpha (IL-1a), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-a) and platelet-derived growth factor(PDGF). However, it is unknown whether cytokines and growth factors expressed by gingival epithelium are released in amounts sufficient to regulate remodeling in connective tissues of the periodontium.[6]

Connective tissue (fibroblast)

The dominant cell types are fibroblasts in the gingiva and fibroblast-like cells (called periodontal ligament cells) in the periodontal ligament. These cells express a variety of membrane and intracellular receptors, making the cells sensitive to regulate by many physiological and pathological, paracrine and endocrine signaling molecules.[6] During inflammation, resident gingival fibroblasts are triggered by cytokines(released by macrophages) to enhance their synthesis of cytokines. IL-1 is the most potent regulator of extracellular matrix turnover by enhancing the expression of several matrix metalloproteinase. Interleukin-1 beta (IL-1b) and TNF-a stimulate the expression and release of interleukin-6 (IL-6), leukemia inhibitory factor and Interleukin-11 (IL-11) in human gingival fibroblasts.[8]

Interleukins play a major role in initiation and progression of inflammatory process. However, a variety of different interleukins are involved in acute inflammation. These are summarized in Table 2

Interleukins Involved in Chronic Inflammation

Chronic inflammation may develop following acute inflammation and may last for weeks or months, and in some instances for years.

The detailed description of interleukins involved in Chronic Inflammation is shown in Table 4.

EVIDENCE

A variety of studies have been conducted to elicit the function and structure of interleukins.These are summarized in Table 5.

Role of Interleukins in Pathogensis of Gingival Diseases

Gingival Enlargement[9]

Phenytoin drug is used for treatment of epilepsy.It reacts with phenotypically distinct subpopulation of gingival fibroblast and cause an increase in protein synthesis and cell proliferation rate. IL1 and 6 found in higher levels in gingival crevicular fluid in phenytoin induced gingival over growth. It is suggested that this interleukin play indirect role in complex mechanism of phenytoin induced gingival over growth.[9]

Role of Interleukins in Pathogenesis of Periodontal Diseases

IL- I is known to stimulate the proliferation of keratinocytes, fibroblasts, and endothelial cells in an autocrine or paracrine fashion, and to enhance fibroblast synthesis of type I procollagen, collagenase, hyaluronate, fibronectin, and prostaglandin E2. IL-I is, therefore, a critical component in the homeostasis of periodontal tissues.[6, 10] These mediators may be responsible for effecting connective tissue destruction, leading to loss of attachment. IL-1a, IL 1b, and TNF-a stimulate bone resorption and inhibit bone formation. It synergizes the bone-resorptive actions of TNF-alpha, induces the production of matrix metalloproteinase (MMPs), gives rise to an elevated level of procollagenase in both gingival fibroblasts and periodontal ligament (PDL) cells.[6] No significant change in tissue inhibitors of metalloproteinase (TIMP) synthesis and mRNA was observed after treatment of gingival fibroblasts and PDL cells with IL- I b. In addition, IL-1 stimulates plasminogen activator in gingival fibroblasts, resulting in the generation of plasmin which is a putative, naturally occurring, activator of several matrix metalloproteinase.
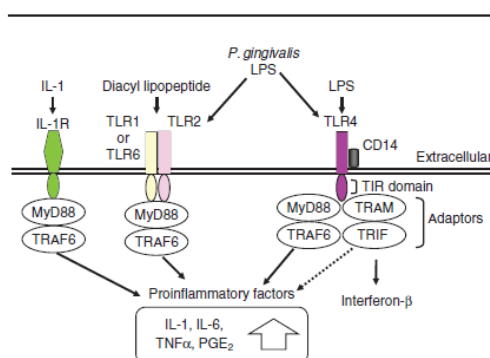

Figure 2: Immune responses induced by interleukin-1, diacyllipopeptide and lipopolysaccharide induce the production of proinfiammatory factors in the target cells.

Table1: Classification of Cytokines

Pro-inflammatory cytokines	Anti-inflammatory cytokines	Chemokines
IL-1 b, IL-2, IL-6, IL-8, IL-12, IL- 17, IFN-g TNF-a	IL-4, IL-5, IL-10, IL-13, TGF-b	IL-8, MCP-1, MIP-1beta

