Immunological Insights into Periodontal Disease Pathogenesis - A Review

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Abstract- Periodontal diseases are chronic inflammatory diseases of multifactorial etiology, common in all human populations, which may result in the gradual destruction of the supporting tissue of the teeth and ultimately tooth loss. Accumulation of plaque has been accepted as the primary initiator of periodontal disease, but it is not solely responsible for the destruction that may follow. The destruction seen in periodontal disease is a consequence of the interaction between the host and microorganisms present in plaque which results in the activation of the host's inflammatory and immune responses, leading to loss of collagen and bone supporting the tooth. In recent years, research has elucidated the contribution of host-microbe interaction to both disease initiation and disease progression. Epidemiological and clinical studies indicate variation in susceptibility to periodontal disease despite the long-term presence of the oral biofilm, in addition to increased susceptibility and greater severity of periodontal disease in patients with an impaired immune response. However, the immune response initiated by periodontal disease seems to be much broader. This review attempts to enlighten the various immune mechanisms involved in periodontal disease initiation and progression.

Keywords: Periodontitis, Immunology, Interleukins, Pathogens.

Introduction:
Periodontal diseases are chronic inflammatory diseases of multifactorial etiology1, common in all human populations, which may result in the gradual destruction of the supporting tissues of the teeth and ultimately tooth loss. The prevalence of periodontal disease as reported by the Adult Dental Health Survey (2008) is 45%, of which 9% suffer from the severe form of the disease2. The survey reported a marked reduction in moderate chronic periodontitis when compared to the 1998 survey, which was attributed to an improvement in oral hygiene practices and promotion of oral health. However, it is interesting to note that the prevalence of severe disease has increased from 6% to 9% which may be attributed to current diagnostic and management techniques which are limited in their ability to identify high-risk individuals, assess true periodontal status, and monitor response to therapy.

Accumulation of plaque has been accepted as the primary initiator of periodontal disease3, but it is not solely responsible for the destruction that may follow. The destruction seen in periodontal disease is a consequence of the interaction between the host and microorganisms present in plaque which results in the activation of the host's inflammatory and immune responses, leading to the loss of collagen and bone supporting the tooth4. Although the role of bacteria is undisputed in the initiation of periodontitis, the quantity and types of bacteria have not been sufficient to explain the significant differences in disease severity between individuals1.

The wide variations in susceptibility to periodontal disease seem to be associated with several secondary genetic, environmental, and behavioral risk factors5. All forms of the disease, however, have a common series of underlying events leading to tissue breakdown and loss of attachment. Although multiple factors have been cited as influencing the progression of periodontal disease, there is overwhelming evidence that it is the uncontrolled inflammatory and immune responses that largely drive tissue destruction and therefore the important role played by the host inflammatory and immune response has been the focus of much research in the last several years.

In recent years, research has elucidated the contribution of host-microbe interaction to both disease initiation and disease progression. Epidemiological and clinical studies indicate variation in susceptibility to periodontal disease despite the long-term presence of the oral biofilm6, in addition to increased susceptibility and greater severity of periodontal disease in patients with an impaired immune response7. These variations may be attributed to an altered host response which is regulated by inflammatory mediators such as cytokines, which play a prominent role in amplifying the immune response resulting in degradation of the periodontal tissue and subsequent collection of host and bacterial products in the GCF.

Therefore, extensive research has been carried out in the last few years to identify biomarkers that have the potential to diagnose accurately disease activity, prognosis, and response to therapy8,9. However, our limited understanding of the
pathogenesis of periodontitis limits the implementation of markers as adjunctive diagnostic and prognostic tools in the management of patients with periodontal disease.

