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Pro-Inflammatory Mediators In Periodontal Disease- Review Article

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ABSTRACT
Periodontal disease such as periodontitis is a chronic inflammatory condition of the periodontium that involves interaction between bacterial products, inflammatory mediators and cell population. The inflammatory and immune response due to the long-term presence of subgingival biofilm are protective by intent but results in tissue damage. Substances such as antigen, lipopolysaccharides and other virulence factors are released from the subgingival biofilm which enters into the gingival tissue and an inflammatory response is initiated and leads to the activation of host defense cells. The main reason of the tissue damage is mostly because of the host response which leads to clinical signs and symptoms of periodontal disease, due towhichit is at times referred to as bystander damage.Inflammatory mediators released as a result of cellular activation leads to tissue destruction and bone resorption.

KEYWORDS: Cytokine, Prostaglandins,Matrixmetalloproteinase, Chemokines

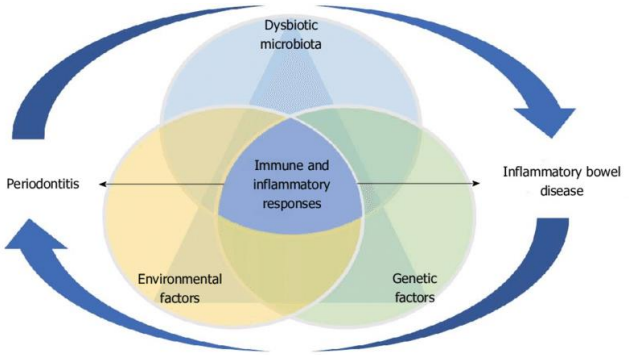
INTRODUCTION

Periodontal disease is one of the most prevalent diseases in the world. Milder reversible form of periodontal disease is the 'gingivitis' which causes inflammation of gingiva.In individuals susceptible to the disease, gingivitis progress into more severe periodontitis which causes destruction of the supporting tissues of the teeth [1]. Around 5-10% of the population is affected by severe periodontitis [2]. The clinical criteria of periodontitis include bleeding on probing, periodontal pocket depth, clinical attachment loss [3].The destruction of the periodontal tissue is due to the result of host immune inflammatory response caused by periodontal microorganism [4].

