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# HOST-MODULATION – THE PATH TOWARDS THE FUTURE IN PERIODONTAL THERAPY

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## ABSTRACT

Periodontitis is an inflammatory disease resulting in the destruction of the periodontal apparatus affecting a very wide range of population all over the world. The pathologic periodontal bacteria contribute to the initiation of periodontitis and its progression is regulated by interactions between the host immune response and bacterial factors. During this interaction, inflammation process is driven by the inflammatory mediators which comprise of connected group of cytokines and chemokines that are released continuously by various immune cells. When these mediators exceed or are produced for a longer duration can lead to host tissue destruction. Hence, host modulation aims at bringing these enzymes and mediators to normal level and prevent further tissue damage. This article enumerates the various host factors, microbial virulence factors, host-mediated inflammatory mediators and their respective target drugs which help in the resolution of the inflammatory processes and also the future therapeutics that would act as targets against the periodontal disease.

**KEYWORDS:** Antibiotics, Anti-cytokine, Cytokines, Host-modulation, Interleukin.

## INTRODUCTION

Isn't inflammation the process that is supposed to be good for our bodies and not something that causes harm to so many different aspects of the body? As we learn more about the biological mechanisms of inflammation, it becomes clear that this process is more complicated than was once thought.

Inflammation is a local response (reaction) of living vascularized tissues to endogenous and exogenous stimuli. The term is derived from the Latin "inflammare" meaning to burn. Inflammation is fundamentally destined to localize and eliminate the causative agent and to limit tissue injury. Thus, inflammation is a physiologic (protective) response to injury.[1]

Now the inflammatory process significantly affects the periodontium. Periodontitis is multifactorial origin inflammatory disease which represents with destruction of periodontium due to upregulation of immune response. It is initiated with the plaque biofilm releasing a variety of biologically active products as gram-positive and gram-negative bacteria colonize the tooth surface. These products include endotoxins, cytokines and protein toxins. These molecules penetrate the gingival epithelium and initiate a host response that eventually results in gingivitis.[2] As the biofilm continues to proliferate, soluble compounds penetrate the sulcular epithelium. This, in turn, signals the gingival epithelium to produce chemical mediators including interleukin–1 beta (IL-1,), prostaglandins, tumour necrosis factor alpha (TNF-α), and matrix metalloproteinases.[3]

As the inflammatory process progresses, additional mediators are produced, and more cell types are recruited to the area including neutrophils, T-cells, and monocytes. Continued inflammation results in signaling of fibroblasts and production of pro inflammatory cytokines both by local cells and within the liver. But at times the host is unable to counter the excessive inflammatory mediators in the body even after the elimination of the causative factors and in such cases; measures can be taken to alter the host responses.[3]

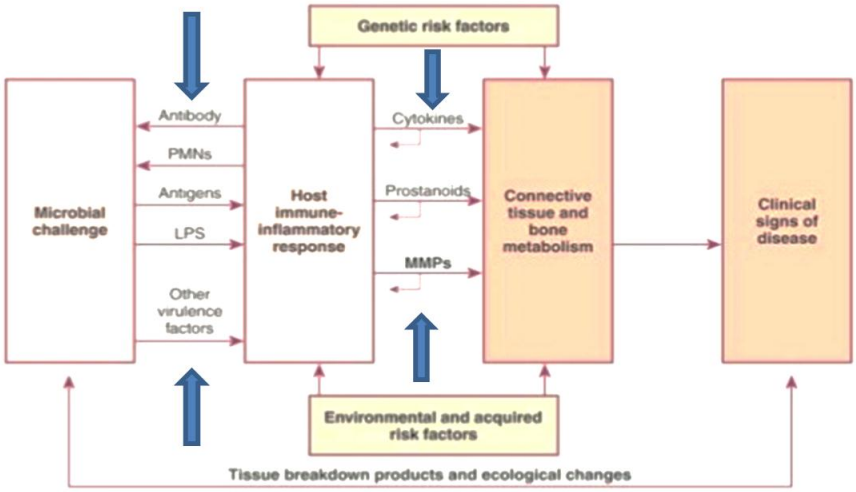
Knowledge of how immune mechanisms and inflammatory responses are regulated is critical for understanding the pathogenesis of complex diseases, such as periodontitis. In this article we will be discussing about how the host immune and inflammatory responses can be targeted to achieve better therapeutic intervention at the immune level to achieve periodontal stability.