Table2: Interleukins Involved In Acute Inflammation

IL	Synonyms	Source	Includes	Genes Mapped to Chromosome	Structure	cDNA	Function
IL-1	endogenous pyrogen (EP), mononuclear cell factor, and lymphocyte activating factor (LAF)	Mainly. Monocytes, although other cells may contribute in disease states. Microbial products such as LPS or endotoxin, potently upregulate IL-l synthesis.	Group of nine or more proteins consisting of ILIaIL-Ib, IL, antagonist (IL-Ira), IL-18 (also called IL-Iy), and the recently cloned and undetermined IL18, Il1 E, ILI£ IL- IH4, ILT, and IL-IHI.	Long arm of chromosome 2,except IL-18.[28]		cDNAs for IL-la and b were cloned in 1984. They are encoded by two different genes, both located on human chromosome 2. Their size ranges from 22-31 kDa for cell-associated molecules, and 17.5 kDa for the secreted molecule	Critical for innate immunity involving responses to agents.[28] Both IL-1a and IL-lb can trigger fever by enhancing prostaglandin E2 (PGE2) synthesis by various endothelium of the hypothalamus and can stimulate T cell proliferation. IL-1 elicits the release of histamine from mast cells at the site of inflammation which triggers early vasodilatation and increase of vascular permeability.[1]
IL 6	IFN-b2, hybridoma/ plasmacytoma growth factor, hepatocyte-stimulating factor, B cell stimulatory factor 2 (BSF-2), and B cell differentiation factor (BCDF).	A variety of cells including mononuclear phagocytes, T cells and fibroblasts. Up-regulation of IL-6 production has been observed in a variety of chronic inflammatory and autoimmune disorders.[1]		Chromosome 7 in humans	Glycoprotein ranging from 21 to 28 (Da depending on the degree of post-translational modification.	cDNA was cloned in 1986	The stimulation of acute phase protein synthesis by the liver, IL-6 acts as a growth factor for mature B cells and induces their final maturation into antibody-producing plasma cells. It is involved in T - cell activation and differentiation, and participates in the induction of IL- 2 and IL-2 receptor expression. Some of the regulatory effects of IL-6 involve inhibition of TNF production, providing negative feedback for limiting the acute inflammatory response[1]
IL11		Bone marrow stromal cells and by some fibroblasts		Located on the long arm of chromosome 19	Molecular weight24 kDa	cDNA was cloned in 1990.	A functional homologue of IL6 and can replace IL-6 for the proliferation of certain plasmacytoma cell lines and in the induction of acute phase protein secretion in the liver. Stimulation of T cell-dependent B cell immunoglobulin secretion, increased platelet production, and induction of IL-6 expression by T cells.[1]

IL-8	Neutrophil chemotactic factor Neutrophil activating protein (NAP- 1) serves as a prototype for discussing the biologic properties of rapidly growing family of inflammatory mediators	Avariety of cells including monocytes, T lymphocytes, neutrophils, vascular endothelial cells, dermal fibroblasts, keratinocyte, hepatocytes, and human gastric cancer cells. The production is not constitutive but occurs ordinarily in the presence of inflammatory stimuli such as LPS, IL-1, and TNF.	belong to a chemotactic cytokine Family protein.	Chromosome 4 in humans	Consists of 72 amino acids in its mature form, is identified as a basic heparin-binding protein	cDNA was cloned by three different laboratories between 1987 and 1989	Responsible for the chemotactic migration and activation of neutrophils and other cell types (such as monocytes, lymphocytes, and eosinophils) at sites of inflammation. Its main inflammatory impact lies in its chemotactic effects on neutrophils and its ability to stimulate granulocyte activity. enhancing neutrophil adherence to endothelial cells and facilitating their diapedesis through vessel walls. [1]Thus, IL-8 mediates the recruitment and activation of neutrophils in inflamed tissue.[29]
IL-16 [1]	originally identified as a chemotactic factor known as lymphocyte chemoattractant factor or lymphotactin.	unusual cytokine-preformed IL-16 is stored in CD8+ lymphocyteand is secreted upon stimulation with histamine / serotonin.	The only member of the "C" family of chemokines.	human chromosome 1.			Induces chemotaxis of CD4+ T lymphocytes and is believed to initiate T-cell mediated inflammation in asthma.[1]
IL17		is a product of activated T lymphocytes				human IL-17 cDNA was cloned in 1995 based on homology with murine CTLA8 1.9 Kb cDNA was found to encode a protein of 17.5 kDa homologous to a product of Herpes virus saimiri (HVS13).	Stimulation of IL-6 and IL-8 production and enhanced ICAM1 expression on human foreskin fibroblasts.[1]

Table3.The cytokines known to mediate chronic inflammatory processes can be divided into [1]

Participating in humoral inflammation	Contributing to cellular inflammation
IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-13, and transforming growth factor-b (TGF-b)	as IL-1,IL-2,IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, interferons (IFNs), IFN-g inducing factor GF-b, and TNF-a and –b.

