ROLE OF INTERLEUKINS IN THE ETIOPATHOGENESIS OF PERIODONTAL DISEASES

Dr. Rupali Mahajan, Dr. Kanupriya Sharma, Dr. Swati Bhalla, Dr. Rohan Vashisht, Dr. Neha Kalia

Abstract:

Periodontitis is an infectious disease that results in the destruction of the structures that support the teeth, namely, alveolar bone and connective tissue attachment to teeth. It is initiated by pathogenic bacteria, which trigger an inflammatory response that is effective in preventing significant microbial colonization of the gingival tissues. In some individuals, the reaction to bacteria may lead to an excessive host response, resulting in periodontal tissue destruction.

Cytokines play an important role in the pathology associated with chronic inflammatory diseases. The cytokines which are molecularly and chemically well defined are called interleukin and different interleukins play a significant role in the pathogenesis of periodontitis. In this review article the specific roles of different interleukins are hereby explained.

Keywords

Cytokines, Interleukins, Periodontal Disease, Inflammatory disease

Correspondence:

Dr. Rupali Mahajan
Senior Lecturer
Department of Periodontology
National Dental College & Hospital
Dera Bassi, Mohali, Punjab
Email: rupali123mahajan@gmail.com
INTRODUCTION:
Cytokines are special type of messenger molecules that take message from one area to another and modulate their function in inflammation and immunological function.¹

These are low-molecular weight proteins involved in the initiation and effector stages of immunity and inflammation, in which they regulate the amplitude and duration of the response. In other words, Cytokines are cell regulators that have a major influence on the production and activation of different effector cells,³ since they appear at various stages of inflammation, hence act as biomarkers.

A) Cells producing cytokines:
1) Leukocytes
2) Endothelial cells

 Included in the group of cytokines are interleukins, interferons, growth factors, and colony stimulating factors, various activating and inhibitory factors. These cytokines play an important role in numerous biological activities including proliferation, development, differentiation, homeostasis, regeneration, repair and inflammation.⁵

B) Nature of Cytokines(Figure 1)⁶:
1. Autocrine
2. Paracrine
3. Endocrine

Interleukins: The cytokines which are molecularly and chemically well defined are called interleukin.⁷

Lymphokines: Cytokines produced by lymphocytes.
Monokines: Cytokines produced by monocyte and macrophage system.

C) PROPERTIES OF CYTOKINES:
1. Pleotropic: Act on more than one cell type. eg.: IL-4
2. Redundancy: More than one cytokine can do the same thing. eg: IL-2, IL-4, IL-5
3. Synergy: Two or more cytokines cooperate to produce an effect that different or greater than the combined effect of the two cytokines when functioning separately. eg: IL-4, IL-5 induces class switch to IgE.
4. Antagonist: Two or more cytokines work against each other. Eg: IFN-Y blocks class switch to IgE induced by IL-4.⁸
D) 1) Classification by Jan Lindhe:  

**Proinflammatory cytokines:** E.g IL-1, IL-6, and TNF

**Chemotactic cytokines:** E.g IL-8

**Lymphocytes signaling cytokines:** E.g Cytokines released by TH1: IL-2, IFN.

Cytokines released by TH2: IL-4, IL-5, IL-10 and IL-13.

2) Classification based on inflammatory action:

**Chemotactic:** IL-8, MIP-1, MCP-1, RANTES  
**Pro-inflammatory:** IL-1α, IL-1β, TNF-α, IL-6  
**Anti-inflammatory:** IL-1Ra, IL-4, IL-10  
**Growth factor:** PDGF, EGF, FGF, IGF, VEGF  
**Immunoregulatory:** IFN-γ, IL-2, 4, 5, 7

E) i) **INTERLEUKIN-1:**  
It is a proinflammatory cytokine that has a large array of biological activities and directly regulates several genes expressed during inflammation.  
**Source:**  
- Macrophages, monocytes, lymphocytes, osteoblast and fibroblast.

Some of the structural features and biological activities of IL-1 relevant to periodontal disease include the following:

1. **Modifies endothelial lining:** IL1/TNF act over the endothelial lining of the blood vessel and cause contraction and retraction of the endothelial cells, thus increasing interendothelial gaps. Lymphocytes come out as inflammatory infiltrate.

2. **Express selectins, integrins and other adhesion molecules on fibroblasts, endothelial cells and immunocytes - lymphocytes, neutrophils, and monocytes.** These adhesion molecules permit immunoocytes to attach to and then migrate through the endothelial wall of the vasculature to enable chemotaxis to the site of infectious challenge. It also creates homing receptors for lymphocytes and monocytes to enable these cells to attach directly to connective tissue cells and thereby become a resident cell as part of an inflammatory.

