Review Article

Host modulation therapy- An innovative paradigm in dentistry

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ABSTRACT

Inflammation comprises a series of events that leads to a host response against trauma and microbial invasion, resulting in liquefaction of surrounding tissues to prevent microbial metastasis, and eventually to healing of injured tissue compartments. Thus, by definition, the host response involves not only the mechanisms of defence but also processes of repair of damage that occurs by the direct effect of invaders or trauma or host systems. Periodontal diseases are inflammatory processes in which microbial etiologic factors induce a series of host responses that mediate an inflammatory cascade of events in an attempt to protect and heal the periodontal tissues. The adjunctive use of host modulation therapy can enhance therapeutic responses, slow the progression of the disease, and allow for more predictable management of patients, particularly in those patients at increased risk caused by factors beyond the reach of conventional therapeutic approaches.

Key words: Host modulation, NSAIDs, Bisphosphonates, immune-inflammatory response, MMPs

INTRODUCTION

Periodontal disease is a chronic bacterial infection of the periodontium affecting the tissues surrounding and supporting the teeth. Periodontal disease progression is associated with subgingival bacterial colonization and biofilm formation resulting in inflammation of soft tissues, degradation of collagen fibers, as well as resorption of the alveolar bone there by weakening the periodontium surrounding the teeth. Since the fundamental role of microorganisms in its etiology was systematically demonstrated some forty years ago, research efforts have long focused on identifying the pathogenic microorganisms and their virulence factors [1]. To treat periodontal diseases as an infectious disease, numerous therapeutic strategies aimed at eradication of periodontal pathogens have been studied over the years, including local and systemic delivery of antimicrobial and antibiotic agents.

In the current paradigm of periodontal disease, specific periodontal pathogens are necessary for disease initiation. However, the extent and severity of tissue destruction are largely dependent on the nature of the host-microbial interactions. These interactions are dynamic, since both the microbial composition of the dental biofilm and the competency of host immune responses can vary, in the same individual, over time.

This concept was developed in parallel to the advances on the understanding of the immune response, and research on periodontal disease has been emphasizing mechanisms of host-microbial interactions to understand the disease process, as well as for the development of novel therapeutic strategies [2]. The importance of host-microbial interactions is reinforced by epidemiological data indicating different susceptibilities to periodontal disease among individuals, in spite of the long-term presence of oral biofilm [3-5]. Other studies demonstrating increased susceptibility and greater severity of periodontal disease in individuals with impaired immune response due to systemic conditions also indicate the significance of the host response to the bacterial challenge [6].

Host can be “the organism from which a parasite obtains its nourishment,” or in the transplantation of the tissue, “the individual who receives the graft.” Modulation is “the alteration of function or status of something in response to a stimulus or an altered chemical or physical environment”. Host modulation therapy (HMT) is a treatment concept that aims to reduce tissue destruction and stabilize or even regenerate the periodontium by modifying or down regulating destructive aspects of the host response and up regulating protective or regenerative responses [7].

HISTORICAL ASPECT

By the 1930s, it was generally believed that all bacteria on the teeth could cause periodontal disease and that the amount of bacteria accumulated was directly related to the incidence and severity of disease. In 1973 Socransky and his collegues found that sites of advanced bone loss harbored an anaerobic microaerophilic Gram-negative flora that was totally different from the primarily facultative Gram-positive organisms found at adjacent healthy sites. In 1976, Page and Schroeder summarized the pathogenesis of periodontitis with regard to the major histopathologic events that occurred from health to advanced disease with the description of four lesions: the initial lesion, the early lesion, the established lesion, and the advanced lesion. [8] These important findings lead to the birth of the concept of Host Modulation which aimed to control the destructive aspects of the host response in periodontal disease without compromising the host immunity. HMT was first introduced to dentistry by Ray C Williams and Lorne Golub (1990).

PATHOGENESIS OF PERIODONTITIS

Various models of disease, has been putforth to describe the etiopathogenesis of periodontal disease which includes,

Linear model depicting the principal etiologic role for bacteria in the initiation and progression of periodontal disease [9].

