

Host Modulation- Promising Direction In Periodontal Therapy

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ABSTRACT : The primary etiology of the periodontal disease is chronic inflammation due to bacterial infection. It is the host's reaction to the presence of bacteria that mediates tissue destruction. Since the destruction of periodontium is believed to be due to the host response, it is intellectual and logical to consider therapeutic approaches that modulate the host response in addition to antibacterial approaches in periodontal therapy. Improved knowledge of bacterium –host interactions and of the process leading to tissue destruction will help to identify targets for host modulation to reduce periodontitis in selected situations. The objective of this article is to review and update the fundamental scientific concepts of host modulation and to furnish an approach to the main types of therapy used, based on the scientific literature.

KEYWORDS : Periodontitis, Anti-Inflammatory, Host Response, Pathogenesis, Adjunctive Therapy.

I. INTRODUCTION

In recent years, there is a paradigm shift in our understanding of the etiopathogenesis of periodontal disease. Periodontal disease is considered as an inflammatory disease initiated by tooth associated biofilm. However, the progression of the disease and destruction of periodontal tissues is due to series of complex interactions between micro biota and host immune responses[1]. It is becoming clear day to day that inflammation is the major determinant of susceptibility for periodontitis. But our understanding of relationship of etiologic agents of periodontitis to the pathogenesis is not as clear as it was once thought. Today the clinical management of periodontal disease is based on 3 steps:

- Reduction of the bacterial burden.
- Modification of environmental and behavioral risk factors.
- Modulation of host responses.

With the current understanding of the host response and periodontal disease pathogenesis, it is intuitive that pharmaceutical inhibition of host response pathway may be an adjunctive or alternative strategy for treating periodontal disease.

II. HOST MODULATION

Host modulation means modulating destructive or damaging aspects of inflammatory response that develops in face of the challenge presented by the subgingival bacterial plaque. Host modulation is not a new concept. However, in medicine the host modulation strategies are successfully used in the treatment of disorders such as rheumatoid arthritis and osteoporosis. In periodontitis a variety of pharmacological agents have been studied for possible role as host modulators in prevention and management of periodontal disease. These include non steroidal anti-inflammatory drugs, bone sparing agents, anticytokine drugs and anti matrix metallo proteinases.

2.1 Non Steroidal Anti-Inflammatory Drugs:

Arachidonic acid is liberated from plasma membrane phospholipids via the enzyme phospholipase-2. Free arachidonic acid can be metabolized to cyclooxygenase or lipoxygenase pathways. Cyclooxygenase-2 is inducible and thought to be involved in inflammation, cellular differentiation and mitogenesis. Cyclooxygenase - 1 and cyclooxygenase-2 produce prostaglandin[2], prostacyclin and thromboxin whereas lipoxygenases produce leukotrienes and other hydroxyl eicosatetraenoic acids[3]. And these enzymes have been implicated in wide range of events in inflammatory diseases. Anti-inflammatory drugs block the cyclooxygenase pathways and inhibit inflammation.

Utilizing canine experiment periodontitis model Nyman[4] and associates investigated the modulation of arachidonic acid metabolites with systemic indomethacin and demonstrated that systemic doses of non steroidal anti-inflammatory drugs suppresses alveolar bone resorption and gingival inflammation. Similar findings have been reported in ligature-induced periodontitis in squirrel, monkeys with systemic administration of indomethacin. Non steroidal anti inflammatory drug flurbiprofen [5] successfully blocks the progression of recurring periodontal disease in animal models. Propionic acid derivative ibuprofen was effective in blocking alveolar bone loss in naturally occurring periodontitis among beagle dogs[6]. Topical application of piroxicam in gel and liquid forms significantly reduced gingivitis in a preclinical trial [7]. 1% ketoprofen cream has also shown similar results in rhesus monkey model [8]. Concurrently there is substantial data from human cross sectional and cohort studies indicating periodontal disease inhibition with non steroidal anti-inflammatory drugs. Waite et al[9] have noticed lower gingival index and shallower pocket depth in patients who are on non steroidal anti-inflammatory drugs for arthritis and ankylosing spondylitis compared to individuals not taking non steroidal anti-inflammatory drugs. In a cohort study 75 patients who are on aspirin and indomethacin [10] for arthritis had significantly fewer sites with proximal bone loss as compared to healthy controls. Jeffcoat et al [11] have reported less alveolar bone loss in patients who are on systemic flurbiprofen (15mg bid) in compared to placebo treatment. Systemic Naproxen [12] along with mechanical debridement in rapidly progressing periodontitis has shown significant reduction in inflammatory periodontal condition. In another study, mechanical scaling and acetyl salicylic acid resulted in synergistic reduction in gingival inflammation, probing pocket depth and clinical attachment loss. The non steroidal anti-inflammatory drugs suffer from serious disadvantages that essentially preclude their use as an adjunctive treatment for periodontal disease. Daily administration of these drugs for extended period of time is associated with significant unwanted effects including gastrointestinal problems, hemorrhage, renal and hepatic impairments. Once the drugs are withdrawn there is going to be a rebounding effect resulting in severe tissue damage.

