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HOST MODULATION THERAPY: A REVIEW

Medical Science

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KEYWORDS

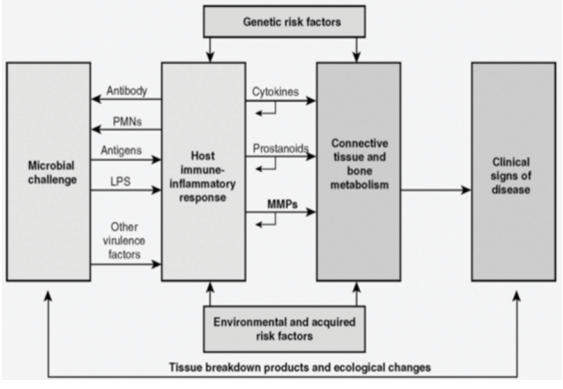
INTRODUCTION

Host response refers to the response of the body against invading or threatening factors. The concept of host modulation was first introduced to dentistry by Williams and Golub. Periodontitis is defined as "inflammatory disease of the supporting structures of teeth caused by specific micro-organisms resulting in progressive destruction of periodontal ligament and alveolar bone with pocket formation, recession or both". Periodontitis is a multi-factorial disease involving bacterial biofilm and the generation of an inflammatory response, including the production of cytokines eicosanoids and matrix metalloproteinases[1]. Microbial plaque has been implicated to be the primary etiological factor in chronic inflammatory periodontal disease.

Host modulation therapy is a treatment concept that aims to reduce tissue destruction and stabilize or even regenerate the periodontium by modifying or downregulating destructive aspects of host response and upregulating protective or regenerative responses. HMT's offer the opportunity for modulating or reducing this destruction by treating aspects of the chronic inflammatory response. HMT's do not "switch off" normal defense mechanisms or inflammation, they ameliorate excessive or pathologically elevated inflammatory processes to enhance the opportunities for wound healing and periodontal stability[2]. HMT's can also modulate osteoclast and osteoblast function but should not impact normal tissue turnover. HMT's are systemically or locally delivered pharmaceuticals that are prescribed as part of periodontal therapy and are used as adjuncts to conventional periodontal treatment's such as scaling and root planning (SRP) and surgery. A variety of different drugs classes have been evaluated as host modulation agents, including the NSAID's,bisphosphonates ,tetracyclines , enamel matrix proteins, growth factor and bone morphogenetic proteins[3].

GENERAL REVIEW

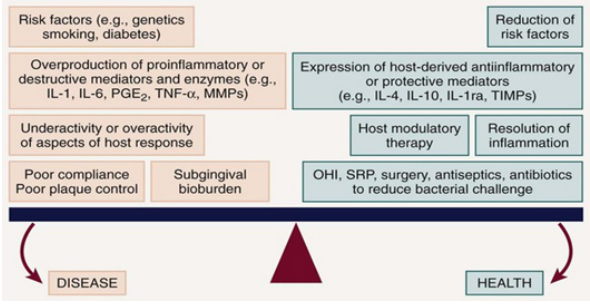
Schematic illustration of the pathogenesis of periodontitis



The Microbial challenge presented by subgingival plaque bacteria results in an upregulated host immune-inflammatory response in the periodontal tissue that is characterized by the excessive production of inflammatory cytokines, prostanoides and enzymes, including matrix metalloproteinases[4]. Theses proinflammatory mediators are responsible for the majority of periodontal breakdown that occurs, leading to the clinical signs and symptoms of periodontitis.The process is modified by environmental and acquired risk factors and genetic susceptibility.

Thus, a host immune-inflammatory response is established in the gingival tissues, and the clinical signs of gingivitis develop as the tissues become more edematous and erythematous. 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 (chronic gingivitis) may persist indefinitely. In disease-susceptible individuals, however, inflammatory events extend apically and laterally to involve deeper connective tissues and alveolar bone[5].