Table 4: Interleukin Involved In Chronic Inflammation

IL	Other Name	Source	Genes mapped to chromosome	Structure	cDNA	Function
IL2	Originally known as T cell growth factor (TCGF).	Mainly by activated T helper cells.	Long arm of chromosome 4.	15 kDa glycoprotein	The human IL-2 cDNA was cloned in 1983	Acts as a growth factor/activator for T cells, NK cells, and B cells and promotes the development of lymphokine-activated killer (LAK) cells. It therefore plays a critical role in regulating both cellular and humoral chronic inflammatory responses. Binding of IL-2 to the IL-2 receptor on T lymphocytes leads to cell proliferation, increased lymphokine secretion(IFNg,lymphotoxin,IL-4, IL-3, IL-5, GM-CSF), and enhanced expression of class II MHC molecules.[1]
IL3	multi-CSF	activated T cells and mast cells	localized to chromosome 5	The molecular weight of IL-3 ranges from 14 to 36 kDa	The cloning of the corresponding Cdna was reported in 1984	-Stimulates eosinophils and B cell differentiation -Inhibits lymphokine activated killer (LAK) cell activity. -IL-3 shares activities with GM-CSF,not only stimulates the effectors Ieucocytes, but can also regulate their localization to inflammatory sites by the acting on endothelium. -The ability of IL-3 to enhance MHC class II expression is not limited to monocytes, eosinophils and neutrophils but also encompasses endothelial cells. -stimulates secretion of the circulating cytokines IL-6 and G-CSF by the vascular endothelium suggests an alternative, indirect mechanism by which IL-3 could influence haemopoiesis in the bone marrow. [23]
IL4		CD4+ Thcells,mast cells, basophils.	Human chromosome5	Expressed as a 15-19 kDa protein and exists as a dimer	cDNA was cloned in 1986.	It induces CD4+ T cells to differentiate into TH2 cells while suppressing the development of Th1 cells. It also acts as a B cell, T cell, and mast cell growth factor, it enhances class II MHC expression on B cells, and it promotes immunoglobulin class switching to IgG 1 and IgE. In fact, IL-4 is necessary for IgE response induction, and its absence also leads to significantly lower levels of IgG1 in T cell-dependent immune responses. The stimulatory effect of IL-4 on IgG1 and IgE production and on MHC class II induction are down-regulated by IFN-g, a cytokine whose functions are antagonized by IL-4 and vice versa. IL-4 also stimulates collagen and IL-6 production by human dermal fibroblasts, and may thus play a role in the pathogenesis of fibrotic diseases such as systemic sclerosis.

IL5	as B cell growth factor II (BCGFII) and T cell replacing factor (TRF)	produced by CD4+ T helper cells well as NK cells	chromosome 5 in humans.	a protein of 20-22 kDa which has an apparent molecular weight of 45 kDa upon dimerization. Exists as a dimer linked by disulfide bonds.	is cloned in 1987	Involved in eosinophil differentiation and activation and stimulation of immunoglobulin class switching to IgA. It also includes increased activation of B cell proliferation and enhancement of T cell cytotoxicity. The combined production of IL-4 and IL-5 by CD4+ TH2 cells. Therefore, results in IgE and IgA production and mast cell and eosinophil stimulation.[1]
IL-7 [30]		IL-7, a cytokine purified as a pre-B cell growth factor, is a bone marrow and thymic stromal cell product	Human chromosome 8	25 kDa	cDNA was cloned in 1989.	It stimulates the development of pre-B and pre-T cells and acts as a growth factor for B cells, T cells, and early lymphocytes.
IL 9[31]	Was known as mast cell growth-enhancing activity (MEA) and murine T-cell growth factor P40	CD4 T helper (TH2) cells as well as some B lymphomas. Its production is IL-4 and IL-10, and thus IL-2-dependent	human chromosome 5		cDNA was cloned in 1989	Involved in early hematopoietic ontogeny, can influence pro inflammatory cytokines such as TNF, ILI , INF and also affect differentiation and functioning of both Th17 and Treg cells. IL9- mediated signaling responses have been dependent on the Janus kinase (JAK-1)-signal transducer and activator of transcription pathways. 15is regulatory in nature in that it inhibits lymphokine production by IFN-g-producing CD4+ T cells and enhances the growth of CD8+ T cells. In addition, IL-9 promotes the production of immunoglobulins by B cells and the proliferation of mast cells.
IL 10[1]	B cell-derived T cell growth factor Cytokine synthesis inhibitory factor (CSIF) because it inhibits IFN1-g production by activated T cells. IL-10 is considered a T cell cross-regulatory factor and has thus been referred to as an "anticytokine".	Produced by a variety of cell types, Including CD4+ T cells, activated CD8+ T cells, and activated B cells		18kDa protein	The cDNA for human IL-10 was cloned in 1990	-Reduction of antigen-specific T cell proliferation, Inhibition of IL-2-induced IFN-g production by NK cells, and inhibition of IL-4 and IFN-g induced MHC class II expression on monocytes. Since IL-10 can be produced by TH2 cells and inhibits TH1 function by preventing TH1 cytokine production (such as IFN-g IL-10 also acts as a co-differentiation factor for cytotoxic T cells and a co-factor for T cell growth. Human IL-10 (hIL-10) shares 84% identity at the amino acid level with a homolog, viral IL-10 (vIL-10), which is encoded by the Epstein-Barr virus. vIL- 10 shares will hiLe10 inhibitory effects on cytokine production and stimulatory effects on B cell growth.[1]