**Innate Immunity in periodontal diseases:**
The epithelial tissues play a key role in innate response because they are in constant contact with bacterial products. It is now recognized that epithelial cells also constitutively express a diverse range of antimicrobial peptides and their synthesis is upregulated in response to periodontal bacteria. These peptides belong to four families (α-defensins, β-defensins, cathelicidins, saposins) that have been found in humans. Innate recognition of bacteria and their products by the host involves a sophisticated array of receptors providing specificity to pathogen detection. Through these receptors, cells can directly respond to conserved pathogen-associated microbial patterns (PAMPs) and host danger-associated molecular patterns (DAMPs). These molecular motifs are recognized by pattern recognition receptors (PRRs) on immune cell surfaces. PAMPs associated with periodontal disease are bacterial lipopolysaccharides, lipopolysaccharides, peptidoglycan, fimbriae, flagellin, heat shock proteins, and DNA. The toll-like receptor (TLR) family is the best-characterized class of PRRs and detects multiple PAMPs. In the context of periodontal disease, TLR-2 and TLR-4 play important roles in bacterial antigen sensing. TLR signaling occurs in a manner that is dependent on the adaptor molecule myeloid differentiation primary response gene (MyD88) or occurs independently via TIR-domain-containing adapter inducing Interferon-β (TRIF). All TLRs except for TLR-3 signal via MyD88; however, TLR-4 engages both MyD88 and TRIF signaling pathways. Neutrophils are the first innate immune cells to migrate to the site of infection. Neutrophils utilize relevant Toll-like receptors to recognize and respond to different types of microbial challenges. Like neutrophils, macrophages/monocytes also play a key role in host defense by recognizing, engulfing, and killing microorganisms.

**Adaptive Immunity in periodontal diseases:**
The adaptive immunity is activated when there is a breach in the epithelial barrier, with its antimicrobial peptides and other components of innate systems. The immune response in periodontal disease is governed by the net effect of T-helper 1 (Th1) and T-helper 2 (Th2) cytokines. The differentiation of Th1 and Th2 cell subsets is determined by antigen, nature of the antigen-presenting cell, and co-stimulatory molecules, as a cofactor with IL-12, can enhance the maturation of naïve T cells to Th1 cells. Th1 cytokines include interleukin-2 and Interferon-γ and promote cell-mediated immunity, while the Th2 cytokine, interleukin-4, suppresses cell-mediated responses and enhances humoral immunity. However, there are controversial data about the Th1/Th2 immune response in periodontal disease. Studies over the past decade or so have supported the hypothesis that Th1 cells are associated with stable lesions and Th2 cells are associated with disease progression. However, other studies have reported a predominance of Th1-type cells or reduced Th2 responses in diseased tissues. Recently, a new subset of T-helper cells, Th17 cells, characterized by the production of interleukin-17, has been described. This subset may have both destructive and protective effects in periodontal diseases.

On the other hand, the integrity of bone tissues depends on the interdependency between the osteoclasts and osteoblasts. The major regulatory mechanism of osteoclast activity is modulated by three novel members of the TNF family of receptors, RANK (receptor activator of nuclear factor-β), osteoprotegerin (OPG), and the RANK ligand (RANKL). RANK is expressed on osteoclasts and its precursors, while RANKL is expressed particularly on osteoblasts under homeostatic conditions. Interactions between RANK and RANKL are required for the differentiation and activation of osteoclast precursor cells to osteoclasts. OPG, a soluble decoy receptor produced by osteoblasts, narrows stromal cells, and other cells, strongly inhibits bone resorption by preventing RANK-RANKL interaction.

RANKL also induces the production of some substances, such as MCP-1/CCL2, which could contribute to bone resorption. Osteoblasts are found to express chemokine receptors during synthesis, which can modulate their function through the binding of chemokines. Additionally, an osteoclast can produce important chemokines that are involved in the recruitment of neutrophils and different lymphocyte subsets, suggesting a role for osteoblasts in the development of the inflammatory immune reaction. Furthermore, the production of chemokines, with the consequent chemotraction of inflammatory cells, may contribute to the disruption of bone homeostasis, resulting in bone resorption.

**Complement System**
In cases of periodontal disease, the host defense also is dependent on a functional complement system, which coordinates the recruitment and activation of inflammatory cells, bacterial opsonization, phagocytosis, and lysis. In addition, complement can amplify the TLR4-mediated inflammatory response toward bacterial LPS challenge. The complement system is critical to the linking of innate and adaptive immunity by regulating the activation of both B cells and T cells, either directly or through effects on antigen-presenting cells. The activation of the complement cascade involves the sequential activation and proteolytic cleavage of a series of serum proteins via three distinct mechanisms.
namely the classical, lectin, and alternative. Classical pathway activation occurs in response to antigen-antibody complexes that are recognized by the Clq subunit of C1. However, the lectin pathway is triggered through the interaction of a secreted pattern-recognition receptor (mannose-binding lectin) with specific carbohydrate groups on the surface of a variety of microorganisms. Both the classical and the lectin pathways then proceed through C4 and C2 cleavage for the generation of the classical lectin C3 convertase (C4bC2b). The alternative pathway also serves as a positive feedback loop for the classical and lectin pathways. All three pathways converge at the third component of complement (C3), which upon activation by pathway-specific C3 convertases leads to the generation of key effector molecules. These include the C3a and C5a anaphylatoxins, which activate specific G-protein-coupled receptors and which mediate the mobilization and activation of leukocytes. Also important are the C3b opsonins, which promote phagocytosis through complement receptors, and the C5b-9 membrane attack complex, which can lyse targeted pathogens. 