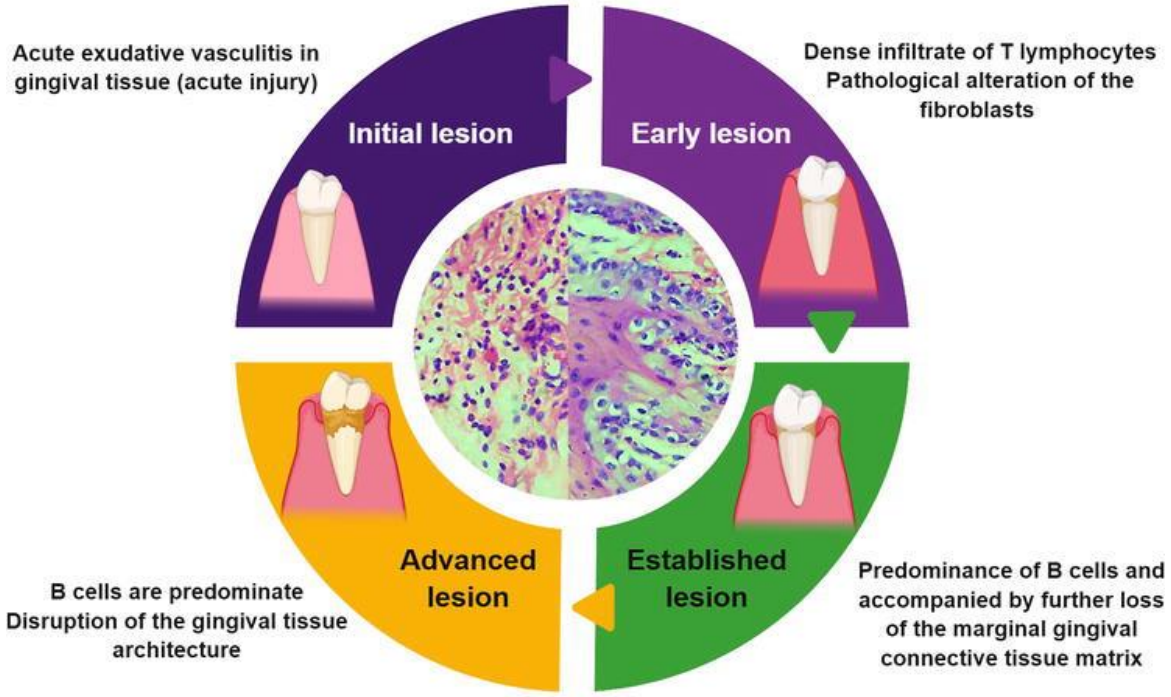
The host response is mediated by B & T lymphocytes,monocyte, macrophages and neutrophils. These are triggered to produce inflammatory mediators such as cytokines,chemokines, arachidonic acid metabolites and proteolytic enzymes. These mediators contribute to the degradation of tissue and bone resorption by activation of several host degradation pathways [5].They also play a critical role in periodontal tissue breakdown [6]. Recently, the increased level of inflammatory mediators and immune response is identified to be due to the contribution of resident cells of gingival connective tissue [7]. The host response in the periodontal tissue is complex, with regard to cell infiltration, polymorphonuclear leukocytes, which are the first to arrive, are dominant cell type in junctional epithelium and gingival sulcus. One important effector mechanism present in periodontal tissue by the inflammatory mediator is the stimulation of formation of osteoclast, which is the major cell type responsible for bone resorption [8]

Pathogenesis Of Periodontal Disease

Periodontitis is a chronic multifactorial disease. It is characterized by inflammation of the periodontal tissue mediated by host. It is associated with dysbiotic plaque biofilm, which leads to destruction of periodontal ligament and alveolar bone and loss of periodontal ligament attachment [9]The periodontitis is caused by around 500 bacterial species which belongs to the complex subgingival microbial community [10]. Usually few species in the subgingival biofilm identified as putative pathogens. There is strong evidence that *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia, are* important periodontal pathogens when present in sufficient numbers and in susceptible host [11]. Bacterial components of the host such as Lipopolysaccharides, toxins and antigens initiate immune and inflammatory response and triggers an antibody response resulting in activation of defense cells such as polymorphonuclear leukocytes to produce cytokines, chemokines, proteolytic enzymes etc. If immune and inflammatory responses are not sufficient, then a chronic inflammatory response develops leading to inflammation of periodontal tissue and results in periodontal damage [4].