Where do we need to target?

Now we know the pathogenesis of periodontal disease and also that non-surgical periodontal therapy helps in achieving and eliminating the causative factors of a periodontal disease. Then the question arises is that – "Is non-surgical periodontal therapy enough or can the host

be targeted in a better way to deal with periodontitis?" To achieve homeostasis we need host innate immunity and acquired immunity functioning of the body against the causative agents of periodontitis. These can be modulated to function in an enhanced and optimised way by modulating the host inflammatory and immune systems specifically.[4] The targets being antibody, PMNs, antigen, LPS, cytokines, prostaglandins, MMPs as shown in the figure.(Fig 1)

**Fig 1**




**Host Factors - Saliva and Epithelium**

**Saliva**

Saliva plays an important role in inhibiting the development of periodontitis in the early stages by its action to inhibit bacterial adherence, neutralize lipopolysaccharides, inhibit destructive enzymes, inhibit bacterial growth, lysing of the bacterial cell walls and neutralizing bacterial hydrogen peroxidase.[5]

In some of the patients who have hyposalivation or xerostomia there is no role of saliva in the host defence. Here the host can be modulated by the use of agents like:

- Pilocarpine is a parasympathomimetic medication with muscarinic action.
- Cevimeline is a salivary gland stimulant with a stronger affinity for M3 muscarinic receptors.
- Anethole trithione is a cholagogue that has been shown to improve oral symptoms and increase the salivary flow in patients with xerostomia and hyposalivation. More studies are necessary to prove the efficacy of this medication.[6]

**Antimicrobial peptides**

Oral epithelium works in several ways for the conservation of the underlying tissues. As a physical barricade, it can counter unbroken microbial oppositions from dental plaque by the production of chemokines, cytokines, and antimicrobial peptides (AMPs), which enhance inflammation and immune response in oral epithelial tissues. These epithelial antimicrobial peptides are considered to be paramount for the innate immunity of the host.[7]

The various AMPs expressed in saliva and Gingival crevicular fluid include, Adrenomedullin, Cathelicidin/LL-37, Histatin1, Histatin3, Statherin, NeuropeptideY. The first AMPs identified in the oral epithelium were defensin, Lingual Anti-microbial Peptide (LAP). Defensins have also shown to inhibit LPS-stimulated inflammatory responses in host cells. Cathelicidin (LL-37): By activating antigen-presenting cells, it presents as a hemoattractant for immune cells, including monocytes, T cells, etc. There is a specific correlation amongst multiplication in LL-37 levels and periodontal inflammation. It is also known to cause an elevation in mucosal thickness in the gingiva. It miraculously neutralizes the activity of LPS and thus help protect the tissues from their harmful effects. Systems which specifically target the AMPs to the bacteria are being developed. Their antimicrobial activity and selectivity help kill bacteria in mixed cultures.

To overcome the problems of toxicity, peptide mimetics with the ability to retain their properties as AMPs are being developed with a favorable therapeutic index and stability; one such mimetic being XOMA 629. Topical and local applications under the names of Pexiganan (MSI-78), Iseganan (IB-367), P113, and KSL have successfully been used as adjunct to standard oral hygiene care, mouthrinse for oral candidiasis in HIV patients, prevention of plaque-mediated dental diseases, and control of biofilms. Furthermore, coated AMPs are used to prevent the biofilm formation on implants.[8]

**Toll gates: An emerging therapeutic target**

In the oral epithelium, complementary defense mechanisms are present. Epithelial cells have tight intercellular junctions that impede the entry of bacteria and their metabolites. Lipopolysaccharide is a cell-wall component of all gram-negative microorganisms. Once

exposed to lipopolysaccharide, a series of complex mechanisms are triggered, which lead to extracellular matrix degradation and the initiation of osteoclastogenesis.[4]

These include toll-like receptors and related proteins that regulate apoptosis, inflammation and immune responses. TLRs play a key role in chronic inflammation and autoimmunity by inducing the production of high levels of pro inflammatory cytokines.[4]

Pathogens have developed strategies to evade TLR signaling. For example, Porphyromonas gingivalis alters the proportion of lipid A moieties and increases its virulence through manipulation of innate immune response. It causes degradation of essential TLR co-receptor (CD14) or immunostimulatory cytokines.