3. **Stimulating endothelial cells and macrophage** to produce chemokines that contributes to the diapedesis, chemotaxis and the recruitment of leukocytes [Figure 2].

   IL1/TNF act over the endothelial cell, send signals to the cytoplasm of endothelial cell then to nucleus to synthesize new proteins.

   The new protein formed is IL-8 which is also a chemokine.

**Figure 2: Production of IL-8 from IL-1 acting over endothelial cell**

4. **Act** on liver to produce C-reactive proteins which acts as a biomarker during inflammation. Other proteins released are fibrinogen, haptoglobin, alpha-1 antitrypsin and ceruloplasmin.

5. **In the bone marrow** it increases levels of preformed neutrophils: so that more number of leukocyte arrive at the site of inflammation.
6. **IL-1/TNF** act as pyrogens and stimulate the hypothalamus to produce fever and this is the reason fever occurs in inflammation.

7. **IL-1α and IL-1β** are potent stimulators of connective tissue catabolism. These molecules stimulate bone resorption directly and trigger the release of large amounts of PGE2 from fibroblasts and monocytes. PGE2, in turn, is a moderately potent stimulator of vasodilation, edema and bone resorption.

IL-1 also stimulates the secretion of matrix metalloproteinases (MMPs), which serve to degrade the extracellular matrix.

8. **IL-1** activates immunocytes, IL-1 upregulates the expression of MHC proteins to facilitate antigen presentation and activation of T and B-cells. It promotes B-cell activation, proliferation, clonal expansion, and antibody secretion.

It serves to "prime" phagocytic monocytes and neutrophils by up-regulating receptors for complement and immunoglobulin.

9. **IL-1** is **autostimulatory** in that it triggers the release of IL-1 from many other cells to amplify the IL-1 signal. The activity of IL-1 is suppressed and controlled by the release of a specific inhibitor protein which serves as an IL-1 receptor antagonist (IL-ra), it binds and occupies the IL-1 receptor, but does not activate the cell. IL-1ra synthesis can be triggered by steroids and anti-inflammatory cytokines, such as IL-4 and IL-10.

10. **Bacterial immunosuppressive** factors, such as that produced by Prevotella intermedia and short chain fatty acids such as butyric and propionic acid inhibit IL-1 production and there by inhibit lymphocytic proliferation. Other bacterial factors, such as the A. actinomycetemcomitans capsular polysaccharide, trigger IL-1 release (as well as PGE2) and thereby elicit osteoclast formation and bone resorption in organ culture.

11. **Stimulate** the T-helper cell to produce IL-2 which further causes proliferation of T-helper cells for both humoral and cell mediated immunity.

**12. Stimulates** epithelial cells to proliferate and produce collagen: With regard to homeostasis of Periodontal tissue, stimulation of the proliferation of keratinocytes, fibroblasts and endothelial cells is important. Furthermore, interleukin-1 enhances fibroblast synthesis of type I procollagen, collagenase, hyaluronic acid, fibronectin and prostaglandin E.

**ii) Interleukin – 2 (Figure 3)**

IL-2 is an autocrine and paracrine growth factor secreted by activated T lymphocytes and is essential for clonal T-cell proliferation.

**iii) Interleukin-3 (Previously known as multispecific hemopoietin)**

**Figure 3: Action of IL-2**

**Sources:** IL-3 is made primarily by T-lymphocytes.

**Functions:**
- IL-3 supports the growth of multilineage bone marrow stem cells.
- Interleukin-3 stimulates the growth precursors of all the hemopoietic lineages (red cells, granulocytes, macrophages and probably lymphocytes).
A minor population of T cells (CD4 CD8, with the cx43 TCR) also grows in response to IL-3.

**iv) Interleukin-4 (Previously known as B cell activating or differentiating factor-1**

**Sources:**
- IL-4 is produced mainly by TH2 cells and mast cells
Functions [Figure 4]:
- IL-4 acts on B cells to induce activation and differentiation, leading in particular to the production of IgG1 and IgE.
- It also acts on T cells as a growth and activation factor and promotes TH2 cell differentiation.
- On macrophages, it induces MHC class II expression.
- IL-4 is a major stimulus for production of IgE and the development of TH2 cells for defense against helminths and arthropods. It also antagonizes the effects of IF-γ and thus inhibits cell-mediated immunity.
- It inhibits production of pro-inflammatory cytokines such as IL-1 and TNF-α.
- Excess IL-4 plays a part in allergic disease, causing high IgE production.14