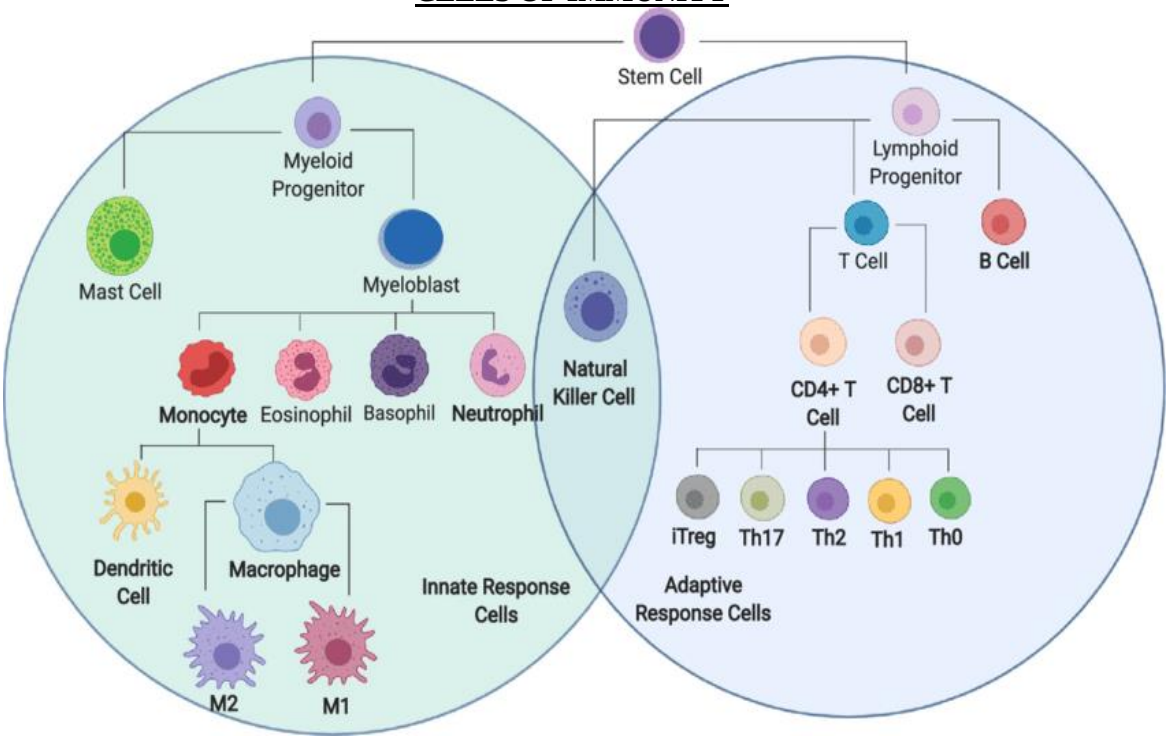
Periodontal Histopathology



IMMUNE RESPONSE IN PERIODONTAL PATHOGEN

Immunity: All The Mechanism Used By The Body To Protect Itself From All Foreign Materials.

CELLS OF IMMUNITY



Innate Immunity

Innate immune system activation, results in inflammation, in response to exogenous and endogenous factors such as microorganisms, infection etc.. Inflammation is a protective response characterized by redness, swelling, heat, pain etc. [12].

Adaptive Immunity

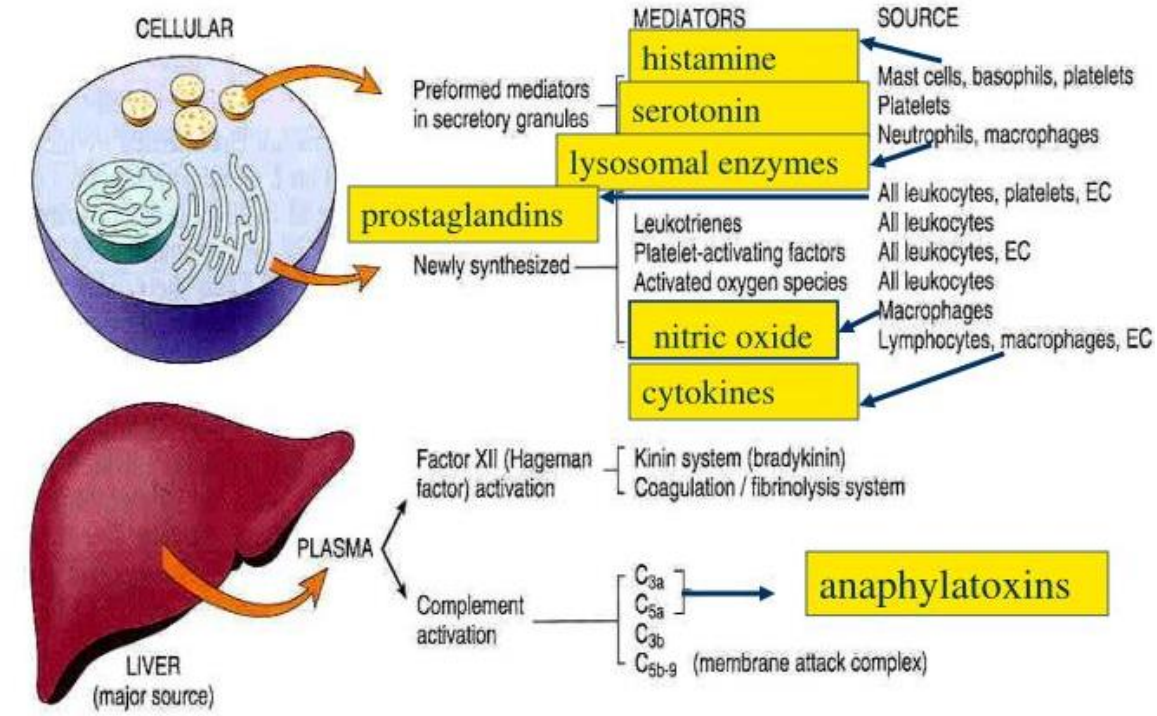
When the inflammatory response becomes chronic, the lymphocytes release inflammatory and immune mediators while invading through the periodontal tissues which alter the metabolism of bone and gets converted into periodontitis from gingivitis [13]. ,