TLRs as vaccine adjuvants: Adjuvants are compounds that are generally added to killed whole organism or subunit vaccine to enhance the immune response against co-inoculated antigens.[9]

They improve the efficacy of vaccine in newborns, elderly or in immunocompromised individuals. Adjuvants exert their actions by recruiting professional antigen-presenting cells (APCs) to the vaccination site, increasing the delivery of antigens to APCs, or by activating APCs to produce cytokines and by triggering T-cell responses.[9] TLR adjuvants that are currently under research which can prove to be one of the highly efficient compounds against cancer are listed in the table below. (Table. 1).[10] These drugs would be a potential treatment option in the field of periodontology.

Table 1.

| COMPOUND | COMPANY | TARGET | DRUG CLASS | CLINICAL PHASE |
|---|---|---|---|---|
| Rintatolimod | Hemispherx Biopharma | TLR3 | dsRNA molecule | Preclinical |
| SMP-105 | Dainippon Sumitomo Pharma | TLR2 | Autoclaved mycobacteria | Preclinical |
| IPH-3102 | Innate Pharma | TLR3 | dsRNA mimic | Preclinical |
| IMO-2055 | Idera Pharmaceuticals | TLR9 | CpG oligonucleotide | Phase I |
| MGN-1706 | Mologen | TLR9 | Non-coding stem-loop DNA | Phase I |
| OM-174 | OM Pharma | TLR2, TLR4 | Lipid-A derivative | Phase I |
| ISS1018 | Dynavax Technologies | TLR9 | Short DNA oligonucleotide | Phase II |
| Agatolimod | Pfizer | TLR9 | CpG oligonucleotide. | Phase II |
| 852A | 3M Pharmaceuticals | TLR7 | Small-molecule ssRNA | Phase II |
| Imiquimod | 3M Pharmaceuticals | TLR7 | Small-molecule ssRNA | Phase II |
| Cadi-05 | Cadila Pharmaceuticals | polyTLR | Autoclaved mycobacteria | Phase II |

**Microbial Virulence Factors**

**Complement**

P. gingivalis and certain other periodontitis-associated bacteria can suppress complement activation through the action of specific proteolytic enzymes. The gingipains of P. gingivalis, interpain A of Prevotella intermedia, and karilysin of Tannerella forsythia can all block complement activation by degrading the central complement component C3, or upstream components of the complement cascade such as the pattern-recognition molecules mannose-binding lectin and ficolins. It is possible that a certain pathway is overactivated and contributes to unwarranted inflammation, while another pathway is activated in a controlled manner and contributes to host defense.[11]

Complement-targeting drugs that are being put to practical use

- C1 inhibitor (C1-INH) (Berinert®)
- Eculizumab, an anti-C5 monoclonal antibody (Soliris®)
- Eculizumab is a humanized anti-C5 monoclonal antibody that binds to the α chain of C5. This

prevents C5 from being cleaved into C5a and C5b by C5 convertase.
- CCX168 was recently developed to inhibit inflammation caused by C5a. CCX168 is an orally administered C5a receptor antagonist.[12]

**Bacterial enzyme inhibition**

Plaque bacteria produce a number of metabolic waste products which contribute directly tissue damage. P.gingivalis produces 2 classes of cysteine proteases known as GINGIPAINS. The gingipains modulate the immune system and disrupt immune- inflammatory responses. Potentially leading to increased tissue damage. These can reduce the concentration of cytokines and digest and inactivate TNF-α.[13] Benzamidine derivatives inhibit the activity of RgpA and RgpB. Among these derivatives, bis-benzamidine, with a urea linker, was the most potent for Rgp inhibition. Application of low concentrations of zinc increased the benzamide derivative inhibition of Rgps by two- to threefold.[14]