Circa model emphasizing a central role for the host immunoinflammatory response in the clinical development and progression of periodontal disease [10].

In 1997, non-linear model demonstrating various factors contributing to the pathogenesis of periodontitis based on pathways and processes known at the time. The model implied that there were a range of host responses and a range of clinical expressions of disease that were primarily determined by genetic and environmental factors that modified the host response. Each combination of genetic variations and environmental factors may define a specific gene expression pattern [10].

Biologic systems model (Kornman KS 2008). (Figure-1)

A biologic systems model (Figure-1) representing the pathogenesis of periodontitis may be defined by the bacterial components, environmental factors, and host–genetic variations associated with disease. Level A depicts the biologic mechanisms involved in immunoinflammatory responses and in bone and connective tissue metabolism, and level B depicts the observable clinical parameters and biomarkers. In level B, the products produced by different microbial complexes are represented by arrays. These products activate the immunoinflammatory mechanisms, which subsequently influence the behavior of bone and connective tissue metabolism.

Fig.1: Biologic systems model

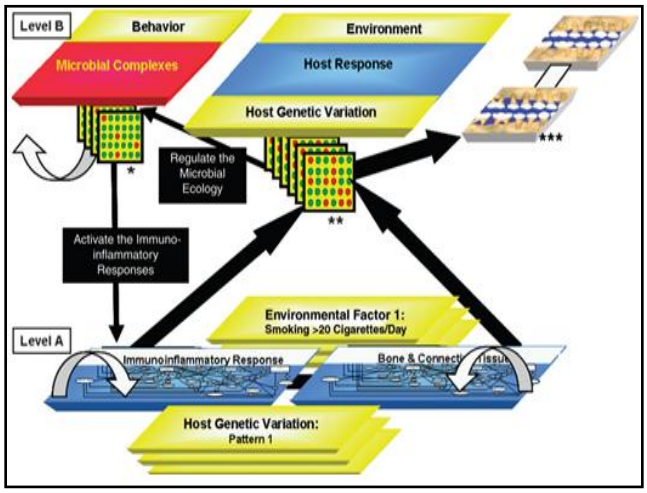
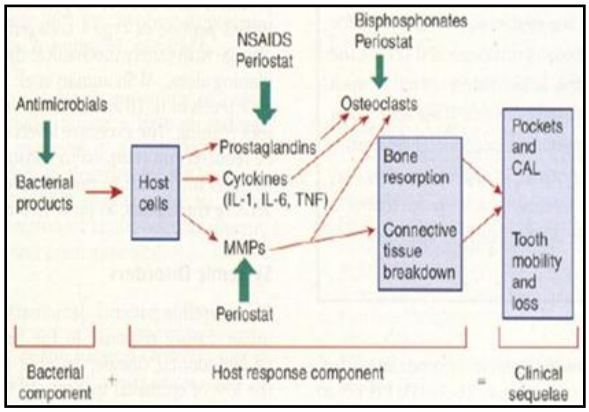


Fig. 2: Potential target for host modulation



In the past, therapeutic efforts were focused on the mechanical or chemotherapeutic removal of bacterial flora. It has been recognized that genetic (IL-1 composite phenotype), environmental (smoking) and acquired (diabetes) risk factors can increase a patient's susceptibility to developing periodontitis. For such individuals, extreme bacterial control or host modulation along with bacterial control seem to be an appropriate strategy.

"There are compelling data from studies in animals and humans indicating that pharmacologic agents that modulate host response may be efficacious in slowing down the progression of periodontitis" (Williams RC, 1990) [11].

HOST MODULATION THERAPY (HMT)

Periodontal therapy basically constitutes the non surgical and surgical therapeutic procedures. Changing paradigm in clinical research lead to the newer treatment approach of host modulation therapy. HMT is a treatment concept that aims to reduce tissue destruction and stabilize or even regenerate the periodontium by modifying or down regulating destructive aspects of the host response and upregulating protective or regenerative response. These are systemically or locally delivered pharmaceuticals that are prescribed as part of periodontal therapy and used as adjuncts to conventional periodontal therapy.