Host Derived Inflammatory Mediators

Majority of tissue damage in periodontal disease derives from the excessive and dysregulated production of a variety of inflammatory mediators and enzyme which are broadly classified as follows:

CYTOKINES
PROSTAGLANDINS
MATRIXMETALLOPROTEINASE

CYTOKINES



Cytokines play a fundamental role in inflammation and they are key inflammatory mediators in periodontal disease. They are soluble proteins and they act as messenger to transmit signal from one cell to another. They contribute to many biological processessuch as wound healing, hematopoiesis, systemic and local inflammatory responses [14].Cytokines are very effective in lower concentrations. They are produced transiently in tissues and they act locally in the tissues in which they are produced [15]. They are secreted by variety of cells types such as neutrophils,monocyte, macrophages, keratinocyte etc .Cytokines signal broadcast and amplify immune responses and they are fundamentally important for regulating immune inflammatory response and for combating infections. The prolonged and excessive production of cytokines and other mediators in periodontium leads to tissue damage that characterizes the clinical signs of the disease.

An inflammatory cytokine is induced during the course of inflammatory response and is associated with onset and progression of inflammation. Proinflammatory mediators are classified into IL-1α, IL-1β, IL-6, IL-8 and TNF-α [16]. They enhance the bactericidal capacity of the phagocyte and take the innate cell population to the site of infection and direct the specific immune response to the invading microbes [17].

Cytokines involved in chemotaxis of the responsive cell is known as chemokines. The chemokines such as IL-8, Monocyte chemoattractant protein -1,and macrophage inflammatory protein -1α attracts leukocyte to the inflammation site. IL-8 is secreted by various cells such as monocyte, lymphocyte, epithelial cells, endothelial cells, fibroblasts in response to IL-1, TNFα and LPS [18].

The balance between anti-inflammatory cytokines and proinflammatory events is crucial for determining disease progression. Some of the anti-inflammatory cytokines are IL-10, TGF- β, IL-11Ra.

Cytokine Levels In The Gingival Crevicular Fluid And In Gingival Tissue[19]