Chlorhexidine, tetracyclines, and non-antimicrobial chemically modified tetracycline derivatives have all been reported to inhibit gingipains and inhibition was increased by the addition of zinc. Gingipain inhibition by sword bean extract and canavanine.[15] Gingipain inhibition by cranberry-derived polyphenols.[16] Gingipain inhibition by green tea-derived polyphenols.[14]

Vaccination with gingipains has been reported to yield a protective effect against P. gingivalis infection. The vaccines tested were mainly peptide and DNA vaccines. While DNA vaccines induce both cellular and humoral immunity, peptide vaccines induce only humoral immunity.[17]

**Antibiotics**

Possess unique non-antibacterial characteristics- collagenase inhibition, inhibition of neutrophil chemotaxis, anti-inflammatory effects, inhibition of microbial attachment and root surface conditioning, arrest bone loss and suppress A. actinomycetemcomitans levels in conjunction with scaling and root planing. Tetracycline, minocycline and doxycycline are semisynthetic members of the tetracycline group that have been used in periodontal therapy.[18] Azithromycin exerted acute effects on the release of neutrophil granular enzymes, on oxidative burst and oxidative protective mechanisms; there was a prolonged degranulation of circulating neutrophils, which could represent a potential anti‑inflammatory effect in the treatment of subacute, noninfective inflammatory responses. Its effectiveness against Gram‑negative bacteria, the ability to penetrate biofilm, and a long antibacterial half‑life and short course make it an attractive antibiotic option as an adjunct to the management of advanced inflammatory periodontitis. Azithromycin appears to exert a long‑term healing influence on the periodontal tissues. This property may be related to its effect on changing the macrophage phenotype, thus increasing the production of anti‑inflammatory cytokines and favoring healing.[19]

**Host derived inflammatory mediators**

**Anti cytokine therapy**

Cytokines are a category of signaling proteins and glycoproteins, and are used extensively in cellular communication. The excessive production or retention of these can lead to prolonged inflammation of the periodontium. Anticytokine therapy for periodontal diseases mainly targets TNF-α, IL-1ß, and IL-6, because they are essential for the initiation of inflammatory immune reactions and are produced for prolonged periods in inflammatory disease.[20] Cytokine biology reveals that there are some subsets of cytokines which are pro-inflammatory cytokines which stimulate the inflammatory responses and cause tissue destruction. The other subset is of anti-inflammatory cytokines which prevent an inflammatory response, hence arrests tissue destruction. Treatment strategies that aim to down regulate pro-inflammatory cytokines or up regulate anti-inflammatory cytokines can be aimed for periodontal therapy.[21]

**Anti- IL-1 therapy**

IL-1 is one of the most important cytokines that plays a role in periodontal tissue destruction. The focus on IL-1 for effective anti-cytokine therapy lies on decreasing the levels of IL-1α and IL-1β whereas increasing the levels of IL-1RA. Anti- IL-1 therapy strategies in the suppression of IL-1 have been based on the blockade of transcription, translation, secretion or receptor blockade. Anakinra (Kineret®) is the only FDA approved recombinant, non-glycosylated form of human IL-1RA. The drug claims that most clinical responses would be achieved on administration of 100mg of drug subcutaneously within 12 weeks of enrolment in Rheumatoid arthritis patients. Its role in periodontitis is however to be explored. Care should be taken for its administration as it may cause adverse reactions like infections, immunogenicity, malignancies and a decrease in the total white blood cell and platelet count.[21] Gemfibrozil (Gem), a lipid lowering drug has shown to upregulate IL-1RA in mouse. Furthermore, it has been shown that Gem suppresses IL-1β mediated neuronal apoptosis via upregulation of IL-1RA.[23]

