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The Role Of Inflammatory Mediators in Periodontal Disease

Nicky Arviana*, Agus Susanto**

*Periodontic Resident in Department of Periodontics, Faculty of Dentistry Padjadjaran University
**Lecturer, Department of Periodontics, Faculty of Dentistry, Padjadjaran University, Bandung, Indonesia
Email :drg.nickyarviana@gmail.com

ABSTRACT

Periodontal disease is a pathological condition that involves inflammation of the tooth supporting structure. Periodontitis, so it called, is characterized by periodontal pocket formation, clinical attachment loss, and alveolar bone resorption. It is initiated by microbial biofilms formed on the teeth and involving interactions between bacterial products, numerous cell populations and inflammatory mediators. The host defense system, including the innate and adaptive immunity is responsible for eliminating bacteria invading the periodontal tissue. Failure to eliminate the bacteria will result in a continuous state of inflammation where the inflammatory cells will continue to produce inflammatory mediators in order to eradicate the bacterial invaders. These inflammatory mediators have the capability to alter the connective tissue and alveolar bone metabolism resulting in tissue and bone destruction. The characteristic of tissue and bone destruction is a result of inflammatory mediators such as cytokines, chemokines, arachidonic acid metabolites, and proteolytic enzymes. This review summarizes the pathogenesis of periodontitis with the main focus on inflammatory mediators and their role in periodontal disease.

Key words: periodontitis, inflammatory mediator

INTRODUCTION

Periodontitis is defined as an inflammatory disease of supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with increased probing depth formation, recession, or both1. It is one of the most common chronic inflammatory diseases in aged populations2. It has been generally accepted that periodontitis is initiated by microbial biofilms in dental plaque3. The invading bacteria and their endotoxins will trigger
host response and inflammation process occurs. Inflammation process is a necessary component for the host defense against pathogens and contributes in wound healing\(^3\). When inflammation remains unresolved, it evolves into a chronic state because host immune and inflammatory responses are insufficient to remove the bacteria. In chronic inflammation, the balance between tissue destruction and healing is maintained, but it can tilt towards destruction\(^3\).

Destruction of periodontium is the characteristic of periodontitis, is generally accepted to be a result of the host-immune inflammatory response caused by bacteria. Traditionally, host response has been thought to be triggered by immune cells such as T and B lymphocytes, neutrophils, and macrophages, but it has been revealed that resident cells in gingival connective tissue also play as important contributors in mediating inflammation. These cells are triggered to release inflammatory mediators including cytokines, chemokines, prostaglandines, and proteolytic enzymes, which could cause tissue degradation and bone resorption by activating osteoclast and several distinct host degradative pathways\(^3\).

**PATHOGENESIS OF PERIODONTITIS**

![Schematic overview of the pathogenesis of periodontitis](image)

Figure 1. Schematic overview of the pathogenesis of periodontitis\(^3\)
Inflammatory periodontal disease is a consequence of the interaction of environmental, genetic, host, and microbial factors. Periodontitis is initiated by dental plaque bacteria. The bacterial infection begins in the gingival epithelium leading to gingivitis, and will progress into the underlying connective tissue leading to periodontitis. Bacterial components such as Lypopolisaccharide (LPS), antigens, and toxins will induce host response which activates immune cells and triggers an antibody response directed towards reducing the magnitude of the microbial challenge. It will result in the production of inflammatory mediators such as cytokines, chemokines, prostaglandins, and proteolytic enzymes i.e. matrix metalloproteinases (MMP). When the host’s immune system cannot resolve the infection, a chronic inflammatory response develops leading to periodontal inflammation and periodontal damage, i.e. loss of attachment and alveolar bone.

**Host Response**

Bacterial components, such as lypopolischarides, peptidoglycans, lipoteichoic acids, proteases, and toxins, could instigate host response by stimulating various inflammatory cell types as well as resident cells of the tissue. Periodontal epithelium provides a physical barrier to infection and has an active role in the innate host defense, because it is in constant contact with bacterial products. It can participate in the infection by signaling further innate and acquired immune responses. It can also respond to bacteria by increasing their proliferation, by altering their cell signaling events, and by changing the cell differentiation and cell death and altering tissue homeostasis. The integrity of the epithelial barrier is specifically disrupted by different microbial pathogens that attack cell-cell junctions and thereby dissociate cells from each other. Families of natural antibiotic peptides or proteins are expressed in epithelium and by neutrophil.

