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Immunoinflammatory Reponse In Periodontal Disease

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ABSTRACT
The body has developed defense mechanisms to control and to cope up with the constant attack of microorganisms. Host response to the bacterial challenge presented by subgingival plaque is the most important determinant of disease severity. Periodontitis is multifactorial infectious disease of the supporting structures of the teeth, characterized by destruction of the bone and connective tissue. Specific periodontopathic bacteria and their virulence factors are the primary etiologic agents. However, interaction of host defense mechanisms and these etiological agents plays an important role in the onset and progression of the disease.
Key words- Periodontitis, host defense, HMT

I. INTRODUCTION

The body has three lines of defense mechanism i.e Physical barriers, Defensive Cells, Proteins, Inflammation, and Fever and the Immune System. These are a combination of physical and chemical barriers that prevent all types of foreign agents from penetrating the outer layer of the body. Host can be defined as “the organism from which a parasite obtains its nourishment,” or in transplantation of tissue, “the individual who receives the graft.” Modulation is defined as “the alteration of function or status of something in response to a stimulus or an altered chemical or physical environment”.

Periodontitis is multifactorial infectious disease It encompasses the hard and soft tissue, microbial colonization (with or without invasion), inflammatory responses and adaptive immune responses. Periodontitis is defined as, ‘an inflammatory disease of the supporting tissues of the teeth caused by specific micro-organisms or groups of specific micro-organisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both.[1]

Bacteria are always present in the periodontal milieu. After accumulation of subgingival plaque, variety of microbial substances like microbial peptides, bacterial antigens diffuse across the epithelium into the connective tissue. The interaction of microorganisms with the host determines the course and extent of the resulting diseases. Microorganisms may exert pathogenic effects directly by causing tissue destruction or indirectly by stimulating and modulating host responses.

Host Modulatory Therapy (HMT) is a treatment concept that aims to reduce tissue destruction and stabilize or even regenerate the periodontium by modifying or downregulating destructive aspects of the host response and upregulating protective or regenerative responses. HMTs are systemically or locally delivered pharmaceuticals that are prescribed as part of periodontal therapy and are used as adjuncts to conventional periodontal treatments such as scaling and root planing and surgery.[2]

PATHOBIOLOGY OF PERIODONTAL DISEASE PROGRESSION

Microbial colonization occurs at gingival sites where they produce enzymes or other by-products necessary for maintenance of metabolic and/or nutritional status. These products include cytoplasmic membranes, peptidoglycans (PGN), outer membrane proteins, lipopolysaccharide (LPS), fimbriae, lipo teichoic acids (LTA), proteases, heat-shock proteins (HSPs), formyl-methionyl-leucyl-phenylalanine (FMLP), and toxins.[3] Once immune and inflammatory processes are initiated against pathogens, various inflammatory molecules, such as matrix metalloproteinases, cytokines and prostaglandins are released from leukocytes, fibroblasts or other tissue-derived cells. These eventually breakdown extra-cellular matrices such as collagen as well as host cell membranes in order to produce nutrients for their growth and thus deveope gingivitis.[4]
This response is essentially protective in intent to combat the bacterial infection and prevent ingress of bacteria into the tissues. In persons who are not susceptible to periodontitis (disease resistant), these primary defence mechanisms control the infection, and chronic inflammation (i.e. chronic gingivitis) may persist indefinitely. In disease susceptible individuals, however, inflammatory events extend

