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# Host modulation therapy in the treatment of periodontal disease

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## Abstract

Periodontitis is multifactorial infectious disease of the supporting structures of the teeth associated with dysbiosis of the periodontal microbiome which affects 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. The tissue damage and alveolar bone resorption characteristics of the disease are due to destructive innate host response to pathogenic subgingival biofilms. The underlying biological mechanisms of this response are characterized by the production of host derived inflammatory mediators including cytokines and lipid mediators by neutrophils, monocytes, lymphocytes and fibroblasts. Antimicrobial therapies both local and systemic administration along with mechanical debridement is one of the mainstay in periodontal treatment strategies, which answered microbial etiology of periodontal diseases. Host Modulation Therapy 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 host response and up regulating protective or regenerative responses. The purpose of this review is to focus on various host modulation therapies as adjunt to mechanical debridement for treatment of periodontitis.

**Keywords:** Periodontitis, Host Modulation, Bisphosphonates, Nonsteroidal Anti-Inflammatory Drugs, Tetracycline, Cytokines

## Introduction

Periodontitis is a chronic inflammatory disease associated with dysbiosis of the periodontal microbiome which affects the supporting structures of the teeth (periodontium).[1,2] Bacteria present in the dental plaque initiate gingival inflammation and the host immune inflammatory response produces cytokines, chemokines, and matrix-degrading enzymes enzymes (e.g. hyaluronidases, collagenases, proteases) in an attempt to eliminate periodontal pathogens.

Inflammation appears to be an important ecological change as tissue destruction releases nutrients (for

example, degraded collagen, haem-containing compounds, sources of amino acids and iron) favoring the growth of gram negative and proteolytic species of bacteria. , termed inflammophilic pathobionts, creating a "dysbiotic" microbiome.[1,3,4]

In Periodontal health the microbial challenge is controlled by host inflammatory and immune response,the inflammation is resolved and tissue healing ensues.[5]

However , in individuals who are susceptible to periodontitis, the host immune response is ineffective and dysregulated . A poorly controlled host immune response does not control the dysbiotic insult and a nonresolving inflammation sets in that sustains dysbiotic microbiota and is the main cause of periodontal tissue destruction. The host response can be influenced by genetic ,environmental(e.g. smoking, diet, and stress) and systemic health status in either protective or destructive direction.[3]

Mechanical removal of plaque and its bacterial contents by nonsurgical and surgical techniques is considered as a 'gold standard' treatment for periodontitis.[6] The objective of this treatment is to reduce the chronic challenge presented by the subgingival plaque bacteria, such that inflammatory responses in the periodontal tissues are reduced[7]. However, some patients do not respond predictably to routine reduction of the bacterial challenge and may benefit from control of specific host mediators as an adjunctive therapy in addition to bacterial control.[8]

Host modulation therapy refers to a treatment concept in which drug therapies are used as an adjunct to conventional periodontal treatment to ameliorate destructive aspects of the host inflammatory response.[9]

Host modulation is indirectly an antimicrobial approach as inflammation control should limit the nutrient supply (inflammatory tissue breakdown products) that sustains dysbiosis, thereby restoring ecological conditions that favour microbiotas compatible with periodontal health.[10]

Host modulatory therapies could include systemically or locally delivered pharmaceuticals that are prescribed as adjuncts to other forms of periodontal treatment.[7]

**Systemically Administered Agents**

**MMP Inhibitors**

Matrix metalloproteinases (MMPs) are group of proteolytic enzymes primarily responsible for the destruction of the connective tissue constituents (e.g., collagen fibers and proteoglycan ground substance) in the gingiva, periodontal ligament and alveolar bone during the development of periodontitis.[11]

In 1985, tetracyclines were discovered to have anticollagenolytic activity and were proposed as a host-modulating agent for periodontal treatment.[11]

The Tetracycline(TC) family, which includes doxycycline, consists of broad spectrum bacteriostatic antibiotics that act by inhibiting bacterial protein synthesis.[12]