IL-1 α

ROLE: Proinflammatory

CHANGE IN PERIODONTIUM: Increased in GCF with correlation to clinical parameters

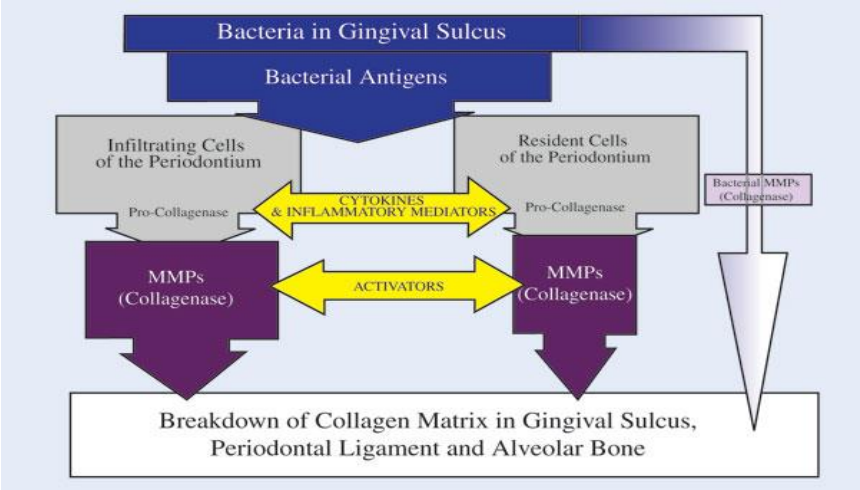
CHANGE AFTER TREATMENT: Decreased in GCF

IL-1β
ROLE: Proinflammatory
CHANGE IN PERIODONTIUM: Increased in GCF with correlation to clinical parameters and increased protein expression
CHANGE AFTER TREATMENT: Increased concentration in GCF and decreased total amount in GCF
IL-4
ROLE : Anti-inflammatory
CHANGE IN PERIODONTIUM: Decreased total amount in GCF, Increased total amount in GCF, Decreased concentration in GCFand Increased concentration in GCF
CHANGE AFTER TREATMENT : Increased in GCF
IL-6
ROLE : Proinflammatory
CHANGE IN PERIODONTIUM : Increased in GCF with correlation to clinical parameters
CHANGE AFTER TREATMENT : Decreased in GCF
IL-8
ROLE : Chemokines
CHANGE IN PERIODONTIUM : Increased in GCF with correlation to clinical parameters
CHANGE AFTER TREATMENT : Decreased in GCF
IL-10
ROLE : Anti-inflammatory
CHANGE IN PERIODONTIUM : Increased total amount in GCF correlated to clinical parameters,Increased concentration in GCF and Decreased concentration in GCF
CHANGE AFTER TREATMENT : Decreased in GCF
IL-12 (p40)
ROLE : Proinflammatory
CHANGE IN PERIODONTIUM : Increased in GCF and increased protein expression
CHANGE AFTER TREATMENT : Decreased in GCF
IL-17
ROLE : Proinflammatory
CHANGE IN PERIODONTIUM : Increased mRNA expression and Increased in GCF
CHANGE AFTER TREATMENT: Decreased in GCF
IL-18
ROLE : Proinflammatory
CHANGE IN PERIODONTIUM: Increased in GCF with correlation to clinical parameters
CHANGE AFTER TREATMENT: Decreased in GCF
IL-21
ROLE : Proinflammatory
CHANGE IN PERIODONTIUM: Increased in GCF
CHANGE AFTER TREATMENT: Decreased in GCF
IFN-γ
ROLE : Proinflammatory
CHANGE IN PERIODONTIUM : Increased mRNA expression and Increased in GCF
CHANGE AFTER TREATMENT: Decreased in GCF and nochanges in GCF
TNFα
ROLE : Proinflammatory
CHANGE IN PERIODONTIUM : Increased in GCF with correlation to clinical parameters and increased protein expression
CHANGE AFTER TREATMENT :Increased concentration in GCF, No change in GCF and Decreased in GCF
MCP-1
ROLE : Chemokines
CHANGE IN PERIODONTIUM : Increased mRNA expression and Increased in GCF
CHANGE AFTER TREATMENT: Decreased in GCF

RANTES
ROLE : Chemokines
CHANGE IN PERIODONTIUM : Increased mRNA expression and Increased in GCF
CHANGE AFTER TREATMENT: Decreased in GCF
MIP1α,
ROLE : Chemokines
CHANGE IN PERIODONTIUM : Increased in GCF
CHANGE AFTER TREATMENT : Decreased in GCF