2.2 Cytokine Inhibitors:

Cytokines means, "cell protein". They transmit information from cell to cell via autocrine and paracrine mechanism. The cytokines can be proinflammatory or anti-inflammatory. IL-1 β and TNF- α are known for their role in periodontal inflammation and tissue destruction. Studies have shown that the GCF levels of these cytokines increases in periodontal disease [13]. Following specific binding to the receptors on the cell surfaces, IL-1 β and TNF- α trigger intercellular signaling events and catabolic cell behavior. To counterbalance the catabolic activity of cytokines and to maintain homeostasis, both IL-1 β and TNF- α have endogenous inhibitors. In addition, the IL-1b level increases rapidly in experimental gingivitis [14,15], and IL-1b is produced by a variety of cells in the periodontal area, including monocytes, gingival fibroblasts[16], and PMNs [17]. IL-1b regulates the fibroblast phenotype [18], including increases in collagenase production[19,20] and decreases in collagen production from gingival fibroblasts[21]. The IL-1 receptor antagonist which has a structure related to IL-1, compete with IL-1 to bind with its receptors without triggering signal transduction. These endogenous inhibitors also occur in soluble form as competitive antagonist of IL-1 and TNF α . This receptor antagonist has been used successfully in many inflammatory conditions to modulate the host response. In non human primates, ligature induced periodontitis progression has been partially inhibited. However, the use of cytokines antagonist to treat human disease has to be evaluated further, because of many unresolved issues [22]. Importance among them are systemic implication associated with altering cytokines levels on tissue homeostasis and the method of administering and maintaining cytokine levels for a long time. Anti-inflammatory cytokines IL-4, IL-10, IL-1 [23] and transforming growth factor β (TGF- β) have been implicated in suppressing destructive inflammatory response. IL-4 and IL-10 target macrophages and inhibit the release of IL-1, TNF- α and reactive oxygen species. IL-4 is also known to induce apoptosis-programmed cell death that reduces the number of infiltrated macrophages. IL-4 is also shown to up regulate production of IL-1 receptor antagonist.

Exogenous IL-4 has been administered to modulate the inflammatory response in experimental arthritis and it has been observed that IL-4 reduces the inflammatory response [24]. Recombinant IL-11 is reported to inhibit TNF α , IL-1 and nitric oxide production and reduce disease progression in ligature induced periodontal canine model [25]. Granulocyte colony stimulating factor (G-CSF) has been reported in a 15 year long study in improving periodontal condition in cases of cyclic neutropenia [26].

2.3 Bone sparing agents:

The therapeutic strategies used to prevent and manage osteoporosis, osteopenia may also inhibit periodontal bone loss. Bisphosphonates are non biodegradable analogue of pyrophosphate, that have high affinity for calcium phosphate crystals and that inhibit osteoclast activity [27]. These compounds also appear to inhibit MMP activity through a mechanism that involves chelation of cations. They are used successfully in

the clinical management of osteoporosis. One of these drugs Alendronate has been evaluated in ligature induced periodontitis model and assessed for changes in bone density [28]. Alendronate inhibited the loss of bone density in these models. However, minimal effects were demonstrated on clinical parameter. Studies using topical administration of bisphosphonates have reported reduction in bone and root resorption associated with orthodontic tooth movement [29,30]. However, further randomized control longitudinal studies are required to evaluate the effectiveness as well as side effects of these drugs in the treatment of the periodontal disease.

2.4 Lipoxin, resolvins and protectins:

Various inflammatory mediators like arachidonic acid metabolites and cytokines are released as host defense during periodontal infection to counteract the bacteria. But the recent concept of host bacterial interactions suggest that more than the destruction by bacterial virulence, it is the failure to resolve and heal is a cause of local tissue destruction. Resolution is a biological pathway of restoring homeostasis. Proresolving lipid mediators [31] are a family of novel endogenous chemical mediators, including lipoxins, resolvins and protectins. They are actively biosynthesized in the resolution phase of inflammation and are potent agonists that control the duration and magnitude of inflammation. Lipoxins (lipoxygenase interaction products) were the first proresolving mediators to be recognized. There are three major pathways for lipoxins generation. The first pathway involves the insertion of molecular oxygen to carbon 15 of arachidonic acid and implies the involvement of 15 lipoxygenase (15-LO). The products of 15-LO in epithelial cells and monocytes serve as substrates for neutrophil 5-LO and lead to the formation of trihydroxytetraenes, lipoxins A₄. The second pathway involves interactions that occur within the vasculature between 5-lipoxygenase, present in myeloid cells and 12-lipoxygenase present in platelets.