V) Interleukin-5 (also referred to as 'Eosinophil differentiation factor' - EDF)
Source:
IL-5 is produced mainly by TH2 cells.
Functions [Figure 5]:
- IL-5 is a growth and activating factor for eosinophils as a defense against helminths and arthropods.
- It also stimulates the proliferation and differentiation of antigen-activated B-lymphocytes and the production of IgA.
- It is responsible for eosinophilia of parasitic diseases.15

Interleukin-616
Sources:
The main sources of in vivo IL-6 are stimulated monocytes, fibroblasts, and endothelial cells, macrophages, T & B-cells and keratinocytes. IL-6 release can be elicited by lipopolysaccharides, IL-1, TNF-α, progesterone and estrogen can diminish its synthesis.
Functions:
- It acts on most cells, but is particularly important in inducing B cell to differentiate into antibody-forming cells (AFCs). One of the major functions of IL-6 is the induction of the final maturation of B-cells into immunoglobulin-secreting plasma cells. It stimulates the secretion of antibodies to such a degree that serum IgG1 levels can rise 120-400-fold.
- Stimulates the proliferation of B-lymphocytes
- Increases neutrophil production.
- In the liver it stimulates the production of acute phase proteins.


- IL-6 is considered to be an important growth factor for multiple myeloma malignancy of plasma cells.

The interleukin-6 molecule, in contrast to most cytokines, contains a signal domain which makes the cells release interleukin-6 in large amounts, and interleukin-6 can act as an endocrine cytokine stimulating acute-phase response proteins in the liver and in the thermoregulatory center in the hypothalamus.

Interleukin-7 (initially described as a pre-B-cell growth factor)\[17\]

Interleukin-7 was initially thought to be made by bone marrow stroma. IL-7 made by thymic stroma and acts on thymocytes.

**Sources:**
- IL-7 is also produced by fibroblasts and bone marrow stromal cells.

**Functions:**
- It is a T-cell growth and activation factor.
- It is a macrophage activation factor.
- IL-7 plays a role in the survival and proliferation of immature B-lymphocytes and T-lymphocyte precursors.

Interleukin-8\[18\]. The potential role of IL-8 in periodontal diseases has been reviewed by Bickel. IL-8 is a member of the chemokine family which is a series of structurally related, small molecular weight peptides which have 4 cysteine residues linked by disulfide bridges.

**Sources:**
- They are produced by most cells of the body, especially macrophages and endothelial cells, and are involved in inflammation and cell migration.

**Functions:**
- IL-8 in particular is a powerful inducer of neutrophil chemotaxis.
- The related RANTES induces chemotaxis of memory T cells and monocytes.

Interleukin-9\[17\]

**Sources:**
- Interleukin-9 is secreted by some cultured T-cells and has a growth promoting effects on several hemopoietic cell types.

**Functions:**
- In conjunction with IL-2, IL-3, IL-4 and erythropoietin, it may enhance hemopoiesis in vivo.
- It may facilitate bone marrow derived mast cell growth stimulated by IL-3 and fetal thymocyte growth in response to IL-2.
Interleukin-10 (also known as cytokine synthesis inhibitory factor)\textsuperscript{17}

IL-10 is an inhibitor of activated macrophages and dendritic cells and as such, regulates innate immunity and cell-mediated immunity. IL-10 inhibits their production of IL-12, co-stimulator molecules, and MHC-II molecules, all of which are needed for cell-mediated immunity [Figure 7].

Sources:
IL-10 is produced mainly by macrophages and T\(_{H2}\) cells.

Functions of IL-10:
- IL-10 strongly inhibits the production of IL-1α, IL-1β, IL-6, IL-8, IL-10 itself, IL-12, GM-CSF, G-CSF, M-CSF, TNF-α, IFN-γ
- It inhibits antigen presentation and macrophage production of IL-1, IL-6 and TNF-α
- It is important in B-cell activation

![Figure 7: Action of IL-10](image)

Interleukin-11

Sources:
Interleukin-11 is derived from bone marrow.

Functions:
- It induces IL-6 dependent murine plasmacytoma cells to proliferate.
- It may be important in the formation of platelets.\textsuperscript{17}

Interleukin-12(Figure 8)

Interleukin-12 acts in contrasting way to IL-1β, in that it favors T\(_{H1}\) type response with macrophage and NK cells activation and induces IFN production.

Sources:
It is produced mainly by macrophages and dendritic cells.

Functions:
- It is also an inducer of cell-mediated immunity.
- Increases the killing activity of CTLs and NK cells
- IL-12 is a primary mediator of early innate immune responses to intracellular microbes.\textsuperscript{12}
Interleukin-13
Interleukin-13 has structural and functional similarities to IL-4. It is an important mediator of allergic inflammation and disease. It is encoded by the IL13 gene.