Prostaglandins
The prostaglandins are a group of lipid compounds derived from arachidonic acid, found in the plasma membrane of most cells.Arachidonic acid is metabolized by cyclooxygenase -1 and cyclooxygenase -2 to generate a series of related compounds called the prostanoids and leukotrienes. The leukotrienes play a major role in asthma and allergy and are also involved in bone remodeling [20]. Leukotrienes B4 is seen in the progression of periodontal disease.There is an increase in GCF LTB4 concentration, which are associated with severe periodontal disease and they decrease following periodontal treatment [21]Someleukotrienes have anti-inflammatory activity, one such leukotrienes associated with periodontal disease is Resolvin E1 (RvE1). These anti-inflammatory leukotrienes inhibit osteoclast growth and bone resorption.
Prostaglandins induce wide variety of biological response[22] . They influence vasodilation, vascular permeability,oedema , pain and fever etc and they play a immunoregulatory role in neutrophils and monocyte chemotaxis.
Among prostaglandins, PGE-2 is the most prominent in the pathogenesis of periodontitis [20].COX-2 is upregulated by IL- 1β , TNFα and bacterial LPS , resulting in increased production of PGE2 in inflamed tissues . PGE2 is produced most significantly by macrophages and fibroblasts. PGE2 results in induction of MMPs and osteoclastic bone resorption and it has a major role in contributing to tissue damage that characterizes periodontitis. Overproduction of PGE-2 havea important role in pathobiology of periodontitis[23].The PGE-2 stimulates inflammatory mediators and MMPs , as well as osteoclast via receptor activator of nuclear factor-κBligand (RANKL) [24]. The effect of PGE-2 depends on prostaglandin receptors EP1 through EP4 . The most important receptor related to pathogenesis of periodontitis is the EP2 and EP4 which activate adenylate cyclase and protein kinase A signaling [25].

MATRIX METALLOPROTEINASES (MMPS)
Matrix metalloproteinase is also known as matrixins. MMPs are endogenous $Zn2^{+}$- and Ca^{2+}dependent enzymes. The MMP family has 23 members in humans .Based on substrate specificity and homology MMP family is divided into 6 groups :Collagenases (MMP-1, MMP-8, MMP-13), Gelatinases (MMP-2, MMP-9) ,Stromelysins(MMP-3, MMP-10,MMP-11,MMP-12), Matrilysins(MMP-7, MMP-26),Membrane -type MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24)and other MMPs (MMP-18,MMP-19,MMP-20, MMP-21,MMP23,MMP-27,MMP-28) [26]. The most widely reported MMPs in gingival crevicular fluid are MMP-8 (accounts for 80% of total collagenases protein in GCF), MMP-9, MMP-13 [27]. Inhibitors of MMPs that are found in tissues include tissue inhibitor of metalloproteinase (TIMPs) which are produced by many cell types and the most important in periodontal disease is TIMP-1. TIMPs play a major role in tissue remodeling and the pathology of periodontal tissue destruction [28].



CONCLUSION

The immune and inflammatory response that result from periodontal disease due to the subgingival biofilm formation are complex and mediated by a large number of proinflammatory cytokine and enzymes that function as a network of mediators with overlapping roles and activity .A number of risk factors increase susceptibility to periodontal disease including smoking , diabetes , nutritional factors and stress .There is difference in the individual response to the bacterial challenge due to the differing levels of inflammatory response according to the response profile of an individual patient . Most individual would be considered normal for a given bacterial challenge; they would produce a certain level of inflammatory mediators in the periodontal tissues. For those who are hypperresponder, same bacterial challenge result in greater inflammatory response, which over time would result in increase tissue breakdown which leads to earlier presentation of clinical signs of the disease and clinical presentation of having increased susceptibility to periodontitis. for those individuals who are hyporesponsive produce low level of inflammatory mediators and are somewhat resistant to the development of periodontitis even though plaque may be present and they may have widespread gingivitis .the nature of the inflammatory response will be governed by genetic factors , environmental factors, and it may vary over time with same individual .

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