**Subantimicrobial Dose Doxycycline**

Studies demonstrated that doxycycline was the most potent tetracycline in the inhibition of collagenolytic activities and the use of a low or subantimicrobial dose of doxycycline was shown to be efficient in inhibiting mammalian collagenase activity without developing antibiotic resistance.[11] This novel, "low-dose" formulation (better known as sub-antimicrobial-dose doxycycline,or SDD) reduced the side-effects of systemic antibiotic-dose TC therapy but retained the ability to suppress the tissue-destructive MMPs, to decrease inflammatory mediators(e.g., interleukin-1ß), and to reduce diagnostic biomarkers of bone resorption in the periodontal pocket.[13]

SDD is a 20-mg dose of doxycycline (Periostat) that is FDA approved and ADA accepted. It is indicated as an adjunct to SRP in the treatment of chronic periodontitis.[14]

Several clinical studies conducted to assess the benefits

of the subantimicrobial dose of doxycycline in the treatment of the periodontal disease have demonstrated that SDD as an adjunctive therapy to scaling and root planing is effective in improving the standard parameters of periodontal disease severity, including probing depth, clinical attachment levels, bleeding-on-probing and radiologic assessment of alveolar bone loss.[15]

**Chemically-Modified Tetracycline(CMT)**

CMT are synthesized by removal of a chemical side-chain on the TC molecule ,the dimethylamino group at carbon-4,which eliminates it's antibacterial activity but it retains or even enhances its MMP-inhibitory properties This allows the drug to be used as a non-antibiotic TC at both low and high oral doses.A series of chemically-modified TCs have been developed. [13]

A human study testing chemically modified tetracycline-3 on patients with chronic periodontitis showed modest evidence of efficacy in reducing interleukin-1beta and matrix metalloproteinase-8 in gingival crevicular fluid samples.[16]

**Chemically Modified Curcumins (CMCs)**

CMCs are a group of novel anticollagenolytic compounds synthesized from curcumin, the key ingredient of the natural spice, turmeric. Curcumin is a diphenolic compounds with matrix metalloproteinase-inhibiting active site, the cation-binding beta-diketone moiety.[16]

Since circumin is insoluble and poorly absorbed via oral route, a series of chemically modified curcumins were developed to increase its bioavailability and efficacy.[17] Preliminary cell culture studies on human monocytes stimulated with microbial lipopolysaccharide/endotoxin demonstrated that chemically modified curcumin-2.24 is a potent inhibitor of matrix metalloproteinase-9.Monocyte cell culture studies also demostrated that CMC 2.24 is capable of suppressing the inflammatory mediators interleukin-1beta, interleukin-6, prostaglandin E2, and monocyte chemoattractant protein-1, as well as matrix metalloproteinase-9 secretion.

In animal models of experimental periodontitis CMC 2.24 significantly inhibited alveolar bone loss and markedly reduced inflammatory cytokines and matrix metalloproteinases in the gingival tissues, decreased bone loss, and decreased activation of p65 nuclear factor kappa-light-chain-enhancer of activated B cells and p38 mitogen-activated protein kinase pathways.[16]

**NSAIDS**

The NSAIDs constitute a heterogeneous group of drugs with analgesic, antipyretic and antiinflammatory properties.[18]NSAIDs inhibit cyclooxygenase (COX) – the enzyme responsible for the transformation of arachidonic acid into prostaglandins including PGE2 , a proinflammatory mediator associated with alveolar bone resorption.[19] Various studies have shown that systemic flurbiprofen , indomethacin , naproxen and others, administered daily for periods of up to 3 years,significantly slowed the rate of alveolar bone loss compared to patients treated with placebo.[20]

However long term use of NSAIDS is associated with various side effects like gastrointestinal alterations(dyspepsia), cardiovascular complications(acute MI), increase in bleeding tendency and kidney toxicity.[18]