Rationale of HMT is treating the host side of the host-bacterial interaction. The purpose of host modulation therapy is to restore the balance of proinflammatory or destructive mediators and anti-inflammatory or protective mediators to that seen in healthy individuals [12].

Manipulation of the immune response to suppress unwanted reactions is desirable in conditions such as autoimmunity, allergy, or graft rejection. It is also required in the case of infectious disease to stimulate the protective processes. Strategies to achieve these goals are collectively referred to as modulation of host response and provide a novel concept in treatment. Compared to other modes of treatment against infection, host response modulation potentially has fewer side-effects, is not invasive, and does not require complicated application methods [13, 14].

Various methods of HMT have been developed to block or modify the pathways of periodontitis, as follows,

- Inhibition of arachidonic acid metabolite: NSAIDs
- Inhibition of matrix metalloproteinase (MMPs): Tetracyclines
- Modulation of bone metabolism: Bisphosphonates
- Regulation of immune and inflammatory response: IL1 and TNF-α receptor antagonist, NO_2 inhibition, vaccination, Infusion/ supplementary anti-inflammatory cytokines

INHIBITION OF ARACHIDONIC ACID METABOLITE: THROUGH NSAIDS

Von Euler (1939) first described a characteristic vasoactive fatty acids from human seminal vesicle fluid capable of decreasing blood pressure in rabbits and was named ''prostaglandin'' because it was assumed to originate from the prostate gland.

One of the pathway involved in periodontal disease pathogenesis is the synthesis and release of prostaglandins and other arachidonic acid (AA or ARA) metabolites within periodontal tissues. AA can be metabolized via the cycloxygenase (CO) or lipoxygenase (LO) pathways [15].

Nonsteroidal anti-inflammatory drugs inhibit the formation of prostaglandins, including prostaglandin E2, which is produced by a variety of resident and infiltrating cell types in the periodontium in response to lipopolysaccharide. Various NSAIDs which are under research for HMT are indomethacin, flurbiprofen, naproxen, sulindac, meloxicam, ketoprofen and ibuprofen.

Daily administration for extended periods of time (years rather than months) is necessary for periodontal benefits to become apparent. Prolonged NSAIDs intake leading to the suppression of renal prostaglandin synthesis may result in increased sodium retention, reduced renal blood flow and eventually renal failure, damage to the gastrointestinal tract, Hemorrhage, may affect cardiovascular risks through various mechanisms and has rebound effect. While our understanding of the role of COX-2 in the pathogenesis of periodontitis suggests that inhibition of COX-2 might be a desirable target for therapeutic intervention, serious adverse effects of current formulations preclude their use as an adjunct to periodontal therapy [16].

ANTI- PROTEINASE BLOCKING OF MATRIX METALLOPROTEINASES (MMP'S)

Matrix Metallo Proteinases (MMPs) belong to a group of Zn dependent and calcium requiring endopeptidases, which play a central role in many biological processes like embryogenesis, normal tissue remodeling, wound healing, and angiogenesis, and in diseases such as atheroma, arthritis, cancer, and tissue ulceration [17].

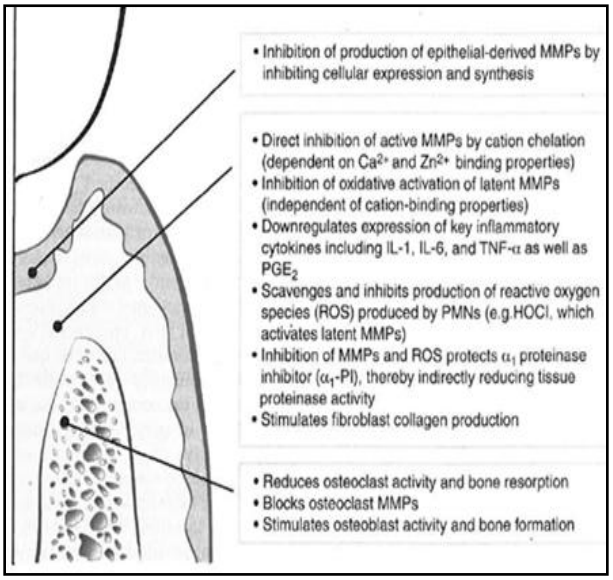
Tissue inhibitors of metalloproteinases (TIMPs) are important controlling factors in the actions of matrix

metalloproteinases, and tissue destruction in disease processes often correlates with an imbalance of matrix metalloproteinases over tissue inhibitors of metalloproteinases. They are of two types:

1. Endogenous inhibitors examples are TIMPs and α-2 Macroglobulin: TIMP's probably control MMP activities pericellularly whereas α2-macroglobulin functions in body fluids. During inflammation, however, α2-macroglobulin escapes the vasculature and also functions in the extracellular matrix.
2. Exogenous: (synthetic inhibitors)
   Exogenous inhibitors include zinc and calcium chelating agents, phosphorous containing peptides, sulfur based inhibitors, hydroxamic acid inhibitors.

Tetracycline is a broad spectrum antimicrobial agent which, apart from their antimicrobial activity also exhibit anticollagenase activity by inhibiting matrix metalloproteinase's. It is one of the effective agents used in host modulation therapy. In addition to its antimicrobial activity, this group of compounds has the capability of inhibiting the activities of neutrophils, osteoclasts, and matrix metalloproteinases, thereby working as an anti-inflammatory agent that inhibits bone destruction.

Fig. 3: Mechanisms of tetracycline in prevention of connective tissue breakdown



Tetracyclines prevent connective tissue breakdown by various mechanisms as shown in figure-3. [18]

Clinical research on the use of tetracycline has lead to the invention of various modifications such as chemically modified tetracycline and Sub antimicrobial dose doxycycline with their merits and demerits in clinical application.

CHEMICALLY MODIFIED TETRACYCLINE'S

Presently, it is accepted that destruction of supporting periodontal tissues is primarily related to host derived enzymes, cytokines and inflammatory mediators. This has led to increased interest in the development of agents. Chemically modified tetracycline's (CMTs) are one such group of drugs which have been viewed as potential host modulating agents. Currently ten CMTs are available but their clinical application is under research.

Sub antimicrobial dose of tetracycline (SDD)

Doxycycline tends to be highly concentrated in GCF at levels 5-10 times greater than serum and show substantivity as they bind to the tooth structure and are slowly released as still active agents. To avoid antibiotic resistance a low dose of 20 mg twice daily was introduced, which was shown, after 2 weeks, to inhibit collagenase activity by 60–80% in the gingival tissues and crevicular fluid of patients with chronic periodontitis [19, 20]. SDD is currently the only FDA approved systemically administered HMT indicated specifically in the treatment of periodontitis. It was previously called LDD and is currently marketed as Periostat.

BISPHOSPHONATES(BPS)

Bisphosphonates were introduced in 1990 for the treatment of osteoporosis and osteolytic tumors. They are second group of drugs under investigation for their ability to modulate the bone loss and prevent bone resorption. They are primarily used to treat hypercalcemia, Paget's disease and osteoporosis. These drugs are non-biodegradable analogs of pyrophosphate that have a high affinity for calcium phosphate crystals and inhibit osteoclast activity [21]. BPs are drugs that suppress bone turnover, primarily through effects on osteoclasts, and are commonly prescribed to prevent skeletal-related events in malignancy and for benign bone diseases such as osteoporosis [22]. Given their affinity to bind to hydroxyapatite crystals and prevent their growth and dissolution and to their ability to increase osteoblast differentiation and inhibit osteoclast recruitment and activity, bisphosphonates are widely used in the management of systemic metabolic bone disorders

such as tumour-induced hypercalcaemia, osteoporosis and Paget's disease [23].

Mechanism of action

Several modes of action have been investigated including BP mediated inhibition of the development of osteoclasts, induction of osteoclastic apoptosis, reduction of activity, prevention of the development of osteoclasts from hematopoietic precursors, and stimulation of production of an osteoclast inhibitory factor. It has also been shown that the BP alendronate caused a rise inintracellular calcium levels in an osteoclast-like cell line. This finding is of great interest since it could suggest the presence of a receptor for BPs on osteoclasts. The proven efficacy of BPs to inhibit osteoclastic bone resorption has led to their use in the management of periodontal diseases as a host modulating factor in the perspective of preventing the alveolar bone loss. BPs could be used in conjunction with regenerative therapies, and even for stimulation of bone growth into and around endosseous implants [24, 25].