IL13	Originally identified as a protein produced by activated murine Th2 lymphocytes and referred to as P600 (K D. Brown 1989).		Human chromosome5, closely linked to the gene encoding IL-4	12-17 kDa protein	The cDNA for IL- 13 was recently cloned	IL-13 exhibits anti-inflammatory activities by inhibiting the production of inflammatory cytokines, such as IL-lb, TNF-a, IL- 8, and IL-6, by human peripheral blood monocytes induced with LPS. Inhibition of inflammatory cytokine production is also a characteristic of two other cytokines produced by TH2 lymphocytes, namely IL-4 and IL-10. In addition, IL-13 enhances monocyte and B lymphocyte differentiation and proliferation, increases CD23 expression, and induces IgG4 and IgE class switching.[1]
IL14[1]		A product of malignant B and T cells as well as normal T cells.		53 kDa growth factor (BCGF)		Induce B cell proliferation. However, IL-14 inhibits immunoglobulin secretion. It has been suggested to play an important role in the aggressive form of B-cell type non-Hodgkin's lymphoma.[1]
IL 12	Natural killer cell stimulatory factor (NKSF) and cytotoxic lymphocyte maturation factor (CLMF),	originally isolated from Epstein-Barr virus transformed B cells. secreted by activated B cells, macrophages, and other antigen presenting cells (APCs) but its production is inhibited by IL-4 and IL-10		It is a heterodimer composed of two subunits of 35 and 40 kDa.	cDNAs for both subunits were cloned in 1991	The biological activities include enhancement of cytotoxic T cells and lymphokine activated ' killer (LAK) cell generation and activation, increased natural killer (NK) cell cytotoxicity, induction of activated T cell and NK cell proliferation, induction of 1FN-g production by NK cells and T cells, and inhibition of IgE synthesis by IL-4-stimulated lymphocytes via IFN-g-dependent and independent mechanisms. In addition, the stimulatory effect of IL-12 on Th1 development is antagonized by IL-4, a cytokine which promotes Th2 cell development. Therefore, IL-12 plays an important role in cell-mediated inflammation and also contributes to the regulation of immunoglobulin production.[1]
IL15[1]	Originally discovered as a T cell stimulatory activity	produced by activated monocyte, epithelial cells, and fibroblasts	Chromosome4	Approximately 15 kDa IL-15 does not exhibit any sequence homology with IL-2		Shares many biologic properties with IL-2 and mediates its activity via a multi-subunit high affinity receptor comprised of a unique alpha chain and the beta and gamma chains of the IL-2R. It stimulates T lymphocyte and NK cell proliferation, as well as CTL and LAK activity. It enhances B cell expansion and immunoglobulin production . It is also a T lymphocyte chemoattractant. IL-15 may be responsible for the recruitment and activation of T lymphocytes in the synovium of patients with rheumatoid arthritis where its levels have been found to be elevated.

Table 5: Review of Literature

AUTHORS AND YEAR	STUDY	RESULTS
1. Carol A. Feghali et al 1997 [1]	Review	This review describes the role of cytokines those involved in acute inflammation and those responsible for chronic inflammation and also summarizes features of the cell-surface receptors that mediate the inflammatory effects of the described cytokines.
2. H. Okada and S.Murakami 1998[2].	Review	In this review, summarized the information regarding cytokine expression in the periodontium and its possible relationship with tissue homeostasis and inflammatory disease progression.
3. Bosshardt DD et al 2005[3]	Review	-
4. Yen-chung.Et al 2010[6]	Review	Its summary of the overall contributions and balance of cytokines during periodontal infection.
5. Bartold PM et al 2000[7]	Review	Describe the interleukins according to Molecular and cell biology of the gingiva.
6. J.A.bochla et al 2008[28]	Review	Interleukin 1 Signal Transduction in Periodontitis
7. Baggiolini et al 2008 [32]	Review	This review describe about Chemokines in pathology and medicine
8. Akihisa Harada et al 1998 [33]	Review	IL-8 plays a causative role in acute inflammation by recruiting and activating neutrophils
9. EijaIKorpelainen et al 2003 [23]	Review	IL-3 was found to regulate endothelial responses related to inflammation, immunity and haemopoiesis. These findings, summarized in this review, offer new insight into the physiological function of IL-3 and may also be of clinical importance , as IL-3 is used in bone marrow reconstitution following cancer therapy.
10. D.T. Grave,D.Cochrane[34]	Review	The contribution of IL-1 and TNF to periodontal destruction
11. JohnJ.Taylor 2010 [10]	Review	Cytokine regulation of immune responses to Porphyromonasgingivalis.
12. Masanori Koide et al 2010 [11]	Review	In this review, summarize the mechanism by which osteoblasts and bone marrow stromal cells regulate osteoclast differentiation and function, and the bacterial strategy for bone resorption in periodontitis and further describe possible therapeutic approaches that may be used to prevent alveolar bone loss in periodontitis.
13. K.V.Arun, Avaneendra Talwar, T.S.S.Kumar 2011 [35]	Review	This review focuses on the subsets, including the recently identified cells of the CD4 lineage, their activation pathways and effectors function in periodontal disease. The roles of Th 17 and regulatory T (Treg) Cells in disease pathogenesis have been explored. Newer Th subsets such as Th9 and Th22 cells and their potential role in periodontal disease have also been outlined.
14. Gemmell E, Yamazaki k, Seymour GJ. 2007 [36]	Review	This review focuses on the role of T cells in periodontal disease, homeostasis and autoimmunity.
15. Gemmell E, Yamazaki K, Seymour GJ 2002 [37]	Review	The roles of interleukin (IL)-1,prostaglandin (PGE 2) and metalloproteinases as the destructive mediators in periodontal disease were largely understood, the control and regulation of these cytokines remained controversial. Two apparently conflicting theories have emerged. One is based on direct observations of human lesions, while the other is based on animal model experiments and the inability to demonstrate IL 4 mrna in gingival extracts. As part of the "Controversy" series, this review is intended to stimulate debate and hence may appear in some places provocative.
16. Palmqvist P et al 2008 [8]	In vitro Cell culture	IL-b and TNF-a regulate IL-6 type cytokines in gingival fibroblasts.
17. R.G.Goodwin et al 1989 [30]	In vitro Cell culture	Human interleukin 7 regulate the molecular cloning and growth factor activity on human and murine B-lineage cells.
18. F.Q. Cunha et al 1999 [38]	In Vitro Cell culture	The effect of IL-4 on responses to intraplantar (i.pl.) Carrageenin ,bradykinin, tnfa, IL-1b, IL-8 and PGE2 was investigated in a model of mechanical hyperalgesia in rats . Also , the celluar source of the IL-4 was investigated. And data suggest that IL-4 released by mast cells limits in amatory hyperalgesia. During the early phase of the in ammatory response the mode of action of the IL 4 appears to be inhibition of the production tnfa, IL-1b and IL-8. In the later phase of the response, in addition to inhibiting the production of pro-in ammatory cytokines, IL 4 also may inhibit the release of pgs.
19. SudhaAgarwal et al 1985 [34]	In Vitro Cell culture	Functional Role of Interleukin 1 in Periodontal Disease; Induction of Interleukin 1 Production by Bacteroidesgingivalis Lipopolysaccharide in Peritoneal Macrophages from C3H/hen and C3H/hej Mice
20. Fujita T, Ashikaga A, et al 2008 [39]	In vitro	Irsogladine maleate counters the interleukin- 1b- induced suppression in gap-junctional intercellular communication but does not affect the interleukin-1b-induced zonulaoccludens protein-1 levels in human gingival epithelial cells.