Antigens and products, such as LPS and peptidoglycans, released by bacteria are recognized by toll-like receptors (TLRs) on the surface of host cells, which initiates an inflammatory response. TLRs family is the best characterized class of pattern recognition receptor (PRRs) on immune cell surfaces and detects multiple PAMPs in the bacterial wall. Examples of PAMPs that are recognized by TLRs include peptidoglycan bacterial lipoproteins, and \( Pg \) LPS. TLRs are expressed on a variety of cells, including both lymphoid and nonlymphoid cells, and on various epithelial surfaces, including dendritic cells. Pathogen recognition by TLRs expressed from epithelial cells leads to the production of cytokines, chemokines and antimicrobial peptides that induce the recruitment of more inflammatory cells to the infected sites.

Through a cascade of events, mast cells are stimulated to release vasoactive amines and preformed tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)), which increases vascular permeability and the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), endothelial adhesion molecule-1 (ELAM-1), and P-selectin on endothelial cell surfaces. This process recruits PMNs into the tissue, where they release lysosomal enzymes, which contribute to tissue degradation. These cells are present in the junctional epithelium in large numbers and appear to wall of the underlying tissues from the bacterial biofilm. The
Figure 2. Inflammatory mediators in the pathogenesis of periodontitis
presents of these cells is the result of the existence of generation of chemotactic factors in the gingival sulcus and underlying tissues.

Macrophages and lymphocytes further invade the tissue in response of vasoactive amines and (TNF-α). Macrophages also produce several cytokines and present antigens to T cells. It also capable of differentiating osteoclasts in response to TNF-α in the presents of receptor activator of NF-κB ligand (RANKL). Periodontal pathogens, such as Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis, have been shown to activate macrophages and stimulate the secretion of proinflammatory and tissue destructive mediators such as IL-1, TNF-α, IL-6, and PGE-2.

When the epithelial barrier, with its antimicrobial peptides and other components of innate systems are breached, the adaptive immune response is activated. Cytokines or interleukins are integral with this response and represent intercellular messengers. The cells responsible in adaptive immune response are the lymphocyte (T-cell and B-cell). Lymphocytes are important immune cells that can produce IL-1, IL-6, IL-17, RANKL, and TNF-α cytokines. It is also secrete a number of inhibitory molecules that directly inhibit osteoclast formation, including osteoprotegerin (OPG), IL-4, IL-10, IL-13, and interferon-γ (IFNγ). As the active resolution of inflammation continues, bacterial antigens eventually encounter antigen presenting cells such as dendritic cells, macrophages and B cells.

When naive CD4 T helper cell (Th0) interact with antigen presenting cells, naive T cells differentiate into various subsets of cells including Th1, Th2, Th17, and regulatory T cells (Treg), depending on the cytokines which they produce. Th17 cells has been hypothesized to be involved in Th1 modulation and enhanced inflammatory mediators production by gingival fibroblast, and maybe the primary source of RANKL production by osteoblasts in periodontal disease. Porphyromonas gingivalis outer membrane protein induced a significant increase in the production of IL-17, and this type of cytokine has been shown to stimulate epithelial, endothelial, and fibroblastic cells to produce IL-6, IL-8, TNF-α, and PGE_2.

Bone resorption, in periodontitis, is a shifted balance towards bone destruction through mechanisms including increased osteoclast activation. The activation of osteoclasts is stimulated by cytokines, such as IL-1β, TNF-α, IL-6, macrophage colony-stimulating factor (M-CSF), IL-17, and PGE_2 (Figure 2). The TNF family RANKL induces the differentiation of osteoclasts in the presence of M-CSF. RANKL is a polypeptide of 314 amino acids, and is identified in lymphocytes, stromal cells, and many other cell types in periodontal tissues. RANK is a receptor found on the surface of osteoclast precursors. When RANK binds to its ligand RANKL, it stimulates the proliferation and differentiation of these precursor cells into mature osteoclasts. OPG (Osteoprotegerin) competes with RANKL by binding to RANK without stimulating any osteoclasts differentiation. OPG is a decoy receptor of RANKL, produced by a variety of cell types including osteoblasts and marrow stromal cells. RANKL/OPG ratio was higher in individuals with periodontitis than in healthy individuals.