**Bisphosphonates**

Bisphosphonates are the chemically stable derivatives of inorganic pyrophosphate and have a very high affinity for bone mineral because they bind to hydroxyapatite crystals.[21] Due to their ability to adsorb to bone mineral in vivo bisphosphonates are delivered to the to sites of active bone remodelling, where they are potent inhibitors of bone resorption mediated by osteoclasts. Bisphosphonates inhibit osteoclast-mediated bone resorption by several mechanisms, depending on the chemical structure of the bisphosphonate and the concentration that is achieved in

the bone microenvironment. The most important route of action is the inhibition of osteoclast function by inducing osteoclast apoptosis.For this reason, bisphosphonates have become the most important class of drugs used to treat diseases involving excessive osteoclast activity, such as Paget's disease, tumor-associated bone disease, and postmenopausal osteoporosis.[22]Because of the above mentioned properties bisphosphonates have been used in the management of experimental periodontitis in animal models yielding favourable results.[23,24]

Human studies that assessed the effect of bisphosphonates as an adjunctive agent to scaling and root planing in periodontal treatment have found significant clinical improvement when compared with placebo, including: probing depth reduction, clinical attachment gain, bleeding on probing reduction , alveolar bone gain and increase in bone mineral density

.Osteonecrosis of the jaw(ONJ) is a serious complication associated with long term use of bisphosphonates.[11]

**Anticytokine Therapy**

Periodontal bacteria trigger the host immune response which causes release of inflammatory mediators and cytokines in the periodontal tissues.Cytokines are peptide mediators responsible for cell signaling and communication. Functions of cytokines vary to include the control of cell proliferation, cell differentiation, immune responses, and inflammatory responsesThe failure to stop this inflammation leads to expansion of the inflammation to include the alveolar bone as well as the periodontal soft tissues. A large network of cytokines such as IL-1β, IL-6, TNF-α, and RANKL. plays a critical role in the pathogenesis of periodontitis leading to soft tissue destruction and bone resorption.[25]

Antagonists to specific host mediators such as IL-1 and TNF may provide a potential treatment modality to combat the disease process.

In nonhuman primate model of experimental periodontitis,inhibitors of two prominent pro-inflammatory cytokines, interleukin-1 (IL-1) and tumor necrosis factor (TNF) reduced the inflammatory cell infiltrate that forms close to bone ,reduced periodontal bone loss and attachment loss.[26]

The effect of TNF antagonist etanercept, which inhibits TNF activity by competitively binding to it and preventing interactions with its cell surface receptors was observed in a rat model of periodontitis.The study demonstrated that treatment with etanercept attenuates TNF-a activity, the infiltration of neutrophils, cell apoptosis, the iNOS, nitrotyrosine formation and the injury of gingivomucosal tissues.[27] A recent systematic review and meta-analysis were conducted of studies to determine the relative effect of anti-rheumatic agents on levels of periodontal inflammation and inflammatory biomarkers in RA patients with periodontitis. Besides other antirheumatic drugs, the effect of various anticytokine drugs like infliximab (monoclonal antibody to tumor necrosis factor), etanercept (a soluble form of tumor necrosis factor receptor), and anakinra (an interleukin-1 receptor antagonist) was also observed.The authors concluded that there is insufficient evidence to determine whether traditional anti-rheumatic agents are beneficial in controlling periodontitis.

Potential side effects associated with anticytokine therapy include increased risk of infection, reemergence of latent TB and malignancy.[28]

**Disruption of Cell Signaling Pathways**

The host response in periodontitis is characterized by high levels of proinflammatory mediators Cytokines and bacterial components activate many signal transduction pathways during the course of periodontitis. These stimuli act on receptors that are coupled to the signal transduction pathways, causing activation of transcription factors and other proteins that control of cytokines, proteases and

many other compounds involved in the inflammatory process. Inhibition of signal transduction pathways would be expected to abolish cell activation by cytokines or other stimuli and the production of pro-inflammatory cytokines.[11]

The advantage of this approach is that expression of various inflammatory mediators requires activation of a limited number of these signaling pathways.[29] The most important signal transduction pathways in periodontal disease include the mitogen activated protein kinase (MAPK), nuclear factor kappa B (NFκB) and janus tyrosine kinase-signal transducer and activator of transcription (JAK/STAT).[11]

**MAPK pathway**

The threemain sub-families of MAPKs are extracellular-regulated kinases (ERK-1/-2), c-Jun N-terminal activated kinases (JNK) and p38.