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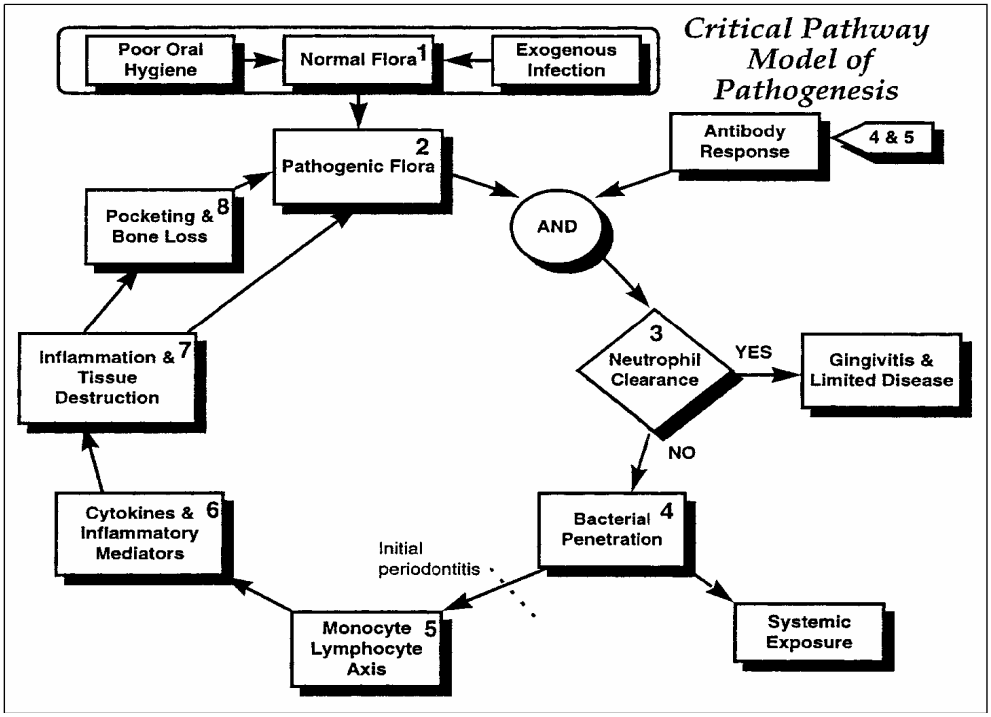
laterally and apicially to involve deeper connective tissues and alveolar bone.



Critical pathway model of periodontal disease pathogenesis[5]

An early part of the host response is the recruitment and migration of polymorphonuclear leukocytes to the site of periodontal infection. If these inflammatory cells clear causative pathogens and their products(such as lipopolysaccharide, endotoxin) via phagocytosis and intra-cellular killing mechanisms, the disease is limited to gingivitis. However, if these mechanisms fail, the disease becomes periodontitis.[5]

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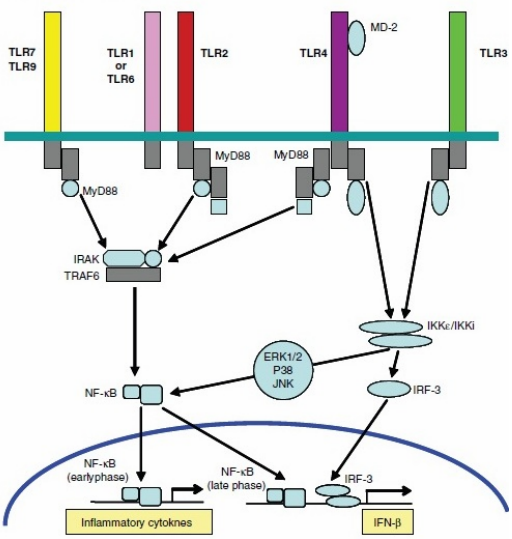
Toll like receptors (TLRs)

TLRs are trans membrane pathogen recognition receptors found on the surface of cells involved in immune responses. To date, at least 10 different TLRs have been characterized and all of them share a similar structure. A broad variety of pathogen associated molecular patterns interact with high specificity with these receptors.



Toll-like receptor (TLR) signalling pathways[6]

HOST-MEDIATED TISSUE DESTRUCTION

In gingivitis and initial periodontal lesions, the majority of tissue damage occurs viaan inflammatory response by the host to the presence of microbes and their product. This is largely mediated by complement, which can be activated through the classic pathway by antigen-antibody complexes. Complement activation occurs in gingival sulcus fluid. Complement activation results in the formation of membrane attack complexes which lyse bacterial cells and components which are vasoactive and chemotactic toward phagocytes. The recruitment of phagocytes to the area results in tissue damage through a variety of mechanisms including the release of lysosomal enzymes.