**Cytokines and chemokines**

Cytokines are small secreted proteins released by cells, have a specific effect on the
interactions and communications between cells. Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both pro-inflammatory cytokines and anti-inflammatory cytokines.

Pro-inflammatory cytokines including IL-1, IL-6, IL-12, IL-17, IL-18, IL-21, TNF-α, and IFN-γ have been demonstrated to be involved in the pathogenesis of periodontitis. These cytokines, predominantly IL-1, IL-6, and TNF-α are produced by resident cells (epithelial cells and fibroblasts) and also phagocytes (neutrophils and macrophages) in periodontal environment. IL-12 and IL-18 is known as a cytokine that is able to enhance the maturation of naive T cells to Th1 cells.

IL-1 is a multifactorial cytokine which is able to activate many cell types with potent inflammatory features. There are two forms of IL-1 that have agonist activity, IL-1α and IL-1β. It is produced by several type of innate immune cells such as PMNs, monocytes, and macrophages after recognition and presentation of microbes to these cells. IL-1β and IL-6 are signature innate cytokines and have been characteristically associated with inflammatory cell migration and osteoclastogenesis. IL-1β expression was elevated in gingival crevicular fluid at sites of recent bone and attachment loss in patients with periodontal disease. IL-17, which the specific cytokine of Th17 cell, is involved in osteoclastogenesis by inducing RANKL expression on osteoblastic cells. The main function is to mediate inflammation by stimulating resident cells to secrete potent pro-inflammatory cytokines like IL-1, IL-6, IL-8, and PGE₂ that exacerbate the inflammatory reaction and tissue destruction.

TNF-α is a multi-effect cytokine that has many functions, from cell migration to tissue destruction. It impacts cell migration by inducing the up-regulation of adhesion molecules to promote rolling and adhesion of neutrophils to the vessel wall, leading to extravasation. It also stimulates the production of chemokines involved in cell migration to infected and inflamed sites. Tumor necrosis factor “family” includes two structurally and functionally related proteins, TNF-α or cachectin mainly produced by monocytes / macrophages and TNF-β or lymphotoxin, a product of lymphoid cells. TNF-α, once produced and secreted, will bind to TNF receptor present in all plasma membrane of most of the cells throughout the body. TNF-α induces the synthesis of IL-1, IL-6, IL-8, PGE₂, and ICAM-1, also MMPs and RANKL which contributes to extracellular matrix degradation and bone resorption.

Chemokines are a large family of chemotactic cytokines that stimulate the recruitment of inflammatory cells. They are produced by a number of cell types in the periodontium, such as fibroblasts, endothelial cells, macrophages, osteoclasts, epithelial cells, polymorphonuclear leukocytes, monocytes, lymphocytes, and mast cells. They are divided into two major families based on their structure, CC and CXC chemokines. They act through receptors referred to as CC chemokine receptor (CCR) and CXC chemokine receptor (CXCR). IL-8/CXCL-8, chemoattractant of PMNs, is found drastically increased...
and have been correlated with disease severity. Another chemokine that contribute to the enhanced severity of periodontal disease is macrophage chemoattractant protein-1 (MCP-1/CCL2), which is supposed to be the major chemoattractant of macrophages\(^5\).

**Prostaglandin E-2**

Prostaglandins are a group of potent arachidonic acid-derived inflammatory mediators with the capacity to induce a wide variety of biological responses, including vasodilatation, vascular permeability; oedema, pain and fever, and the mediator also play an immunoregulatory role in neutrophil and monocyte chemotaxis. They function in both an autocrine and a paracrine fashion and modulate the responses of other hormones. PGE\(_2\) is the most prominent in the pathogenesis of periodontitis\(^3\). PGE\(_2\) is produced by immune cells, osteoblasts, periodontal ligament cells, fibroblasts, and other resident gingival cells and has a wide range of biological effect on the cells of the diseased gingiva\(^3,5\). The actions of PGE\(_2\) include the stimulation of inflammatory mediators and MMPs, as well as osteoclast formation via RANKL\(^3\). Recently, macrophages were shown to secrete more PGE\(_2\) when stimulated with *P. gingivalis* LPS\(^5\).