Inhibitors targeting p38α MAPK pathway have been developed and preclinical and clinical data suggest that they exhibit antiinflammatory activity.Various pharmacological inhibitors capable of inhibiting p38 like SB203580, RWJ 67657, L-167307, VX-745, RPR200765A are known as cytokine suppressive anti-inflammatory drugs (CSAIDs).

Most of these protein kinase inhibitors interfere with phosphorylation or bindin the ATP binding site.RWJ 67657 has been tested in human volunteers who were given endotoxin. After a single oral dose of RWJ 67657, serum levels of the pro-inflammatory cytokines tumor necrosis factor-α, interleukin-6 and interleukin-8 were decreased by 90% compared with their plasma peak.

SD-282, the p38 inhibitor when used in rheumatoid arthritis and periodontitis models demonstrated strong anti-inflammatory action, including blockage of osteolysis.[30]

The specific JNK inhibitor, SP600125, not only diminishes the production of tumor necrosis factor-α, interferon- γ, interleukin-6, COX-2 and matrix metalloproteinase, but also decreases joint destruction in the adjuvant arthritis model.[11]

MAPKs play several physiological roles and suppression of these functions may leadto a number of problem. Reported adverse effects of p38 inhibitors include dizziness, gastrointestinal disturbances, and hepatotoxicity (i.e. cytochrome p450 interaction).[30]

**The NF-κB pathway**

NF-*κ*B consists of a family of transcription factors involved in many different pathways and has a central role in regulating the expression of a wide variety of genes that control both innate and adaptive immune responses. *In vitro* studies have established that both *P. gingivalis* and other periopathogenic bacteria can activate NF-*κ*B in periodontal tissues

Treatment modalities to prevent activation of NF-κB are based on proteasome inhibitors that block degradation of IκB and therefore the release of NF-*κ*B.

The first IKK inhibitor, BMS-345541, was evaluated recently in the collagen-induced arthritis model. When used in a preventive or therapeutic therapy, BMS-345541 improved disease activity scores and decreased both synovial inflammation and joint destruction.[11]

In a recent study topical application of NF-κB decoy oligodeoxynucleotides achieved protection against bone resorption by inhibiting osteoclast differentiationand activation in an experimental periodontitis in beagle dogs .[31]

General blockade of of NF-κB results in unwanted side effects as liver failure related tohepatocyte apoptosis.[29]

**Disruption of The Rankl / Rank/Osteoprotegerin Axis**

Alveolar bone resorption in periodontitis is caused by an increase in osteoclast activity. At the molecular level,

osteoclast activation is regulated by the interplay of three molecules that constitute the RANK/RANKL/OPG axis .The receptor activator of nuclear factor-κB (RANK) receptor is a transmembrane protein expressed in both mature osteoclasts and their progenitors, and its binding to its ligand (RANKL) determines osteoclast differentiation and activation.

Osteoprotegerin ligand (OPG-L) acts as a decoy receptor for RANKL and thus inhibits of osteoclast formation.[32]Human studies on patients with periodontitis revealed that the RANKL/osteoprotegerin ratio was increased in periodontitis when compared with healthy subjects, Also an increased concentration of RANKL and a decreased concentration of OPG were detected in GCF from patients with periodontitis.

In experimental periodontitis studies the use of osteoprotegerin as an inhibitor of bone alveolar destruction was investigated in mice orally infected with *A. actinomycemcomitans* . Inhibition of RANKL function with osteoprotegerin treatment significantly reduced the number of osteoclasts and the alveolar bone destruction.[11]

AMG 162(Denosumab), a specific fully human monoclonal antibody to RANKL, which prevents RANKL binding to RANK, has been developed and tested in a human clinical study. The results show that AMG 162 seems to specifically and profoundly inhibit osteoclastic bone resorption, as indicated by the changes observed in the biochemical markers, urinary NTX/creatinine, and serum NTX.[33]Denosumab has also been used in periodontitis model mice and results suggest that denosumab is a promising candidate to prevent alveolar bone destruction associated with periodontitis.[34]