The complement systems have also been shown to provide a barrier against the spread of bacterial infections; to facilitate clotting mechanisms, to mobilize hematopoietic stem cells and progenitor cells from the bone marrow, to help replenish new leukocytes and to activate the differentiation of specific T-cell subsets. The dysregulation of complement activities may lead to a failure to protect the host against pathogens and amplify inflammatory tissue damage. In the context of periodontal inflammation, complement subversion appears to play a major role in periodontal pathogenesis.

**Inflammatory responses in the Periodontium:**

The molecules that play a role in the pathogenesis of periodontitis can be broadly divided into two main groups: those derived from the subgingival microbiota (i.e; microbial virulence factors) and those derived from the host immune inflammatory response.

1. **Microbial virulence factors:**
The subgingival biofilm initiates and perpetuates inflammatory responses in the gingival and periodontal tissues. The subgingival bacteria also contribute directly to tissue damage by the release of noxious substances. Their primary importance in periodontal pathogenesis is by activating immune-inflammatory responses that, in turn, result in tissue damage.

1a. **Lipopolysaccharides:**
Lipopolysaccharide (LPSs) are large molecules composed of a lipid component and a polysaccharide component. They are found in the outer membrane of gram-negative bacteria; they act as endotoxins. LPS is of key importance for initiating and sustaining inflammatory responses in the gingival and periodontal tissues.

1b. **Bacterial enzymes and Noxious products:**
Noxious agents such as ammonia and hydrogen sulfide as well as short chain carboxylic acids such as butyric acid and propionic acid are detectable in GCF and are found in increasing concentration as the severity of periodontal disease increases. Plaque bacteria produce proteases, which are capable of breaking down structural proteins of periodontium such as collagen, elastin, and fibronectin.

1c. **Microbial invasion and Fimbriae:**
Periodontal pathogens such as P. gingivalis and Aggregatibacter actinomycetemcomitans have been reported to invade the gingival tissues including the connective tissues. P. gingivalis fimbriae stimulate immune responses such as IL-6 secretion, thereby modifying and stimulating immune -responses in the periodontium.

2. **Host-derived Inflammatory mediators:**
The inflammatory and immune processes that develop in the periodontal tissues in response to the long-term presence of the subgingival biofilm are protective by intent but can result in considerable tissue damage, thereby leading to the clinical signs and symptoms of periodontal disease.

**Properties of Key types of Inflammatory mediators in Periodontitis:**

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Proteins that transmit signals from one -cell to another. Bind to cell surface receptors to trigger production of protein by the cell. There are proinflammatory and anti-inflammatory cytokines. A key proinflammatory cytokine is IL-1β, which upregulates inflammatory responses and is produced by multiple cell types in the periodontium.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandins</td>
<td>Prostaglandin E2 (PGE2) is a key inflammatory mediator, stimulating production of other inflammatory mediators and cytokine production. PGE2 also stimulate bone resorption and plays a key role in periodontitis progression.</td>
</tr>
</tbody>
</table>
Matrix Metalloproteinases (MMPs) MMPs include collagenases, which breakdown collagen. Key MMPs in periodontitis include MMP-8 and MMP-9, which are produced by neutrophils as they migrate through periodontal tissues, thus contributing to periodontal tissue breakdown.