**Anti-TNF therapy**

TNF is secreted by monocytes, macrophages, neutrophils, T- cells, Natural Killer cells (NK- cells) following their stimulation by bacterial lipo-polysaccharides. It exists in 2 forms- TNF-α and TNF-β. TNF-α is known to be a potent stimulator of bone resorption and inhibitor of bone formation. TNF-α also has been shown to up-regulate the production of other pro-inflammatory cytokines like IL-1β and IL-6. An attempt to decrease the levels of TNF-α would help to prevent bone resorption hence arrest periodontal tissue destruction.[24]

Infliximab (Remicade®) Infliximab works by inhibiting the effective binding of TNF-α with its receptors.[25] Infliximab has been shown to halt periodontal inflammation and bone resorption in patients with rheumatoid arthritis who routinely have used 200mg of infusions.[26] Etanercept is a fusion protein which is produced by recombinant DNA which fuses the TNF receptor to the constant end of the IgG1 antibody. Hence it has a potential to treat inflammatory diseases by inhibiting TNF-α. An experimental model of periodontitis in rats has shown that etanercept reduces the development of inflammation and tissue injury.[27] Adalimumab is a recombinant human IgG1 monoclonal antibody used as a TNF inhibiting anti-inflammatory drug. It binds to the TNF-α, preventing it from activating TNF receptors. A study carried out in Japan recently has successfully proved decreased gingival index, bleeding on probing, periodontal pocket depth, decreased serum levels of TNF-α and IL-6 on giving adalimumab to patients with rheumatoid arthritis.[28] Golimumab is another monoclonal antibody used as a TNF inhibitor that binds to the specific receptors of both trans-membrane and soluble TNF-α and blocks their action.[29]

**Anti-IL-6 therapy**

Interleukin-6 (IL-6) is an important cytokine involved in the regulation of host response to tissue injury and inflammation. It is produced by many cells like monocytes, osteoblasts, fibroblasts, vascular endothelial cells in response to inflammation.[30] Since IL-6 is one of the most potent pro-inflammatory cytokine which leads to the periodontal destruction, an attempt can be made to reduce the levels of locally produced IL-6 to prevent periodontal tissue destruction. The effect of IL-6 receptor inhibition has been analysed by Kobayashi in patients with periodontitis and a significant decrease in the gingival index, bleeding on probing, probing depth was noted.[31] Recombinant human interleukin-11 (rhIL-11): Interleukin 11 has been shown to have anti-inflammatory effects by inhibition of TNF-α and other proinflammatory cytokines. Cytokine suppressive anti-inflammatory drugs (CSAIDS) / p38inhibitors.[32]

**Resolvins**

Resolvins stimulate the resolution of inflammation through multiple mechanisms, including preventing neutrophil penetration, phagocytosing apoptotic neutrophils to clear the lesion, and enhancing clearance of inflammation within the lesion to promote tissue regeneration.[33] Hasturk et al. showed that, in a rabbit model of human periodontal disease, RvE1 prevents the initiation and progression of tissue destruction.[34]

**Prostaglandin modifiers**

They are potent stimulators of bone formation and resorption and are produced by osteoblasts and PDL cells. They also have inhibitory effects on fully differentiated osteoblasts and osteoclasts. PGE2 is a potent stimulator of alveolar bone resorption.[35]

**NSAIDs**

Anti-inflammatory effects is seen in high doses. They supress signs and symptoms of inflammation such as pain, tenderness, swelling, vasodilatation and leukocyte infiltration but they do not affect the progression of underlying tissue. Anti-inflammatory drugs block the cycloxygenase pathways and inhibit inflammation.[36] Aspirin is a salicylic acid derivative and the oldest anti nflammatory drug still used. Anti-inflammatory action exerted at high doses of 100mg/kg/day. Recently, it was also reported, in a small sample size, that "low-dose" aspirin may reduce the risk of periodontal attachment loss.[37]

Evidence from animal experiments and clinical trials demonstrates that both NSAIDs and selective COX-2 inhibitors are generally responsible for stabilisation of periodontal conditions by reducing the rate of alveolar bone resorption.