**Nitric Oxide Synthase Inhibitors**

NOS Nitric oxide (NO) is a free radical produced by a group of isoenzymes collectively termed NO synthases (NOS). Inducible NOS (iNOS) iNOS is expressed in response to proinfammatory cytokines and bacterial lipopolysaccharide.Large NO concentrations produced by iNOS have a role in nonspecifc immunity, cytostatic/cytotoxic against invading microbial pathogens. Excessive NO or peroxynitrite formation (a toxic product of NO when combining with superoxide) by resident and infiltrating infammatory cells has been implicated pathogenesis of plaque-associated periodontal disease. The excessive local production of NO is beneficial by eliminating invading bacteria but on the other hand is detrimental by inducing inflammation and increased bone resorption.[35]

Treatment with drugs that inhibit iNOS or block the production of nitric oxide may have be used in the treatment of periodontal disease. In this regard iNOS inhibitors like isosorbid, aminoguanidine and Mercaptoethylguanidine have been used in experimental models of periodontitis yielding favourable results.[36]Nitric oxide synthase (NOS) inhibitors have demonstrated protective effects against bone resorption and inflammatory process in ligature-induced periodontitis in rats.[35]

**Specialized Proresolution Mediators**

Complete resolution of inflammation and its return to homeostasis is an active, agonist-mediated process orchestrated by specialized proresolving lipid mediators (SPMs) derived from essential fatty acids. These endogenous agonists of resolution pathways possess pro-resolving, anti-inflammatory, and antifibrotic as well as host-directed antimicrobial actions. Failure of resolution pathways result in uncontrolled inflammation and is involved in the pathogenesis of several chronic inflammatory diseases, including periodontal diseases.[37-39]

Specialized proresolving mediators (SPM) include lipoxins (LX), resolvins (Rv), protectins (PD), and maresins (MaR) .[39]

**Lipoxins**

Lipoxins (LXs) are endogenous proresolution lipid mediators derived from the metabolism of arachidonic acid. LXs are formed at sites of inflammation in a process of bidirectional, transcellular biosynthesis. The functions of lipoxins include decreasing PMN recruitment and release of reactive oxygen (ROS) species at sites of inflammation while promoting monocyte chemotaxis and nonphlogistic phagocytosis of apoptotic PMNs by macrophages(a process of efferocytosis).[40,41]

Aspirin plays an important role in the generation of lipoxins(15-epimeric lipoxins) known as Aspirin triggered lipoxins (ATL).ATL serve as potential endogenous anti-inflammatory signals or mediators of some of aspirin's beneficial actions.[42]

LX have short half life and are rapidly inactivated by monocytes and other cells *in vivo*.So a number of stable analogs have been synthesized that could resist this form of metabolism,maintain their structural integrity, and potentially enhance beneficial bioactions.[39]

**Resolvins**

The term resolvins (resolution-phase interaction products) refers to endogenous chemical mediators that are biosynthesized from the omega 3 fatty acids eicosapentaenoic (EPA) and docosahexaenioc acid(DHA) denoted E series (RvE) and D series (RvD) resolvins, respectively.

Resolvins can also be produced via COX-2–dependent reactions in the presence of aspirin, yielding ‘aspirin-triggered’ (AT) forms, as well as nonaspirin-dependent biosynthetic routes. Both RvD1 and AT-RvD1 limit PMN transendothelial migration and infiltration and regulate leukocyte trafficking to sites of inflammation as well as clearance of neutrophils from mucosal surfaces.[41]

**Protectins**

Protectins(PD) are synthesized from endogenous DHA and are named so because of their potent actions.Neuroprotectin(NPD1) is found in neural tissue and has potent immunomodulatory actions and neuroprotective actions.

Synthetic PD1 attenuates human neutrophil transmigration and infiltration.[38]

**Maresins (macrophage mediators in resolving inflammation)**

Maresins are produced by human macrophages (MF) from endogenous docosahexaenoic acid

(DHA). Maresin’s potent defining actions are limiting neutrophil [PMN]) infiltration as well as enhancing human macrophage uptake of apoptotic PMNs(efferocytosis).[44]

Because SPM enhance host defenses they may serve as agonists for new therapeutic approaches.[43]

Animal studies using experimental model of periodontitis have demonstrated that proresolution mediators can control inflammatory disease, reverse pathologic changes in the human microbiome and promote regeneration of bone and connective tissue attachment (periodontal ligament regeneration) to the tooth.[1]