21.	SudhaAgarwal 1998 [40]	In vitro	Induction of Interleukin 1 Production by Bacteroidesgingivalis Lipopolysaccharide in Peritoneal Macrophages from C3H/hen and C3H/hej Mice
22.	Hosokawa Y 2009 [41]	In vitro	Cytokines differentially regulate CXCL 10 production by interferon-c-stimulated or tumor necrosis factor-a stimulated human gingival fibroblasts.
23.	Steinberg T et al 2006 [42]	In vitro	Analysis of interleukin-1b-modulated mrna gene transcription in human gingival keratinocytes by epithelia –specific cdna microarrays.
24.	Sung Woo Lee et al 2002 [43]	In vitro	Anti-inflammatory effects of IL-4 and IL-10 on Human Polymorphonuclear Leukocytes.
25.	Rawlinson A, 2003 [44]	In vivo	Interleukin 1 and receptor antagonist levels in gingival crevicular fluid in heavy smokers versus non –smokers.
26.	Lester SR, 2009 [45]	In vivo	Relationship between the gingival sulcus depth and interleukin -1 insoform concentrations within the adjacent gingival tissue.
27.	Kaushik R et al 2011 [46]	In vivo	Interleukin-1 Beta Levels in Chronic Periodontitis Patients Before and After Periodontal Phase I Therapy and Healthy Controls-A Case- Control Study

Interleukin-1, diacyllipopeptide and lipopolysaccharide are recognized by interleukin-1 receptor (IL- 1 R), a complex of TLR2 and TLR6, and TLR4, respectively. CD14 is a membrane-anchored glycoprotein that aids the binding of lipopolysaccharide and TLR4. IL-1R and the TLRs possess a common TIR domain. Through their TIR domains, IL-1R and the TLRs activate MyD88 as a common signaling molecule. TRAF6 is a signaling molecule downstream of MyD88. Thus, interleukin-1 and diacyllipopeptide activate the MyD8S / TRAF6 pathway to induce biological responses. In contrast, TLR4 has two signaling pathways: the MyD88 / TRAF6 pathway and the TRAM / TRIF pathway. The TRAM / TRIF pathway plays an essential role in interferon-b production. In macrophages, both the MyD88/TRAF6 and TRAM TRIF pathways are required for lipopolysaccharide-induced biological actions such as interleukin-6 production. Lipopolysaccharide isolated from P. gingivalis was shown to use both TLR4 and a complex of TLR2 plus TLR1 or TLR6 to induce biological responses, PGE2, prostaglandin E2; IL, interleukin; LPS, lipopolysaccharide; MR. Toil-like receptor; TNFa, tumor necrosis factor a; TRAF6, TNF receptor associated factor 6 MyD88, myeloid differentiation factor 88; TIR domain, Toll I IL-1R domain; TRW, TIR domain-containing adaptor-inducing interferon-b; TRAM, TRIF-related adaptor molecule[11].

IL 12 is regarded as a pro-inflammatory cytokine with immunoregulatory function, it may be greatly involved in chronic periodontitis.IL-12 acts not only as an activator of macrophages in the inflamed tissue, increasing their phagocytic and bacteriocidal activity, but also increases the ability of macrophages to produce IL 12 in a powerful positive feedback loop . It acts as both as an inflammatory mediator and also initiate host immune response within the periodontal tissues.[6]It was also suggested that IL-6 may act as an autocrine and/or paracrine factor in bone resorption in pathologic states by stimulating the formation of osteoclasts and the activation of osteoclastic bone resorption.[11]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. [11]

Interleukins in Connective Tissue Destruction

An early event in pathogenesis of periodontal disease is dissolution of approximately 70% of gingival connective tissue. Collagen breakdown may occur by two pathways (intracellular and extracellular). ILI inhibit the intracellular pathway while stimulating extracellular route, induces the production of MMPs and elevated level of procollagenase in both gingival fibroblasts and periodontal ligament, stimulates the plasminogen activator in gingival fibroblast resulting in generation of plasmin which is naturally occurring activator for MMP .