The 5-LO leukotriene A₄ is rapidly taken up by platelets and converted via 12-LO-dependent mechanism into lipoxins. The third major pathway for lipoxins generation involves aspirin and the actions of cyclo-oxygenase (COX-2) and 5-LO. Endothelial and epithelial cells express COX-2 in response to diverse stimuli such as cytokines, hypoxia and bacterial infections [32]. Aspirin acetylates COX-2 and switches its catalytic activity for the conversion of arachidonic acid (C_{20:4}) to 15R-hydroxyeicosatetraenoic acid (15R-HETE) in lieu of prostanoid biosynthesis. 15R-HETE is released from endothelial and epithelial cells and transformed by leukocyte 5-LO, via transcellular routes, to 15-epimer lipoxins or aspirin triggered lipoxins (ATLs), which is more stable and longer acting than the endogenously produced lipoxins. Kim et al [33] in a human study assessed the short term effects (7 days) of the systemic administration of two different concentrations of Aspirin (81 and 325mg/day, by mouth) on clinical periodontal parameters (probing depth, plaque index and bleeding on probing) and GCF levels of 15-epi-LXA₄, LXA₄, LTB₄, PGE₂, IL-6 and IL-1 β in a sample of naturally occurring gingivitis patients using ELISA. They reported that the concentration of 15-epi-LXA₄ was ~ 500-fold higher than the concentration of naturally occurring LXA₄. They observed a negative trend between 15-epi-LXA₄ and PGE₂ (though it was not statistically significant) and concluded that subjects who possessed higher sensitivity to the aspirin mediator anti-inflammatory effects produced more 15-epi-LXA₄. In an animal study Pouliot M et al [34] investigated the impact of LXA₄ and ATL in TNF- α initiated PMN responses in vitro and in vivo using LX analogs that are metabolically more stable. They reported that at nanomolecular levels, ATL and LXA₄ analogs blocked TNF- α stimulated IL-1 β release by isolate human PMN in vitro. In addition when these analogs were added to murine air pouches dramatically inhibited TNF- α stimulated leukocyte trafficking in vivo and concomitantly stimulated IL-4 in pouch exudates. New classes of proresolving lipid mediators have been identified in addition to endogenously derived lipoxins and aspirin triggered lipoxins. Such lipid molecules include resolvins and protectins which are derived from omega 3 poly unsaturated fatty acids, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). EPA is metabolized to resolvin E series and DHA gives rise to resolvin D series and protectins.

2.5 MMP inhibitors:

MMPs are family of gene dependent enzymes play a key role in tissue destruction of periodontal disease. MMPs are secreted by majority of cell types in periodontium including macrophages, neutrophils, fibroblasts, keratinocytes, endothelial cells & osteoclasts. These enzymes are capable of degrading a variety of extracellular matrix molecules including collagens [35]. In healthy tissues MMPs are produced primarily by fibroblast & are concern with the maintenance of periodontal connective tissue. During inflammation there will be up regulation of MMP gene transcription resulting in increased production of MMPs. Regulation of MMP activity involves specific, endogenous tissue inhibitors of MMPs (TIMP) & α macro globulins. They form complexes with active MMPs & their latent precursors, thereby inactivating their action. In periodontal disease MMP-8 & MMP-9 is reported to rise in tissue and GCF [36]. Tetracyclines have the ability to down regulate the expression of MMPs. Today doxycyclin, a tetracycline is the only systemic host response modulator specifically indicated as an adjunctive treatment for periodontitis, and it is approved by US food and drug

administrations for this purpose. Clinical studies have shown that 20mg dose of doxycycline hydrate taken twice daily for period of 3-9 months as an adjunct to root surface instrumentation has shown clinical significant improvement in probing depths & attachment levels compared to patients treated by root surface instrumentation alone. These data demonstrate a very clear benefit of sub antimicrobial dose doxycycline when combined with appropriate and effective conventional therapy. Golub et al[37] showed that a 2 month regimen of SDD significantly decreased both the level of bone type collagen breakdown products and MMP-8 and MMP-13 enzyme levels in chronic periodontitis patients. There is evidence that adjunctive 20 mg sub-antimicrobial dose doxycycline, taken twice daily over 9 months, is beneficial in the treatment of chronic periodontitis.

III. CONCLUSION

It is now understood that, though the primary etiologic factor for periodontal disease is bacteria, the excessive host inflammatory response and / or inadequate resolution of inflammation is critical to the pathogenesis of periodontitis. A class shift is now apparent in management of periodontal disease with the introduction of proresolving compounds such as lipoxins, and their more stable bioactive form ATLs. More recently resolvins and protectins have shown that stimulating resolution pathways go a long way in restoring tissue homeostasis and periodontal healing. To this day only MMP inhibitor, Sub Antimicrobial Low Dose Doxycycline (SDD) has been permitted by FDA in treatment of periodontitis as an adjunctive to conventional therapy. There are many molecules which are being studied and may emerge in future as effective agents of host modulation and treatment of periodontal disease and this direction of research promise a paradigm shift in drug invention and therapeutics for periodontal disease.

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