**Statins**

Statins, also known as HMG-CoA reductase inhibitors, are a class of cholesterol lowering medications used in the management of cardiovascular disease. Apart from their lipid-lowering properties, statins possess pleiotropic effects related to their potential modulation of both innate and adaptative immune system and anti-inflammatory effects Moreover statins also have an inhibitory effects on proinflammatory cytokine production (Interferon-c, tumor necrosis factor-a, interleukin (IL-1b and IL-6) and on chemokines expression.[45]

Statins decrease the levels of metalloproteinases (MMPs) 1/2/8/9 and the inducible nitric oxide synthase (iNOS) enzyme. Moreover statins can promote the differentiation of osteoblasts by stimulating bone morphogenetic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF), helping to stimulate the formation of bone tissue.[46]

In a recent literature review authors concluded that statins(specifically locally delivered) can affect periodontal status, increasing the gain in clinical attachment and decreasing gingival bleeding, probing depth and the magnitude of bone defects.

The authors also considered topically delivered statins as an adjunct treatment for the prevention of periodontal disease in high-risk patients.[46]

**Nutrients**

Omega-3 (ω-3) polyunsaturated fatty acids (PUFAs), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have therapeutic anti-inflammatory and protective actions in inflammatory diseases including periodontitis. In a human study on healthy subjects with advanced chronic periodontitis the control group was treated with scaling and root planing (SRP) and a placebo, whereas the ω-3 group was treated with SRP followed by dietary supplementation of fish oil and aspirin daily.Statistical analyses demonstrated a significant reduction in probing depths and a significant attachment gain after 3 and 6 months in the ω-3 group compared to baseline and the control group . Salivary RANKL and MMP-8 levels showed significant reductions in the ω-3 group in response to treatment in comparison to the control group.[47]

**Teriparatide**

Teriparatide, which consists of the first 34 amino acids of parathyroid hormone, is an anabolic agent approved by the Food and Drug Administration for the treatment of osteoporosis. Multiple clinical trials have shown that teriparatide is associated with increased bone mineral density and a reduced risk of fractures in patients with osteoporosis. In a ligature model of periodontitis in rats intermittent PTH administration (40 μg/kg) was able to protect the tooth site from periodontitis-induced bone resorption. In addition, there was a significant reduction in the number of inflammatory cells at the marginal gingival area in sections obtained from animals receiving PTH compared with control animals.[48]In a human study Intermittent administration of teriparatide was associated with improved clinical outcomes, greater resolution of alveolar bone defects and accelerated osseous wound healing in the oral cavity.[49]

**Probiotics**

Probiotics are living microorganisms which, when administered in adequate amounts, confer a health benefit for the host. Probiotics' exact mechanism of action in the oral cavity isn't fully understood: there may be a direct interaction with the dental plaque, disrupting the biofilm owing to their antimicrobial products and competitive adhesion, and an indirect action as well, modulating the host's immune response.[50] Strains belonging to the Lactobacillus, Streptococcus and Bifidobacterium genera are most commonly investigated as regards probiotics.[51]

In a human study the application of oral treatment with tablets containing the probiotic strain of L. reuteri induces in most of the patients with chronic periodontitis a significant reduction in proinflammatory cytokine response and improvement of clinical parameters (SBI, PPD, CAL).[52] A recent systemic review concluded that Probiotics may provide a safe additional benefit to manual debridement in clinical and biochemical parameters of chronic periodontitis. Nevertheless, more studies are required with larger cohorts on dose, route of administration and strains of probiotics used.[50]

**Herbs**

Herbal extracts have been used in dentistry for reducing inflammation, as antimicrobial plaque agents, for preventing release of histamine and as antiseptics, antioxidants, antimicrobials, antifungals, antibacterials, antivirals and analgesics.[53]In an animal study Epigallocatechin gallate (EGCG), a major polyphenol in green tea suppressed the inflammatory bone resorption induced by LPS in mouse calvarial ex vivo cultures. EGCG acts on osteoblasts to suppress the LPS-induced PGE2 production by inhibiting the expression of COX-2, mPGES-1 and mPGES-2. EGCG also suppressed the expression of RANKL in osteoblasts.[54]Administration of ethanol extract of sumac (*Rhus coriaria* L.) reduced periodontal inflammation, RANKL expression, alveolar bone loss, TOS and OSI levels and increased OPG expression in an experimental periodontitis study in rats.[55]