Interleukins in Bone Destruction

Hausmann speculated that periodontal bone loss was multifactorial, "involving a series of interactions between agent in plaque and mediators in periodontal tissue.[12] Once "critical level of proinflammatory cytokine production is reached, a physiologic response become pathologic. If the

inflammation occurs predominantly in the cementum, it will result in loss of attachment.If occurs near alveolar bone, bone loss occurs. If the inflammatory front does not progress far from the epithelium, the resulting lesion restricted to gingivitis.

PMN's and monocyte of innate immune response produce ILI and TNF a that produces bone resorption. IL6 causes bone resorption in pathological state by stimulating the formation of osteoclast and activation of osteoclastic resorption. 1L8 is potent chemotatic for leukocyte and induces extravasation of neutrophils at the site of inflammation. These neutrophils contribute to local tissue destruction and bone resorption of periodontal tissue. 1L17 which shown to stimulate endothelial cell, fibroblastic cell to produce IL6, IL8 and PGE2 which are good activator for RANKL production by osteoblast and thus influence on osteoclastic bone resorption.

Interleukins in Chronic Periodontitis

Chronic periodontitis is an inflammatory response in the periodontal tissues. Chronic periodontitis in adults typically follows a cyclical course, with some forms remaining stable over many years and other forms progressing with subsequent tooth loss despite extensive treatment.[13] The initial immune response in chronic periodontitis occurs following colonization of the gingival sulcus by periodontopathic bacteria. The presence of the bacteria induces the production of cytokines and chemokines by the gingival epithelium. This results in the expression of adhesion molecules, increased permeability of gingival capillaries and chemotaxis of polymorphonuclear neutrophils through the junctional epithelium and into the gingival sulcus. The specific cytokines and chemokines produced by this initial response lead to a perivascular T-cell / macrophage dominated inflammatory infiltrate in the connective tissues. If this cell-mediated immune response does not control the bacterial challenge, progression to a B-cell /plasma-cell lesion occurs. The antibodies subsequently produced may be protective and control the infection, or may be non-protective with resultant connective tissue destruction and bone loss.[14] The early / stable lesion of chronic periodontitis is dominated by macrophages and T-cells, suggesting that Th1 cytokines are important in the development of this response, while the advanced/progressive lesion of chronic periodontitis, which is characterized by B-cells and plasma cells, is dependent upon Th2 cytokines.[15] Thl cytokines

include interleukin-2 and interferon-gamma and promote cell-mediated immunity, while the Th2 cytokine, interleukin-4, suppresses cell-mediated responses and enhances humoral immunity. A reduced Th l response has been shown in chronic periodontitis, where peripheral blood mononuclear cells obtained from patients with chronic periodontitis and then stimulated with mitogens , Porphyromonas gingivalis and Fusobacteriumnucleatum showed lower levels of Th1 cytokines(IL2,interferon gamma).Additionally, increased levels of Th2 cytokines (IL-4, IL-5, IL-6, IL-9, IL-10, and IL- 13) have been reported in GCF, gingival tissue [15] and peripheral blood of patients with chronic periodontitis. [16]

The role of interleukin-10 in human chronic infections is both complex and critical. It has been implicated in the pathogenesis of chronic periodontitis , is critical in controlling the balance between Thl cells and Th2 cells in chronic periodontitis, whereby an excess of interleukin-10 may shift the balance in favor of a Th2 response and progressive disease, whereas its shortage leads to increased interleukin-1 production and increased tissue destruction.[17] By contrast, high levels of IL 10 may even inhibit B-cell activation and proliferation, hence further illustrating its complex role. Low levels of IL-10 have been demonstrated in chronic periodontitis lesions compared with gingivitis, which may allow continued polyclonal B-cell activation to occur.[18]

Th17 cells are characterized by the production of interleukin-17. Th17 cell development depend upon the presence of interleukin-23 (a monocyte product) and also IL6 and TGF-b. Interleukin-17 expression is higher in chronic periodontitis tissues than in healthy tissues, along with IL-1b andTNF-a.[19] It induces the production of pro-MMP-1 and MMP-3 by gingival fibroblasts. In contrast, interleukin-17 receptor knockout mice showed increased P. gingivalis-induced periodontal bone loss, suggesting its possible protective role ingingivalis-induced tissue destruction.[20-22.]