**Matrix Metalloproteinases**

Maintenance of the extracellular matrix is important for normal development and function of gingival tissue. Proteolytic MMP enzymes and their endogenous inhibitors of metalloproteinases (TIMPs), are involved in the homeostasis of the extracellular matrix in healthy tissue, but they are also key players in the process of tissue destruction in inflammatory diseases. MMPs are also involved in regulating the activities of cytokines and cytokine receptors\(^3\). MMPs degrade extracellular matrix and basement membrane components. This group of 23 human enzymes is classified into collagenases, gelatinases, stromelysins, membrane-type matrix metalloproteinases, and other matrix metalloproteinases, mainly based on the substrate specificity and the molecular structure\(^10\).

The expression and pathologic release of matrix metalloproteinases was originally thought to be limited to neutrophils, but it is now clear that a broad range of human periodontium cell types including gingival epithelial cells, fibroblasts, endothelial cells, monocytes / macrophages, and plasma cell\(^10\). The main stimulatory cytokines for matrix metalloproteinases are IL-1\(\beta\), IL-6, TNF-\(\alpha\), and also bacterial LPS\(^3,10\). It upregulates MMP-1, -3, -8, and -9 expression in gingival fibroblasts\(^3\).

MMP-1 or collagenase-1 from mononuclear phagocytes, fibroblasts and epithelial cells have a wide range of substrates. It digests interstitial collagen, extracellular matrix components and soluble nonmatrix mediators. MMP-9 degrades several types of extracellular matrix, including basement membrane type IV collagen. It is expressed by neutrophils and epithelial cells, and stimulated by several cytokines such as TNF-\(\alpha\), and also bacterial LPS. MMP-13 (collagenase-3) is expressed by the basal cells of the gingival pocket epithelium, it degrades type I, type III, and type IV collagens, as well as fibronectin, tenascin, and some proteoglycans\(^10\).
DISCUSSION

Periodontitis is a consequence of the interaction of environmental, genetic, host, and microbial factors. It is a chronic inflammatory disease in which microbial etiologic factors induce a series of host responses that mediate inflammatory events. The cells contribute to this inflammation including immune cells, and also resident periodontal cells such as gingival and periodontal ligament fibroblasts. They produce several inflammatory mediators in focus of eliminating bacteria and promote healing. These inflammatory mediators are capable to alter connective tissue and bone metabolism, resulting in destruction of tissue and alveolar bone. Cytokines, chemokines, prosta glandins, and matrix metalloproteinases are inflammatory mediators responsible for inflammatory process. Among these groups, cytokines and chemokines such as IL-1, IL-6, IL-8, IL-17, and TNF-α are the major inflammatory mediators responsible for bone destruction in periodontitis by promoting osteoclastogenesis. They could induce another inflammatory mediators such as PGE₂ and MMP which causing tissue destruction by degradating extracellular matrix.

Several alterations found on periodontal disease can be associated with PGE₂, especially when IL-1 and TNF-α is present. Higher levels of PGE₂ have been found in human inflamed gingival tissue, especially from periodontal sites exhibiting recent attachment loss. MMPs are key players in the process of collagen destruction and further tissue destruction in periodontal inflammatory disease. It is also involved in the regulation of cytokines and its receptors. The MMPs levels are found to be higher in inflamed periodontal tissue, where increased levels of inflammatory mediators upregulate MMP expression.

Cytokines such as IL-1 and TNF-α can stimulate osteoclastogenesis by enhancing expression of RANKL and differentiation of osteoclast precursors. It also induces RANKL and OPG expression in several cells, such as osteoblast and fibroblast. PGE₂ also stimulates bone resorption by upregulating RANKL expression and inhibition of OPG expression in osteoblastic cells.

Traditional treatment of periodontitis mainly focuses on decreasing and eliminating microorganism by mechanically removing bacterial biofilm on tooth surfaces and adjacent soft tissue. The development of studies about periodontitis and the role of inflammatory mediators have indicated strong potential for adjunctive host-modulating therapy as new therapeutic strategies in the management of periodontal disease. This host-modulating therapy includes the inhibition of inflammatory mediators such as PGE₂ and cytokines.

CONCLUSION

Periodontitis is an inflammatory disease caused by bacterial challenge, resulting in tissue destruction and bone resorption. During the activity of inflammation, resident cells and immune cells express or produce inflammatory mediators including cytokines, chemokines, PGE₂, MMPs that collectively contributing to the destruction of connective tissue and bone resorption.
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