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HOST-MEDIATED TISSUE INJURY	
	Effects
Complement Activation	
via classic and alternate pathways	Inflammatory response
PMNL degranulation	
Release of	
(a) lysosomal enzymes: collagenase, elastase, glycosidases, phosphatases, cathepsins.	Connective tissue lysis
phospholipase	Prostaglandin production, inflammation
lysozyme	Cell-wall degradation, chemotaxin generation, inflammation
plasminogen	Digests fibrin, complement activation
(b) Reactive oxidants:	
hydroxyl radical $OH^{\cdot}$, singlet oxygen $^1O^2$, super oxide anion, hydrogen peroxide.	Local cellular/tissue damage
Matrix metalloproteinases (MMPs)	
collagenase, stromelysin, gelatinase	Connective tissue matrix degradation

Host mediated tissue destruction[7]

MICROBIAL VIRULENCE FACTORS	
	Effects
Enzymes	
Proteases/peptidases	
Collagenase	
Hyaluronidase/chondroitinase	Connective tissue lysis
Phosphatases	
Phospholipases	
Degradation of:	
(a) Host protease inhibitors	Uncontrolled matrix degradation
(b) Immunoglobulins, Complement	Evasion of host defenses, microbe persistence
(c) Activation of host proteases, *e.g.*, MMPs	Enhanced tissue breakdown
Extracellular vesicles	leukotoxic, inhibit chemotaxis, proteolytic.
Toxins	
Butyric, acetic, propionic, lactic acids, ammonia, indole, H_2S, organic S compounds, chemotaxis inhibitors, leukotoxins.	Impair fibroblasts, cells of immune defenses, delay pathogen elimination
Structural materials	
Capsules, LPS, LTA, peptidoglycan, muramyl dipeptide, polypeptides.	Bone resorption, PMNL degranulation, activate complement, stimulate IL production, amplify inflammatory response.

TISSUE DESTRUCTION IN PERIODONTITIS

1)MMP's

The matrix metalloproteinases are an important family of zinc and calcium dependent endopeptidases secreted or released by a variety of host cells such as polymorphonuclear leucocytes, macrophages, fibroblasts, bone, epithelial and endothelial cells found in periodontium.[8] Matrix metalloprotinases function at neutral pH to degrade the various constituents of extracellular matrix (e.g. collagen, gelatin, laminin, fibronectin & proteoglycan) as their substrate.[9]Matrix metalloproteinases are not constitutively expressed in most tissues but are induced temporarily in response to exogenous signals such as various cytokines, growth factors, cell matrix interactions, and altered cell-cell contacts.

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PATHOLOGICAL ROLE OF MMPs

1. Production of elevated levels of collagenase by diseased gingival tissues in culture.
2. Detection of elevated levels of active rather than latent collagenase in the fluid of the periodontal pocket and in extracts of the adjacent inflamed gingival tissue
3. The presence of matrix metalloproteinase messenger RNA in cells of the periodontal lesions, such as periodontal ligament and gingival fibroblasts as well askeratinocytes, endothelial cells, osteoblasts and even osteoclasts.[10,11]

INHIBITORS OF MMP:

This can be achieved by use of drugs that can –

- Inhibit synthesis and/or release of these enzymes.
- Block the activation of precursor (latent) forms of these MMP.
- Inhibit the activity of mature MMP.
- Stimulate the synthesis of endogenous tissue inhibitors of MMP.
- Protect the host endogenous inhibitors from proteolytic inactivation.

2) cytokines

Host cytokines are a second group of inflammatory mediators highly implicated in periodontal disease and intensely investigated as potential chemotherapeutic targets. They transmit information from one cell to another via autocrine or paracrine mechanisms. Following binding to their complementary receptors, proinflammatory cytokines like interleukin-1 and tumor necrosis factor-α trigger intracellular signaling events and catabolic cell behaviours which can induce connective tissue and alveolar bone destruction.