**Sirtuins**

The sirtuin family comprises a class of Nicotinamide adenine dinucleotide ((NAD(+))-dependent enzymes that have known deacetylase activity.[56] Seven sirtuin isoforms have been identified in humans (Sirt1–7) which differ in their subcellular localization, as a result their substrate preferences and interacting partners and thus, their role in cellular processes However, because of their deacylation activity, the nuclear sirtuins (sirtuins 1, 2, 6, and 7) in particular have been the focus of efficacy studies in several inflammatory diseases. Since sirtuin activation, inhibition, and modulation are involved in several relevant metabolic reactions, related to diseases like type 2 diabetes, the aging process, and inflammation, they constitute an important target for therapeutic intervention.[57]

**WNT Signaling Pathway**

The Wnt signaling pathway is a vital and evolutionarily conserved pathway that regulates growth, development and homeostasis of the organism, and controls cell fate such as proliferation, differentiation, canceration, and apoptosis.[58,59]

The Wingless/integrase-1 (Wnt) family of proteins is involved in various essential functions, including embryonic and postnatal bone formation.[60,61] Wnt signaling pathways play significant roles in immunity and inflammation and abnormal Wnt signaling is implicated in a variety of diseases, for example, bone disorders and metabolic disorders. Wnt signal is regulated by several molecules like members of the dickkopf (DKK) and secreted frizzled-related protein(sFRP) family, Wnt inhibitory factor 1, and sclerostin (Sost).[59,60]

Dickkopf 1 (DKK1) and sclerostin are Wnt signaling inhibitors whose expressions are markedly increased in experimental periodontitis and studies demonstrated that activating the Wnt signaling by systematically administration of sclerostin antibody (SAB) in combination with DKK1 antibody (DAB) reversed mandibular bone loss and enhanced alveolar process healing in estrogen-deficient ovariectomized rats. 3The dual inhibition of sclerostin and DKK-1 using bispecific antibodies may be an effective therapy to ameliorate alveolar bone loss in periodontitis.[61]

Secreted frizzled-related proteins (sFRPs) are a family of five secreted glycoproteins that have been identified as possible negative modulators of the Wnt signal transduction pathway.[62]

The interaction of Wnt proteins with Fz(Frizzled) receptors is inhibited by secreted frizzled-related proteins (sFRPs) either by interacting with Wnt proteins to prevent them from binding to Fz proteins(i.e.,act as decoy receptors) or by forming non-functional complexes with Fz proteins.[60,62]

Wnt5a and sFRP5 comprise a typical ligand/antagonist pair and studies have demonstrated an inverse relationship

in the expression of Wnt5a and sFRP5 in human periodontitis. Moreover treatment with sFRP5 blocked inflammation and bone loss mouse model of ligature-induced periodontitis.Therefore sFRP5 is likely a promising therapeutic agent in the management of periodontitis.[60]

**Locally Administered Agents**

**A number of host-modulating agents** can be applied locally as an adjunctive therapy for the management of periodontitis. Local application is easy, provides a high drug concentration and minimizes the systemic side effects.[63]

**NSAIDS**

Topical NSAIDs could be used to complement the therapy as an adjunct to resolve the inflammatory process and clinical signs of the chronic periodontitis. Human studies utilizing different forms of NSAIDS have reported a reduction of probing depth and gingival crevicular fluid $PGE_2$ levels.[64,65]

**Enamel Matrix Derivative (EMD)**

Enamel matrix derivative (EMD) in the form of a purified acid extract of proteins from pig enamel matrix (Emdogain®; Straumann AG, Basel, Switzerland) has been successfully employed to restore functional periodontal ligament, cementum and alveolar bone in patients with severe attachment loss. The biological effect of EMD is through stimulation of local growth factor secretion and cytokine expression in the treated tissues, inducing a regenerative process that mimics odontogenesis.[66]