**Chair-side diagnostic kits to detect Inflammatory mediators:**
The heterogeneity of periodontal disease onset, patterning, activity, and treatment response has hindered the accurate and reliable diagnosis of periodontal tissue infection. Efforts to develop a chairside biomarker assay kit for rapid periodontal disease diagnosis are continuing worldwide, examples of biomarker assay kits in the market are:

<table>
<thead>
<tr>
<th>Biomarker Classification</th>
<th>Sampling From</th>
<th>Product Name</th>
<th>Detecting Target</th>
<th>Detecting Principle</th>
<th>Analyzing in</th>
</tr>
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<tbody>
<tr>
<td>Biochemical assay</td>
<td>GCF</td>
<td>Periocheck</td>
<td>Neutral proteases</td>
<td>Enzymatic digestion reaction (Colorimetric assays)</td>
<td>Chairside</td>
</tr>
<tr>
<td>Biochemical assay</td>
<td>GCF</td>
<td>PocketWatch</td>
<td>AST</td>
<td>Enzymatic catalysis reaction (Colorimetric assays)</td>
<td>Chairside</td>
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<tr>
<td>Biochemical assay</td>
<td>GCF</td>
<td>PerioGard</td>
<td>AST</td>
<td>Enzymatic catalysis reaction (Colorimetric assays)</td>
<td>Chairside</td>
</tr>
<tr>
<td>Biochemical assay</td>
<td>Oral rinse</td>
<td>PerioSafe</td>
<td>aMMP-8</td>
<td>Lateral flow test with digital reader (OraLyzer®)</td>
<td>Chairside</td>
</tr>
<tr>
<td>Biochemical assay</td>
<td>GCF</td>
<td>ImplantSafe</td>
<td>Blood, leukocytes, and protein</td>
<td>Lateral flow test with dual-wavelength reflectometry</td>
<td>Chairside</td>
</tr>
<tr>
<td>Microbiological assay</td>
<td>Oral rinse</td>
<td>SillHa ST-4910</td>
<td>OMNIgene ORAL/O MR-110</td>
<td>Characterization of virus species of all genome type including Aa</td>
<td>Company or research laboratory</td>
</tr>
<tr>
<td>Microbiological assay</td>
<td>Subgingival plaque</td>
<td>Evalusite</td>
<td>Aa, Pg, Pi</td>
<td>Sandwich enzyme immunoassay (Colorimetric assays)</td>
<td>Chairside</td>
</tr>
<tr>
<td>Microbiological assay</td>
<td>Subgingival plaque</td>
<td>BANA-Enzymatic test kit</td>
<td>Pg, Td, Tf</td>
<td>BANA hydrolysis reaction (Colorimetric assays)</td>
<td>Chairside</td>
</tr>
<tr>
<td>Microbiological assay</td>
<td>Gums and plaque</td>
<td>OMNIgene ORAL/O MR-501, 505</td>
<td>Characterization of virus species of all genome type including Aa</td>
<td>DNA hybridization</td>
<td>Company or research laboratory</td>
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<tr>
<td>Microbiological assay</td>
<td>Saliva</td>
<td>OMNIgene ORAL/O MR-501, 505</td>
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<tr>
<td>Subgingival plaque</td>
<td>Oral rinse</td>
<td>Carpegen Perio Diagnostik</td>
<td>Aa, Pg, Tf, Td, Fn, Pi</td>
<td>Real-time qPCR</td>
<td>Pg, Pt, Fn, Td, Ec</td>
</tr>
<tr>
<td>Subgingival plaque</td>
<td>Microbiological samples/subgingival plaque</td>
<td>iai Pado Test</td>
<td>Aa, Pg, Pi, Td, Tf, Fa</td>
<td>DNA hybridization</td>
<td>Aa, Pg, Td, Fn, Pi, Cr, Pm, Ec, Cs</td>
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<tr>
<td>Genetic assay</td>
<td>Cheek swab</td>
<td>PerioPredict™</td>
<td>genes for IL-1</td>
<td>DNA hybridization</td>
<td>Company laboratory</td>
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<tr>
<td></td>
<td>Oral rinse</td>
<td>MyPerioID®</td>
<td>genes for IL-6 or IL-1</td>
<td>Genetic polymorphisms detection</td>
<td></td>
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**Conclusion:**
In this review, a brief introduction to periodontal disease, focusing on the participation of the host immune system including both innate, adaptive, and complement systems which may interfere in the development and progression of the periodontal disease and the molecules that play a role in the pathogenesis of periodontitis i.e.; microbial virulence factors and host immune-inflammatory responses along with the chairside investigations of inflammatory biomarkers are described. The available data show that the host response is critical in protecting the periodontium from the pathological sequelae of bacterial colonization and invasion. However, to date, no consensus regarding the pattern of the immune response in controlling periodontal disease has been documented. Further research is essential to fully comprehend the immunological basis of periodontal disease, paving the way for innovative treatment approaches and preventive measures.

**REFERENCES:**