Cytokines implicated in suppression of the destructive inflammatory response include IL-4, IL-10, IL- 11, and Transforming Growth Factor-β. Both IL-4 and IL-10 can target macrophages and inhibit the release of IL-1, TNF, reactive oxygen intermediates, and nitrous oxide. The evidence that IL-4 is deficient in diseased periodontal tissues.[12]

Currently, anticytokine therapy using anti-IL-1 or anti- tumour necrosis factor-α monoclonal antibodies and soluble tumour necrosis factor receptors have been approved for the treatment of rheumatoid arthritis, crohn's disease, juvenile arthritis and psoriatic arthritis with research continuing on periodontal disease.[13]

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Interaction of T- and B-cell functions in periodontitis

Lymphocytes	Factors	Functions	Association
T-helper 1, T-helper 2, T-helper 17 and regulatory T-cells	T-bet, Trans-acting T-cell specific transcription factor-3, forkhead box P3, retinoic acid receptor-related orphan receptor C2, interleukin-1β, interleukin-10, interleukin-17, RANKL, interferon gamma and transforming growth factor beta-1	mRNA of forkhead box P3, T-bet, RANKL, interleukin-17, interleukin-1β and interferon gamma significantly over-expressed in active lesions	Active and inactive periodontal lesions
T and B-cells	RANKL and osteoprotegerin	Reduction of soluble RANKL release or interference with RANKL expression by T/B-cells	Osteoclastic bone resorption
T-cells	RANKL	Expression of membrane-bound receptor activator of NF-kappaB ligand on T-cells is strictly limited, and the majority of RANKL protein produced by T-cells may be active in the soluble form after shedding	
CD3+ T-cells and CD4+ and CD8+ subpopulations, and CD19+ B-cells		More periodontal breakdown in smoking patients was associated with higher numbers of $CD3^+$ T-cells, as well as with $CD4^+$ and $CD8^+$ T-cell subsets	Smoking and periodontitis
T-helper 17 cells	Interleukin-17 and RANKL	Interleukin-17 and RANKL were abundantly expressed in the alveolar bone of diseased patients, in contrast to low detection in controls	Chronic periodontitis
CD4+ T-cells	RANKL	RANKL mRNA levels were higher in patients with periodontitis than in healthy subjects, and spontaneous and lipopolysaccharide and phytohemagglutinine-stimulated RANKL synthesis were higher also in patients than controls. CD4(+) T lymphocytes were the predominant infiltrate cell subset present in gingival tissues of patients with periodontitis	Levels of RANKL with the CD4(+) T-cell activity present in gingival tissues of patients with chronic periodontitis
T and B-cells	CD86 and CD83 expression on B-cells	High levels of interferon gamma and minimal interleukin-5 produced by stimulated T-cells through B-cells activated with *Aggregatibacter actinomycetemcomitans or Porphyromonas gingivalis*	Severe periodontitis tissues

CONNECTIVE TISSUE ALTERATION-TISSUE DESTRUCTION IN PERIODONTITIS

MMP's

The matrix metalloproteinases are an important family of zinc and calcium dependent endopeptidases secreted or released by a variety of host cells such as polymorphonuclear leucocytes, macrophages, fibroblasts, bone, epithelial and endothelial cells found in periodontium.[14]

CLASSIFICATION

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There are three major groups-

i) Specific collagenases – cleave interstitial collagens. These are MMP's – 1,2,8,9,13,14,18
ii) Gelatinases – degrade types IV, V, VII and XI collagens and act synergistically with collagenase by degrading denatured collagens (gelatins). These are MMP-2,9
iii) Stromelysins – have broader specificity and can degrade basement membrane collagens as well as proteoglycans and matrix glycoproteins. These are MMP's-3, 10, 11
iv) Others – these include Matrilysin, Metalloelastase and recently cloned Membrane bound metalloelastase which include MMP's-14,15,16,17,24,25.[19]

FUNCTIONS

- The main function of MMPs is to catalyze the breakdown of proteins in cell plasma membrane or within the extracellular matrix.
- These proteinases are involved in a number of physiological events such as embryonic development, involution of post-partum uterus, tissue remodelling, salivary gland morphogenesis and tooth eruption.