Classification: Bisphosphonates are classifies as,

- **Non-nitrogenousn Non-*N*-containing bisphosphonates**: Etidronate (Didronel) - 1 (potency relative to that of etidronate)
  Clodronate
  Tiludronate

Non-nitrogenous bisphosphonates are metabolized in the cell to compounds that replace the terminal pyrophosphate moiety of ATP, forming a nonfunctional molecule that competes with adenosine triphosphate (ATP) in the cellular energy metabolism. The osteoclast initiates apoptosis and dies, leading to an overall decrease in the breakdown of bone.

- **Nitrogenous *N*-containing bisphosphonates**:
  Pamidronate (APD, Aredia)
  Neridronate Olpadronate
  Alendronate (Fosamax)
  Ibandronate (Boniva)
  Risedronate (Actonel)
  Zoledronate (Zometa, Aclasta)

Nitrogenous bisphosphonates act on bone metabolism by binding and blocking the enzyme essential for connecting some small proteins to the cell membrane. These proteins can affect osteoclastogenesis, cell survival, and cytoskeletal dynamics. In particular, the cytoskeleton is vital for maintaining the "ruffled border" that is required for contact between a resorbing osteoclast and a bone surface.

Long-term use may suppress bone turnover and compromise healing of even physiologic micro-injuries within bone. Clinically, ONJ is essentially exposed bone in the maxilla or mandible that does not heal within 8 weeks of identification. Patients with previous dental problems might have a higher risk of osteonecrosis of the jaw [26].

Mode of administration of bisphosphonates: Oral and intravenous route has been utilized to administration of BPs . The risk of esophageal irritation places special requirements on how this oral drug is taken. The patient should take the drug only upon rising for the day with 8 oz. of water, and stand, walk, or sit, and remain fasting for 30–45 minutes afterwards (preferably 1–2 hours), then eat breakfast. No other medications should be taken for this time. Lying down or reclining after taking the drug and prior to eating breakfast may cause gastroesophageal reflux and esophageal irritation.

ANTI-CYTOKINE THERAPY

Cytokines are defined as regulatory proteins controlling the survival, growth, differentiation and functions of cells. Cytokines are produced transiently at generally low concentrations, act and are degraded in a local environment. This is documented by the fact that cytokine-producing cells are often physically located immediately adjacent to the responding cells. Moreover, the responding cell destroys the cytokine that it responds to in the process of receptor-mediated endocytosis. Cytokines function as a network, are produced by different cell types and share overlapping features. This phenomenon is called biological redundancy. While very few biological responses are mediated by only one cytokine, many responses can be achieved by several different cytokines [27].

Down regulation of cytokines is mainly brought about by three mechanisms:

i. cytokine receptor antagonist: Cytokine receptor antagonists bind to the receptor present on the target cell and prevent the cytokine from binding to the target cell. Therefore, there is no activation of the target cell.

ii. Soluble cytokine receptors: Soluble cytokine receptors are derived from the proteolytic cleavage of the extracellular domain of cell-bound cytokine receptors. Soluble receptors can be found in blood

and extracellular fluid. They cause: 1.Downregulation- Soluble receptors bind to the cytokine in solution and prevent signaling. 2. Transactivation-Soluble receptors bind the cytokine and docks on otherwise non-responsive cells and activate them. Out of all these soluble receptors (sIL-1R, sTNF-RI, sTNF-RII, sIL-6R) only sIL-6R is an agonist in function, the rest are all antagonist in function and bring about the down regulation of cytokines [28].

iii. Anti-cytokine antibodies: are also antagonist in function and them lower down the levels of cytokines. (Anti IL-6 Ab, Anti TNF- Ab)

Commercially Available Preparations anti-cytokines [29]

Infliximab (Remicade, Monoclonal Ab to TNF-α)
Etanercept (Enbrel) (soluble form of TNF receptor)
Anakinra (Kineret) (Ril-1RA) :It is an interleukin-1 (IL-1) receptor antagonist.
However, the harsh enzymatic environment in periodontal lesions may destroy the soluble cytokine antagonists prior to their peak activity, which may necessitate more frequent administration of the active agents to the defects.