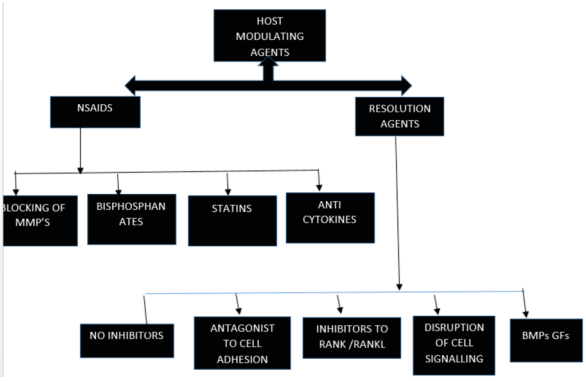
The Periodontal Balance



The balance between periodontal breakdown and periodontal stability is tipped towards disease by risk factors, excessive production of inflammatory cytokines and enzymes (IL-1 and IL-6, interlukins-1 and -6, PGE2, prostaglandins E2, TNF-α, MMP's, matrix metalloproteinases) , underactivity or over activity of aspects of the immune-inflammatory host response, poor compliance and a pathogenic microflora[6]. The balance can be tipped toward health by risk factor modification, upregulation and restoration of balance between naturally occurring inhibitors of inflammation (IL-4, IL-10 tissue TIMP's tissue inhibitors of metalloproteinases), HMT (host modulatory therapy) and antibacterial treatment such as OHI, SRP, surgery, antiseptic and antibiotics.[7]

The use of chemotherapeutic agents or drugs specifically designed to treat periodontal diseases is emerging to aid as a risk reduction strategy. Intervention in periodontal disease can now include HMT as one of the available adjunctive treatment options. The term adjunctive is meant to imply "in addition to conventional therapies" or "in addition to other established therapies." For the management of periodontal diseases, conventional approaches were initially mechanical in nature, that is, surgery, as well as scaling and root planning (SRP)[8]. Initially, adjunctive therapies were solely antimicrobial such as the use of antiseptics and antibiotics (local and/or systemic). New adjunctive approaches involve modulation of the host response. Researchers are also investigating HMTs, which aim to modify or reduce destructive aspects of the host response so that the immune-inflammatory response to plaque is less damaging to the periodontal tissues. Removal of plaque by SRP targets one aspect of the pathogenic process by reducing the bacterial burden and therefore the antigenic challenge that drives the inflammatory response in the host tissues. However, the bacterial challenge is never completely eliminated after SRP, and recolonization by bacterial species occurs. HMTs offer the potential for downregulating destructive aspects and upregulating protective aspects of the host response so that, in combination with conventional treatments to reduce the bacterial burden, the balance between health (resolution of inflammation and wound healing) and disease progression (continued proinflammatory events) is tipped in the direction of a healing response[9].

HOST MODULATING AGENTS[10]



1. Antiproteinase blocking of matrix metalloproteinases

An important group of proteolytic enzymes present in the periodontal tissues is formed by the matrix metalloproteinases, which include collagenases, gelatinases and metalloelastases. Matrix metalloproteinase-8(MMP-8) is the predominant type of collagenase found in diseased periodontal tissues and initiates the degradation of collagen. Its reduction was observed after mechanical periodontal therapy, a sub antimicrobial dose of doxycycline further suppressed matrix metalloproteinase-8 levels, confirming the +host-modulation effect of a subantimicrobial dose of doxycycline. Matrix metalloproteinase-13 and cross-linked carboxytreminal telopeptide of Type I collagen(ICTP) are related to bone resorption and their decrease after a subantimicrobial dose of doxycycline therapy Lee et al 20046 is consistent with the ability of a subantimicrobial dose of doxycycline to function as a bone-sparing agent[11].

2. Nonsteroidal anti-inflammatory drugs

Another family of pharmacological agents that has been well studied as an inhibitor of the host response in periodontal disease is represented by the nonsteroidal anti-inflammatory drugs (NSAIDs). These agents have been shown to prevent prostanoid formation. In this process, arachidonic acid liberated from membrane phospholipids of cells after tissue damage or stimulus is metabolically transformed, via cyclooxygenase or lipooxygenase pathways, in compounds with potent biological activities. The cyclooxygenase enzymes are recognized to have two isoforms: cyclooxygenase 1 (COX-1), which is a constitutive enzyme present in most cells, and cyclooxygenase 2 (COX-2), which is inducible and is present in cells involved in the inflammatory processes. The cyclooxygenase pathway produces prostaglandins, prostacyclin and thromboxane, called prostanoids[12]. In periodontal diseases, prostaglandin E2 has been extensively correlated with inflammation and bone resorption Offenbacher et al 19938. Suppression of osteoclast differentiation, as measured by decreased osteoclast numbers and concomitant decreased alveolar bone resorption, is the most frequent sequela following systemic or local delivery of NSAIDs.