A Cochrane review(2009) has shown that the application of EMD during surgery showed statistically significant improvements in PAL (1.1 mm) and PPD reduction (0.9 mm) when compared to a placebo or a control.[67]

A systematic review of the treatment of intrabony defects with EMD showed a significant additional gain in CAL of 1.30 mm compared with open-flap debridement, EDTA, or placebo.[68] In a prospective clinical study the EMD therapy yielded statistically significant gains in CAL and reductions in PD at 2 years, when compared with the preoperative data.[69]

**Platelet Derived Growth Factor**

Platelet-derived growth factor (PDGF) is a thoroughly studied growth factor and has broad wound healing activities in both hard and soft tissue.

Studies have demonstrated that PDGF is a potent chemotactic and mitogenic factor for gingival and periodontal ligament fibroblasts, cementoblasts and osteoblasts.A combination of purified recombinant human PDGF (rhPDGF) with synthetic ceramic matrices (beta-tricalcium phosphate [β-TCP]) has been approved by FDA and is used as a periodontal regenerative agent.[70,71]A large multicentre randomized clinical trial demonstrated that the use of rhPDGF-BB is safe and effective in the treatment of periodontal osseous defects. Treatment withrhPDGF-BB stimulated a significant increase in the rate of CAL gain, reduced gingival recession ,and improved bone fill as compared to a b-TCP bone substitute.[72]

**BONE Morphogenetic Protein**

BMPs are multifunctional cytokines belonging to the TGF-β superfamily. BMPs have a variety of functions involving tissue morphogenesis, regeneration, healing, and cell differentiation processes.They are also known to play a role in osteogenesis and chondrogenesis . These proteins are commercially available as INFUSE Bone Graft. It consists of a mix of two components: recombinant human bone morphogenetic protein-2 (rhBMP-2) placed on an absorbable collagen sponge. Many studies have demonstrated that BMPs promote the regeneration of bone and also periodontal tissues including alveolar bone, cementum, and PDL.[73-75]

**Bisphosphonates**

Because of the adverse effects associated with systemic bisphosphonate administration the topical use of BPs with a drug-delivery system methods have been proposed. The Animal studies have suggested topical application of bisphosphonates is effective for preventing alveolar bone loss in experimental periodontitis.[76,77]Topical application of a novel synthetic bisphosphonate TRK-530 has anti–bone-resorption, anti-inflammatory,and anti-calculogenic effects. [78]

**Hypochlorous Acid And Taurine-N-Monochloramine**

HOCl and TauCl are end-products of the PMN respiratory burst. They act synergistically and have antibacterial and anti inflammmatory properties. HOCl and TauCl modulate the inflammatory response and promote healing and repair by neutralization of proinflammatory cytokines and chemokines, direct neutralization of metalloproteinases and release activated growth factors.Based on above mentioned properties both compounds can be developed as host-modulating therapies for the treatment of periodontitis.[79,80]

**Cimetidine**

Cimetidine is a specific competitive his tamine( H2) receptor antagonist . cimetidine has a strong immuno modulating effect and it enhance host defenses and reduce inflammation by inhibition of suppressor T-cell function , an increase in interleukin-2 production, by inhibiting the formation of reactive oxygen inflammatory products.and enhancement of natural killer cell activity. Topical application of cimetidine in a rabbit periodontitis model resulted in prevention of inflammatory cell infiltration, connective-tissue destruction and bone loss.[81]

**Conclusion**

The purpose of host modulatory therapy is to restore the balance between, proinflammatory mediators and anti-inflammatory mediators and enzyme inhibitors.They can be systemically administered or locally delivered and used as adjuncts to scaling and root planning.Various host modulation therapies include chemically modified tetracyclines, nonsteroidal anti-inflammatory drugs, bisphosphonates and anti- inflammatory cytokines. The determination that periodontal tissue destruction is primarily due to the host response has created areas of research directed at altering an individual's reaction to the bacterial challenge.So it was concluded that various host modulatory therapies (HMT) can be employed to block pathways responsible for periodontal tissue breakdown. Host response modulation represents a significant step forward for clinicians as well as for patients to achieve long-term treatment objectives , such as prevention of tooth loss.

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