Sources:
IL-13 is cytokine secreted by many cell types, but especially T helper type 2 (Th2) cells.

Functions:
- IL-13 increases the production of IgE by B-lymphocytes, inhibits macrophages, and increases mucus production.
- It promotes B-cell division.
- It is a potent modulator of human monocyte and B-cell function.
- It acts as a co-stimulatory signal for human B cells.
- IL-13 specifically induces physiological changes in parasitized organs that are required to expel the offending organisms or their products. For example, expulsion from the gut of a variety of mouse helminths requires IL-13 secreted by Th2 cells.18

Interleukin-14 (previously known as High-molecular weight B cell growth factor)
Functions:
- It predominantly acts to enhance the proliferation of B-cells and to induce memory B-cell production and maintenance.
- Inhibits immunoglobulin secretion.12

Interleukin-15
It shares many biological properties of IL-2

Sources:
IL-15 is produced by various cells including macrophages.

Functions:
- IL-15 stimulates NK cell proliferation and proliferation of T-lymphocytes.
- Interleukin-15 is a T-cell growth factor.12

Interleukin-16 (previously called lymphocyte chemoattractant factor-LCF)
It recruits and activates many other cells expressing the CD4 molecule, including monocytes, eosinophils, and dendritic cells.

Sources:
Variety of cells (including lymphocytes and some epithelial cells).

Functions:
- Interleukin-16 is also known as ‘Lymphocyte chemo attractant’.
- It induces IL-2 receptor expression by T-lymphocytes.
- Chemoattractant for certain immune cells expressing the cell surface molecule CD4.12
Interleukin-17
Interleukin-17 (IL-17) is a proinflammatory cytokine derived from T cells.

Sources:
Produced mainly by cells of the Th1/Th0 phenotype (CD4+ T cells) but not cells of the Th2 phenotype. Recent findings have defined IL-17-producing cells as a new Th cell lineage; renamed Th17. Th17 cells are highly proinflammatory and can mediate autoimmune diseases.

Induction:
It is proposed that induction of Th17 responses requires three distinct steps: induction, amplification and stabilization, whereby TGF-β plus IL-6 induce differentiation of Th17 cells, IL-21 amplifies the frequency of Th17 cells, and IL-23 stabilizes the phenotype of previously differentiated Th17 cells.

Loss of any of one of the members in this pathway (IL-21 or IL-23) severely limits the Th17 response. IL-17 has been shown to stimulate epithelial, endothelial and fibroblastic cells to produce IL-6, IL-8, and PGE₂. In addition, IL-17 induces receptor activator of nuclear factor kappa B ligand (RANKL) production by osteoblasts.

Functions:
- Interleukin-17 may be an initiator of T-cell-dependent inflammatory reactions and part of the cytokine network linking the immune system to hematopoiesis.
- Enhances cytokine secretion.
- Members of the IL-17 and -17R families are unique in amino acid sequence, with little homology to other cytokine classes. Thus, few predictions about their function could be made simply on the basis of sequence similarities with other molecules.¹⁹

Interleukin-27
Interleukin-27 is a novel member of the interleukin-6 / interleukin-12 family of cytokines, which consist of a heterodimer of interleukin-12 p40-related protein and interleukin-12 p35-related protein p28. Interleukin-27 has many effects on immune and nonimmune cells, including the differentiation of T helper cells.

When osteoclast formation was induced by macrophage colony-stimulating factor / RANKL, co-treatment with interleukin-27 resulted in partial inhibition of osteoclastogenesis. The importance of interleukin-27 as a regulator of osteoclast formation must await confirmation by other groups and elucidation of the molecular mechanisms.²¹

REFERENCES:


Authors Information

Dr. Rupali Mahajan
Senior Lecturer
Department of Periodontology
National Dental College & Hospital
Dera Bassi, Mohali, Punjab

Dr. Kanupriya Sharma
Post Graduate Student
Department of Periodontology
Genesis Institute of Dental Sciences and Research
Ferozpur Moga Road, Punjab

Dr. Swati Bhalla
Post Graduate Student
Department of Periodontology
National Dental College & Hospital
Dera Bassi, Mohali, Punjab

Dr. Rohan Vashisht
Post Graduate Student
Department of Periodontology
National Dental College & Hospital
Dera Bassi, Mohali, Punjab

Dr. Neha Kalia
Post Graduate Student
Department of Periodontology
National Dental College & Hospital
Dera Bassi, Mohali, Punjab