3. Bone sparing drugs

Alveolar bone resorption is the principal sequel and the cause of tooth loss in patients afflicted by periodontal disease. The use of bone-sparing drugs that inhibit alveolar bone resorption is another field in host-modulation therapy. Bisphosphonates are a class of drugs structurally similar to pyrophosphate, a component of human metabolism. It binds to the hydroxyapatite crystals of bone and prevents their dissolution by interfering with osteoclasts function through a variety of direct and indirect mechanisms. The antiresorptive properties of bisphosphonates change according to their side chains. In periodontics, their use was proposed for a diagnostic and therapeutic approach in order to detect changes of metabolic activities at bone. As a therapeutic agent, bisphosphonates were shown to reduce alveolar bone loss and increase mineral density, significant in periodontally diseased tissues suggesting the potential of inhibitors of NF-κB in managing periodontitis. Despite the encouraging therapeutic results, further long-term studies are warranted to determine the relative risk–benefit ratio of bisphosphonate therapy[13].

4. Proinflammatory cytokine inhibition

The immune system is a dynamic equilibrium, with inflammatory responses mediated by T-helper type 1 cells, IL-1b, interferon-Ic (IFN-c), and tumor necrosis factor-α (TNF-α) being counterbalanced by endogenous anti-inflammatory responses mediated by T regulatory type 1 cell, T-helper type 3 cells, IL-4, IL-10, and transforming growth factor-b (TGF-b). These pathways regulate homeostatic stability of immune system. The inflammatory disease process is characterized by domination of proinflammatory cytokine mediators. Within these parameters, blocking production of proinflammatory cytokines through soluble antagonists of IL-1 and TNF-α is a potentially therapeutic approach to modulate the host's immune response. Proinflammatory cytokines play a decisive role in the generation of the inflammatory and destructive responses in rheumatoid arthritis. The results indicate a primary role for TNF-α in the mediation of altered mucosal immune function. Clinical responses in patients treated with a single infusion of anti- TNF-α persisted for as long as 1 year. The prolonged period of clinical benefit shows that the effect of short-term tumor necrosis factor-a elimination remained long after the monoclonal antibody had been cleared.

5. Lipoxins and resolvins:

It has been further proposed that lipoxin generation and its relationship to prostaglandin E2 and leukotriene-B4 can be an important marker for the pathogenesis of periodontal disease. Activated neutrophils from localized aggressive periodontitis patients produce lipoxins, whereas healthy neutrophils do not. Lipoxin analogs were also shown to rapidly promote macrophage phagocytosis of apoptotic neutrophil in a thioglycolate-induced peritonitis, supporting a role for lipoxins as proresolution signals in inflammation.

These newly described molecules, termed resolvins(resolution phase interaction products) and docosatrienes, display potent anti-inflammatory and immunoregulatory properties. Unlike other products identified earlier from omega-3 fatty acids that are similar in structure to eicosanoids but less potent or devoid of bioactions, the resolvins, docosatrienes, and neuroprotectins evoke potent biological actions in vitro and in vivo.

6. Disruption of cell signaling pathways for treating periodontitis

Strategies for preventing cell activation seek to inhibit the intracellular transduction of signals produced when ligands bind to their membrane receptors. Signal transduction pathways are activated by cytokines, bacterial proteins, lipopolysaccharide, or environmental stress. These stimuli act on receptors that are coupled to the signal transduction pathways, causing activation of transcription factors and other proteins that control the production of cytokines, proteases and many other compounds involved in the inflammatory process. Other signal transduction pathways of fundamental importance in inflammation, involve immunoreceptors like integrins, selectins, G-protein coupled receptors and steroid hormone receptors. Therapeutic strategies have been directed towards many of these major signalling pathways, notably MAPK and NF-κB. When a ligand binds to its membrane receptor such as lipopolysaccharide-binding toll-like receptor- 4, the receptor undergoes a conformational change resulting in phosphorylation of the receptor itself or of a receptor-associated enzyme.