Some other potent anti-inflammatory drugs

- Diclofenac
- Indomethacin
- Piroxicam
- Ibuprofen

Nyman and associates investigated the modulation of arachidonic acid metabolites with systemic indomethacin and demonstrated that a systemic dose of non-steroidal anti-inflammatory drugs suppresses alveolar bone resorption and gingival inflammation.[38] Non-steroidal anti-inflammatory drug flurbiprofen successfully blocks the progression of recurring periodontal disease in animal models.[39]

**Triclosan**: A compound which has received interest as both an antibacterial and anti‑inflammatory agent is triclosan. Triclosan also inhibits COX and LOX and thus may interfere with the production of AA metabolites.[40]

**Matrix metalloproteinase Inhibitors**- MMPs are the prime mediators involved in tissue destruction in various pathological conditions including periodontitis. It is a family of proteolytic enzymes that degrade extracellular matrix molecules such as collagen, gelatin and elastin.[41]

Contemporary periodontal modulation therapy aims at reduction of activated MMPs level and/or increasing the MMPs inhibitors either endogenous (host derived) or exogenous (synthetic) inhibitors, causing a decrease in collagen destruction which ultimately leads to gain in clinical attachment levels and probing depth reduction.

**MMP Inhibitors**

1. Endogenous (natural) inhibitors: These MMPs inhibitors are natural or host derived

a. Tissue Inhibitors of Metalloproteinases (TIMPs): TIMPs binds irreversibly with activated MMPs forming non-covalent complexes e.g. TIMP-1, TIMP-2, TIMP-3 etc.

b. $\mu^2$-macroglobulin: It causes regulation of MMP in body fluids.

2. Exogenous (synthetic) inhibitors: These inhibitors are synthetically developed to cease the effect of MMPs by different pathways.

a. Zinc- and Calcium-Chelating Agents: e.g. Ethylenediaminetetraacetic acid (EDTA).

b. Phosphorus containing peptide.

c. Sulphur based inhibitors e.g. Mercaptan derivatives.

d. Peptidyl hydroxamine acid derivatives.[42]

**Chemically modified tetracyclines**

TC is major antiproteinase used in periodontal therapy. Low dose capsules containing 20 mg of doxycycline is a recent approach to non-antibacterial periodontal treatment and is most potent collagenase inhibitor which is commercially available. The group of CMTs constitute of at least 10 analogs plus few special modified CMTs that vary in their MMP specificity and potency.[43]

**Bisphosphonates**

The proven efficacy of Bisphosphonates to inhibit the osteoclastic bone resorption has led to their use in the management of periodontal diseases as a host modulating factor. Till now, there are three generations of BPs existing. The first generation includes etidronate, the second generation includes alendronate and the third generation of BPs includes zoledronate). The non-nitrogen-containing BPs (clodronate and etidronate) can be metabolically incorporated into non-hydrolysable analogues of adenosine tri- phosphate (ATP) that may inhibit ATP-dependent intracellular enzymes such as the osteoclast proton-pumping vacuolar ATPase. The more potent nitrogen-containing BPs (e.g. zoledronate and pamidronate) inhibit the key enzyme, farnesyl pyrophosphate synthase, in the mevalonate pathway, thus, preventing the biosynthesis of isoprenoid compounds, essential for the post-translational modification of small guanosine triphosphate (GTP)-binding proteins which prevent the osteoclastic activity by preventing ruffled border formation in osteoclast.[44]

## CONCLUSION

Disease occurrence in individuals is mainly due to the aberrant host response. An imbalance results from hyper- or hypo responsiveness and lack of sufficient resolution of inflammation, which in turn is responsible for the destruction seen in periodontitis. The control of this destruction by anti-inflammatory processes and pro-resolution processes limits the destruction to the tissues surrounding the teeth. The local inflammatory processes may progress and affect the systemic health. This review article focuses on how host immune and inflammatory responses can be targeted to achieve better therapeutic intervention. Thus Understanding the inflammatory response mechanisms is essential in developing innovative and advanced treatments to prevent periodontal disease so as to provide our patients with the best clinical outcome possible.

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