IL- 1 levels were elevated in GCF at periodontitis sites and that marked reductions of total IL- 1 levels were observed following effective treatment. They also commented that IL-b was detected more frequently than IL-lex in GCF from untreated patients with periodontitis.[21]

Interleukins in Refractory Periodontitis

Reinhardt and colleagues (1993) reported that

elevated levels of IL1a, IL-13, and IL-6 were detected in the GCF of patients with refractory periodontitis. A possible correlation among bleeding index, probing depth, and the IL-6 levels of the crevicular fluid has also been demonstrated. [21]

Interleukins in Aggressive Periodontitis

B-cell/plasma-cell nature of the aggressive periodontitis lesion makes it likely obe Th2-mediated lesion. It has been shown that Th17 cells can be converted to Thl cells or Th2 cells under the influence of interleukin-12 or interleukm-4 respectively, while CD4+, CD25+,forkhead box P3 (Foxp3+) regulatory T-cells can be converted to an interleukin-17-producing cell when co-cultured with dendritic cells selectively activated via dectin-1. These latter findings highlight the complex regulatory networks that are probably operating in both chronic and aggressive peniodontitis.[23]

IL-8 is a chemoattractant for neutrophils expressing the receptor CXCR [1]. Enhanced accumulation of neutrophils in the pocket epithelium and adjacent connective tissue of patients with chronic periodontitis and with generalized aggressive periodontitis (GAP)s was associated with the upregulation of IL8, intercellular adhesion molecule-1, IL-1b and TNF—a expression, which related to the severity and activity of generalized aggressive periodontitis.[24] Anne Havemose-Poulsen in 2005 compared Cytokine Profiles in Peripheral Blood and Whole Blood Cell Cultures Associated With Aggressive Periodontitis, Juvenile idiopathic Arthritis, and Rheumatoid Arthritis, found that two anti-inflammatory cytokines,IL10 and IL1Ra were significantly elevated in GAP patients and patients with aggressive periodontitis and type of arthritis presented with similar components of blood cytokine profiles distinguishing them from individuals free of disease. Interestingly, it has recently been shown that infection of human macrophages with A. actinomycetemcomitans (Aa), a bacterium associated with certain forms of aggressive periodontitis, results in the profound release of activeIL-1b, an effect considerably larger than that induced by LPSand not associated with enhanced secretion of interleukin-6 or TNF. The effect is mainly dependent on the leukotoxin from A. actinomycetemcomitans

Interleukin Polymorphisms and Periodontitis

The systemic immune response, genetic and environmental factors also affect the risk of developing periodontitis. In recent years, studies have demonstrated that periodontitis is associated with elevated levels of a variety of inflammatory biomarkers. Furthermore, genetic variants of some cytokines confer susceptibility to periodontitis.[3] As it is accepted that the immune system plays an important role in the pathogenesis of periodontitis, most genes that are considered to be responsible for the development of periodontitis are also linked to the immune response. These include the genes that affect the expression of IL1, IL-6, TNF-a, and IL-10, E-selectins, Fc-gamma receptor, CD 14, toll-like receptors, caspase recruitment domain 15 and vitamin D receptor.1 Polymorphisms arises as result of insertion and deletion in nucleotide sequence. Genotype polymorphisms have also been associated with disease diagnosis, severity and presence of sub-gingival bacteria. IL8 and IL6 investigated for the relationship between periodontopathic bacteria (Aa &Pg) and bleeding on probing which shows that association is found in both aggressive and severe form of chronic periodontitis.

IL-1 Gene Polymorphism

IL-1 gene cluster is located on chromosome 2. The first study that reported polymorphism for IL-1 gene in relation to periodontitis was presented by Korman et al, in Caucasians. He concluded that IL-1 composite genotype could be considered a putative severity factor for periodontitis in Caucasians. Sensitivity and specificity of IL-1 "Genotype positive" model was depicted by Kornman et al, 1997. [1] Anne Havemose - Poulsen et al. demonstrate that in localized aggressive periodontitis patients, allele 2 of IL - 1 RN VNTR(variable no. of tandem repeats) was associated with significantly higher levels of IL -1a, 6, 10 and TNF - a, whereas allele 2 of IL - 1p +3954 was associated with significantly lower levels of the same cytokine.

IL-4 Gene Polymorphism

IL -4- polymorphism was at the promoter sequence-590 C/T, -33C/T and intron 3. VNTR of IL4 acted in a cooperative fashion andresulted in high production of IL 4. In 2008, Stefan Reichert et al studied the expression or IL-12 R p2 molecule in a crucial regulatory factor in the T helper type differentiation of T cells. They found that single nucleotide polymorphism of the flanking region of IL -12RB2 leads to a very weak cellular immune response. They reported that the frequencies of variant alleles of IL 12 RB2 were significantly higher in aggressive periodontitis patients.

IL-6 Gene Polymorphisms

Shao et al 2009, in the meta-analysis indicate that the IL-6 ,-174 G allele could not modify the risk of chronic periodontitis, but increased risk of aggressive periodontitis. And -572 C/G polymorphism is associated with the pathogenesis of periodontitis, as it predisposes to either chronic or aggressive periodontitis.

IL-10 Gene Polymorphisms

IL-10 gene is located on chromosome 1, in a cluster with closely related IL-genes IL-19, - 24. IL-10 has an inhibitory effect on IL-1a, IL-1b,TNF-a, IL-6,8 and 12. Functional disturbances in IL-10 due to genetic polymorphisms could be detrimental to host tissue and linked to periodontal disease susceptibility.