7. Protein antagonist strategies in the treatment of periodontal diseases:

The RANKL/RANK interaction is responsible for differentiation and maturation of osteoclast precursor cells to activate osteoclasts. Osteoprotegerin acts as a decoy receptor, expressed by osteoblastic cells, which binds to RANKL and inhibits osteoclast development.. The RANKL/osteoprotegerin ratio was found to be significantly increased in the crevicular fluid of patients with periodontitis as compared to healthy patients[14]. In summary, based on pre-clinical animal studies and on preliminary human clinical studies, the osteoprotegerin/ RANKL/RANK axis is a new target for the treatment of destructive periodontal disease and other bone resorption-related diseases. Further studies are necessary to determine the most efficacious therapeutic approach on that molecular interaction.

8. Tumor necrosis factor antagonists to block inflammatory diseases

TNF-α, an inflammatory cytokine that is released by activated monocytes, macrophages and T lymphocytes, promotes inflammatory responses that are important in the pathogenesis of rheumatoid arthritis and periodontal diseases. Reduction of the bacteria and their metabolic by-products through periodontal therapy also results in a decrease in both IL-1 and TNF. Thus, improvement in clinical parameters is paralleled by a decrease in these cytokines, suggesting their significance in the pathogenesis of periodontitis. Blocking the activity

of pro-inflammatory cytokines may be a beneficial therapeutic modality for periodontitis. Thus, gene transfer of TNFR antagonists may offer a more efficient mode of delivery of disease- controlling agents to the periodontal structures and hence blocking of tumor necrosis factor pathways offers significant potential in blocking disease progression. Additional research, both in regards to basic mechanisms as well as clinical studies, are necessary before it can be said that there are causative links between RA and periodontitis.

DISCUSSION

The pathogenesis of periodontal disease is not completely understood but it is well established that it is an infectious disease and that the host immune and inflammatory response to the microbial challenge mediates tissue destruction. Based on this view, the therapeutic strategies for the treatment of periodontal disease have been directed towards two different and complementary paths: antimicrobial therapy and host modulation. Considering that the primary etiology of the disease are bacteria in the plaque and their products, mechanical and chemical approaches to reduce the presence of periodontopathogens in the plaque have been largely used in the treatment of periodontal patients.

Recently, a better understanding of the participation of host immune-inflammatory mediators in the disease progression has increased the investigation of the use of modulating agents as an adjunctive therapy to the periodontal treatment. Inhibition or blockade of proteolytic enzymes, pro-inflammatory mediators and of osteoclast activity has been the focus of these agents, which has led to encouraging results in preclinical and clinical studies. More specifically, four categories of host-modulating agents have been investigated in the periodontal therapy: antiproteinases represented by tetracyclines; anti-inflammatory drugs; bone-sparing drugs represented by antiresorptive agents such as bisphosphonates and immunomodulatory drugs.

According to Keith L. et al high-risk patient population, such as patients with diabetes or refractory periodontal disease, had benefited from systemic matrix metalloproteinase administration particularly SDD when used in combination with SRP or surgical therapy. The potential to down-regulate mediators of inflammation associated with periodontal tissue destruction was investigated during experimental periodontitis in beagle dogs over an 8-week period. The findings indicated that subcutaneous injection of recombinant human IL-11 was able to alter periodontal disease progression measured by changes in attachment level and radiographic bone height. These studies suggest that the conversion from gingivitis to periodontitis is directly associated with the movement of an inflammatory infiltrate toward alveolar bone, and that this activity is at least partially dependent upon IL-1 and/or tumor necrosis factor [15].

.A meta-analysis Presented by Reddy et al in 2003 of six selected clinical studies comparing a long term systemic subantimicrobial dose of doxycycline (20 mg b.i.d. doxycycline) with placebo control in periodontal patients. A statistically significant adjunctive benefit on clinical attachment level and probing depth was found when a subantimicrobial dose of doxycycline was used in combination with scaling and root planning, in both 4–6 mm and >7 mm pocket depth categories. No significant adverse effects were reported in any of the studies. Overall, these studies confirmed the clinical benefits of a subantimicrobial dose of doxycycline therapy observed by previous studies.

External neutralization of inappropriate inflammatory cytokines is a therapeutic strategy that has been attempted in many chronic inflammatory conditions, mostly targeting tumor necrosis factor-α, using either monoclonal antibodies or modified receptor proteins.

Although, host modulation therapy in the field of periodontics is still limited to few FDA approved agents like subantimicrobial dose of doxycycline and locally administered emdogain, future is not very far when other well-known drugs used by physicians for antiresorptive therapy will soon be available for treatment of periodontal diseases. Currently, approved drugs are adjunct to conventional periodontal therapy which 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.

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