These are also responsible for various pathological processes such as periodontal diseases, arthritis, cancer, atherosclerosis, diabetes, pulmonary emphysema and osteoporosis.[15]

INHIBITORS OF MMP:

The role of inhibitors is particularly important because it is the imbalance between the activated MMP and their endogenous inhibitors that leads to pathological breakdown of extracellular matrix in diseases such as periodontitis, arthritis, cancer invasion, etc.Inhibitors of matrixmetalloproteinases are either Endogenous (TIMP and α2 macroglobulin) or Exogenous (synthetic) (Zn^{2+} and Ca^{2+} chelating agents- Phosphorus containing peptides, Sulphur based inhibitors, Peptidyl hydroxamic acid derivative,

AGE AND HOST RESPONSE

The table below represents age changes occurring in specific components of the immune response

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Immune component	Change[a]
Adaptive response	Depressed primary response Shortened memory Decreased secondary response
T-lymphocytes	A variable decrease in blood Majority express activation markers Switch from naive to memory Clonal expansion of $CD8^+$ cells Decreased proliferation to stimuli Decreased protein kinase activation Decreased calcium signals Decrease in major histocompatibility complex restriction Decreased cytotoxicity
B-lymphocytes	Decreased numbers in blood Monoclonal gammopathies Isotype profile changes
Accessory cells	Decreased numbers in lymphoid tissues Decreased IL-1 production Increased IL-1 production
Cytokines	Decreased IL-2 synthesis Decreased IL-2 receptor expression Increased synthesis of IL-6 and tumor necrosis factor α Decreased interferon γ
Innate response Natural killer cells	Increased number in blood Variable cytotoxic activity Increased Same Decreased
Polymorphonuclear leukocytes	Normal activity Cell signal transduction changes
Macrophages	No defect in phagocytosis or killing

II.

III. CONCLUSION

It is now clear that periodontitis is not a single homogeneous disease but rather consists of a family of closely related diseases each of which may vary somewhat in etiology, natural history and response therapy. Nevertheless, a common underlying chain of events in the pathogenesis is shared by all forms of disease. This common chain of events is determined by the bacterial challenge and the host response and is influenced by other factors including genetic and other risk factors that may differ from one form of disease to another. The bacterial challenge is necessary but not sufficient to cause progression of periodontal disease.

REFERENCES

[1]. Newman M, Takei H, Klokkevold P, Carranza's Clinical periodontology, tenth edition, Saunders Elsevier, 2006
[2]. Host modulation therapy: An updated review
[3]. Madianos PN, Bobetsis YA, Kinane DF Generation of inflammatory stimuli: how bacteria set up inflammatory responses in the gingiva J Clin Periodontol 2005; 32 (Suppl. 6): 57–71
[4]. Kirkwood KL, Cirelli JA, Rogers JE, Giannobile WV Novel host response therapeutic approaches to treat periodontal diseasesPeriodontol 2000 2007; 43: 294–315 7
[5]. Offenbacher S Periodontal diseases: pathogenesis Ann Periodontol 1996: 1: 821– 878
[6]. Host responses in periodontal diseases: a preview
[7]. Smalley JW Pathogenic mechanisms in periodontal disease Adv Dent Res 1994; 8(2): 320-328
[8]. Nakamura T, Nitta H, Ishikawa I. Effect of low dose Actinobacillus actinomycetemcomitans lipopolysaccharide pretreatment on cytokine production by human whole blood. Journal of periodontal research. 2004 Apr;39(2):129-35.
[9]. Tam YC, Chan EC. Purification and characterization of hyaluronidase from oral Peptostreptococcus species. Infection and immunity. 1985 Feb 1;47(2):508-13.
[10]. Slots J. Enzymatic characterization of some oral and nonoral gram-negative bacteria with the API ZYM system. Journal of Clinical Microbiology. 1981 Sep 1;14(3):288-94.
[11]. Yamashita YO, Toyoshima KU, Yamazaki MI, Hanada NO, Takehara T. Purification and characterization of alkaline phosphatase of Bacteroides gingivalis 381. Infection and immunity. 1990 Sep 1;58(9):2882-7.

[12]. Graves DT, Oates T, Assuma R Cochran D, Amar S IL-1 and TNF antagonists inhibit the inflammatory response and bone loss in experimental periodontitis J Immunol 1998; 160: 403-409

[13]. Anticytokine Therapy: The Newer Horizons Revisited

[14]. Ejeil AL, Igondjo-Tchen S, Ghomrasseni S, Pellat B, Godeau G, Gogly B. Expression of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in healthy and diseased human gingiva J Periodontol 2003; 74: 188–195

[15]. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res. 2003 May 2;92(8):827-39