Implant Failure And Interleukin Polymorphism

Regarding the timing of implant failure, it can be classified as early when osseointegration fails to occur, or late when the achieved osseointegration is lost after a period of function. Infection, overheating and impaired healing are the main factors associated with early failure of dental implants. Of these, surgical trauma, a consequence of implant insertion, initiates a local inflammatory response that includes the release and activation of a variety of cytokines and growth factors. This local factor production determines the quality of bone formation or the formation of fibrosis. Increased levels of bone resorptive interleukins, such as IL-1, might stimulate an excessive inflammatory response, affecting osseointegration success.

A few studies have analyzed the relationship between interleukin-1 genepolymorphisms and implant failure. Wilson & Nunn (1999) were the first to study the relationship between implant loss and the interleukin-1 composite genotype reported by Kornmanet at (1997) [allele Tat interleukin- IA (889) and at interleukin-1B [p3953) loci]. Their analysis failed to provide a positive correlation, but these results might have been influenced by variables, such smoking and the existence of late and early failure implants in the same sample. Rogers et al. (2002) also found no association between the same. Campos et al 2004 also showed that polymorphism in the interleukin-1 RN (intron 2), interleukin- 1B (511, p3953) and interleukin-1A (889) genes were not associated with early implant failure in a non-smoking Brazilian population.

Interleukins as Diagnostic Marker

The biochemical assessment of periodontal disease can be accomplished using several approaches. The most practical and least-invasive,involves analysis of biologic fluids that are derived from the periodontal tissues or contain specific mediators that are present as a result of periodontal disease. The biologic fluids that have been studied to understand the nature of destructive periodontitis and to identify potential diagnostic markers of active disease include serum (blood), gingival fluid, and saliva.

Blood

Studies of serum antibody levels to periodontal bacteria were among earliest investigations demonstrating that a humoral immune response occurs in patients with periodontitis. More recent studies have demonstrated that patients with periodontitis have elevated antibody titers to subgingival pathogens. The levels of inflammatory cytokines (ie, IL-6) and general markersof inflammation (ie, C-reactive protein) have been shown to be elevated in the blood of patients with periodontitis. Nevertheless, serum markers of periodontitits, or of inflammation, are not currently used as diagnostic tests for periodontitis.[25]

Gingival Crevicular Fluid

GCF is a serum transudate, or more commonly inflammatory exudates, that emanates from the gingival crevice and can be collected from the crevice orifice. GCF has been analysed for diagnostic purposes. Its constituents are derived from a variety of sources including host as well as from microorganisms in the subgingival and supragingival plaque. The collection and analysis of GCF samples provides a non-invasive means to assess the pathophysiological status of the periodontium in a site-specific manner. According to Armitage (2004), more than 65 GCF constituents have been evaluated as potential diagnostic markers of periodontal disease progression. These markers can be divided into three groups: host-derived enzymes and their inhibitors, inflammatory mediators and host-response modifiers, and byproducts of tissue breakdown. The inflammatory cytokines in particular IL-1b, may play an integral role in the etiology of periodontal disease. Lieu et al (1996) demonstrated that with an increase in gingival index and probing, there was a corresponding increase in IL-1b in both the gingival tissue and GCF. Engebretson et al through a longitudinal study suggested that GCF IL-1b expression is genetically influenced and not solely a result of local clinical parameters. Also, a GCF

level of 1L8 was found to be higher in periodontal diseases and was influenced by local IL1 beta activities .[26]

Interleukins as Anti-Inflammatory and Antiresorptive Therapy

As inflammatory cytokines are involved in inflammatory diseases associated with bone loss and have therefore become logical targets for the development of therapeutic agents. One of the first cytokines to be targeted was IL-1 as a result of its key regulatory role in bone resorption in diseases such as rheumatoid arthritis and periodontitis. In addition, agents targeting IL-3,6,15,12 and 23 have been studied. These anti-cytokine agents provide new opportunities to modulate host responses in inflammatory diseases. In particular, most seem to influence the secondary effects of cytokines on RANKL expression and therefore may not influence osteoclast-mediated bone resorption directly. Future efforts in this area, to ensure more effective control of pathologic bone resorption should try to target those cytokines that directly influence osteoclast formation and function. Surprisingly few studies have investigated the effect of interleukin antagonists on periodontitis. One study investigating inflammation and tissue loss in a nonhuman primate model of periodontitis using human soluble interleukin-1 receptor type 1 as an inhibitor of IL-1 reported that the inhibition of IL-1 has a significant effect on the reduction of inflammation, connective tissue attachment loss and bone resorption .Given the emerging use of these agents as anti-inflammatory and anti-resorptive agents, further investigations in experimental models of periodontitis are arranted.[27]

CONCLUSION

Interleukins are key modulators of inflammation. They participate in acute and chronic inflammation in a complex network of interactions. Several cytokines exhibit some redundancy in function and share overlapping properties and structure.Theseplay an important role in a number of different physiologic processes, but if expressed inappropriately, they also induce pathology. Under pathologic conditions such as those that occur in periodontal disease, the balance between pro- and anti-inflammation is directed towards proinflammatory activity .In periodontal tissue destruction three proinflammatory cytokines, IL-1, IL-6, and TNF-a, appear to have a central role.

Better understanding of the pathways regulated by interleukins will allow the identification and/or development of agents for improved modulation of the inflammatory response for the treatment of periodontitis autoimmune, infectious, and neoplastic diseases.

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