NO INHIBITORS

`NO is one of the few gaseous signaling molecules known and is additionally exceptional due to the fact that it is a radical gas. It is a key vertebrate biological messenger, playing a role in a variety of biological processes. Nitric oxide, known as the 'endothelium-derived relaxing factor', or 'EDRF', is biosynthesized endogenously from L-arginine, oxygen and NADPH by various nitric oxide synthase enzymes. In animal experimental periodontitis, the use of pharmacological inhibitors of NO and poly ADP ribose polymerase (PARP) synthases reduces periodontal attachment and bone loss [30, 31].

Antagonists to Cell Adhesion Molecules

P-selectin is a cell adhesion molecule (CAM) on the surfaces of activated endothelial cells, which line the inner surface of blood vessels, and activated platelets. P-selectin plays an essential role in the initial recruitment of leukocytes to the site of injury during inflammation. Several E-selectin and intercellular adhesion molecule-1 inhibitors such as tepoxalin, sodium cromoglycate are under research to be applied in host modulation therapy clinically [32, 33].

Inhibitors to RANK/RANKL Interaction

RANKL is a member of the tumor necrosis factor (TNF) cytokine family which is a ligand for osteoprotegerin and functions as a key factor for osteoclast differentiation and activation. RANKL also has a function in the immune system, where it is expressed by T helper cells and is thought to be involved in dendritic cell maturation. This protein was shown to be a dendritic cell survival factor and is involved in the regulation of T cell-dependent immune response. T cell activation was reported to induce expression of this gene and lead to an increase of osteoclastogenesis and bone loss. Expression of the RANKL gene in osteoblasts/stromal cells is enhanced by:VitaminD3 , PTH, IL-1, IL-6, IL- 17 , TNF-α , BMP-2 , PGE2 [34].

RESOLVINS

The term resolvins (resolution-phase interaction products synthesized from omega 3 PUFA – EPA (Eicosapantaenoic acid) and DHA (Docosahexaenoic acid)) was first introduced to signify that the new structures were endogenous mediators possessing potent anti-inflammatory and immunomodulatory actions demonstrated in the nanogram dose range in vivo. Hence, named resolvins E and D respectively. These include reducing neutrophil traffic and pro-inflammatory cytokines, as well as lowering the magnitude of the inflammatory response in vivo. The terms protectin and neuroprotectin (when generated in neural tissues) were introduced given the anti-inflammatory as well as the protective actions of the DHA-derived mediator NPD1/PD1 in neural systems, stroke and Alzheimer's disease.[91]18R E Series Resolvins from EPA, 17S and 17 R D Series Resolvins from DHA are under study for their application clinically [35].

STATINS

Recent studies suggest that statins possess antiinflammatory properties owing to their ability to reduce the number of inflammatory cells in atherosclerotic plaques. The mechanisms have yet to be fully elucidated but may involve inhibition of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), which are involved in the recruitment of inflammatory cells [26].

CONCLUSION

The adjunctive use of host modulation therapy can enhance therapeutic responses, slow the progression

of the disease, and allow for more predictable management of patients, particularly in those patients at increased risk caused by factors beyond the reach of conventional therapeutic approaches. Clinical trials concerning non-steroidal anti-inflammatory drugs support the basic hypothesis that inhibition of arachidonic acid metabolites slow alveolar bone loss and this approach may be an adjunct to conventional mechanical treatment. In the future a range of HMTs targeting different aspects of the destructive surge of breakdown episodes in the periodontal tissues are likely to be developed as adjunctive treatments for periodontitis. The further development of these agents will permit dentists to treat specific aspects of the underlying biochemical basis for periodontal disease.

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