Host Modulation Therapy: An Overview

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Abstract

Host modulation therapy involves a wide array of therapeutic strategies directed towards modulation of host factors in order to prevent the initiation and progression of periodontal disease. Host modulation is one of the non-surgical periodontal therapeutic approaches employed nowadays as better compliance is often seen among the patients. These strategies are basically aiming at reduction of inflammatory mediators or inhibition of destructive enzymes etc. These approaches are much popular in recent times and employ various therapeutics to attain the same. This review enlists the various strategies and approaches in modulating the host for prevention of periodontal disease.

Keywords: *Host modulation therapy; non-surgical periodontal therapeutic approaches; periodontal disease.*

Introduction

It has been clear that bacteria with unique virulence factors contribute to the initiation of periodontal disease. Host derived enzymes and cytokines also play a major role in degradation of extracellular matrix and destruction of alveolar bone in periodontitis.(1) The bacterial insult activates host defense mechanisms, as result of inflammation and its mediators, leads to destruction of supporting structures of tooth.(2) This mechanism of tissue destruction allows the clinician to think of strategy to manipulate such host derived mechanisms for prevention and treatment of periodontal diseases.

Periodontitis is chronic inflammatory, poly-microbial disease affecting the periodontium.(3) Bacteria are considered as the primary causative agent, which subsequently trigger host response. One of the early inflammatory responses by host is diapedesis. If neutrophils able to combat and delineate the infection, the disease limits itself to gingiva, causing gingivitis.

When the pathogens breach the innate defense mechanism of the host and penetrate the host tissues, the disease of periodontitis sets in. This stimulates release of inflammatory mediators like cytokines which play an important role in combating the pathogens, and in turn also leads to degeneration of tissues. The periodontal tissues when destroyed can be clinically evident as pocket formation and alveolar bone loss.(4)

Risk Factors: Patient's risk factors determine the disease susceptibility of host. The rate of disease progression, its severity and treatment response varies with different individuals. The risk factors like heredity factors, hormonal changes, stress, smoking status, systemic diseases, nutritional deficiency, certain medications, increased occlusal load, local factors etc. play a significant role in determining disease susceptibility of an individual.

Host Modulation: Host is defined as the organism from which a parasite obtains its nourishment/in the

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transplantation of tissue, the individual who receives the graft. And **Modulation** is defined as the alteration of function or status of something in response to a stimulus.

Host modulation therapy demands the use of pharmacological agents designed specifically to aid in treatment and limit the initiation and progression of periodontal disease.[5]

It includes:

- Antimicrobial therapies that can be used to address changes in the microflora
- Host modulation therapy that can be used to address a host response consisting of excessive levels of enzymes, cytokines, prostanoids & excessive osteoclast function that may be related to risk factors.

The different strategies of Host Modulatory Therapies (HMT) to regulate or block the pathogenesis of periodontal disease include:

A. Regulation of immune and inflammatory responses:

1. immunization method
2. regulating ROS
3. regulating cytokines
4. others – NF kb modulators
   – integrin inhibitors

B. Regulation of arachidonic acid metabolities:

1. steroids
2. antioxidants
3. NSAIDs
4. lipoxins
5. triclosan

C. Regulation of excessive production of matrix metalloproteinases:

1. Tetracyclines
2. Hydroxamic peptides

D. Regulation of bone metabolism

1. Antiinflammatory agents
2. osteoprotegrin
3. anti RANKL
4. SERMs
5. bisphosphonates
6. anti integrins
7. CMTs

A. Regulation of Immune And Inflammatory Mechanisms:

1. **Immunization method:** Bacterial plaque is considered to be the causative factor for initiation and also plays an important role in periodontal disease progression. These antigens are potent mediator for producing antibodies in the host system. Thus, new method are developed like use of protective antibodies via immunization for preventing periodontal disease. [6]

Bacterial whole cells, its outer components and synthetic peptides are used as antigen for initiating immunization. The development of periodontal vaccines has been in boom but not successful due to the multi-factorial etiology of periodontal disease and microbial complexity of bio-films.

Identification of microbial species like *Porphyromonas gingivalis*, *Bacteroides forsythus* for initiating specific disease, is necessary for successful development of vaccines.

3. **Regulating Reactive Oxygen Species:** Reactive Oxygen Species are the molecules with one or more unpaired electrons. These are released in excess amount in the event of inflammation. Tissues get exposed to these free radicals and get destroyed. Hydrogen Peroxide and Hypochlorous acids are the oxygen metabolites released by neutrophils and macrophages, take part in tissue destruction. They cause depolymeraization of collagen, hyaluronan, and proteoglycans. However, these free radicals can be neutralized by providing anti-oxidants or inhibitors in abundance.

Nitric Oxide is considered as a free radical, synthesized by endothelial cells by NO synthases (NOS1/2/3), and is produced at higher concentrations in response to inflammatory stimuli. They cause lipid peroxydation, protein and DNA damage and stimulation of cytokine release.

Inhibitor of iNOS: Merkaptoalkyguanides are inhibitors of iNOS are found to decrease inflammation in animal models. They are found to block iNOS, scavenge

peroxynitrite and inhibit cyclo-oxygenase pathway.

3. **Regulating Cytokines:** Cytokines are defined as the chemical mediators of inflammation which are considered as regulatory proteins which involve in controlling cell proliferation, differentiation and specific function of cells. Their action can be paracrine, autocrine or endocrine in nature.

Microbial biofilm constituents stimulate the host to produce proinflammatory cytokines like IL-1b and TNF-α those contribute in connective tissue and alveolar bone destruction. These cytokines are present in diseased periodontal tissues and Gingival Crevicular Fluid (GCF).

The interplay of pro-inflammatory and anti-inflammatory cytokines decide the initiation and progression of periodontal disease. Cytokines which play a role in suppression of the destructive inflammatory response include IL-4, IL-10, IL-11 and TGF-β. [7]

4. **Others**

   a. NF-kβ inhibitors – pyrrolidine dithiocarbomate
      – proteosome inhibitors

   b. Integrin inhibitors – tepoxalin, sodium cromoglycate

B. Regulation of Arachidonic Acid (AA) CASCADE: The tissue damage leads to availability phospholipids which gets degraded by phospholipase A_2 and thereby results in production of free AA. These are further metabolized by two of the important patheways example, Cyclooxygenease (CO) or Lipoxygenase (LO) pathways.

Prostaglandins, prostacyclin and thromboxane, which are the final products of CO pathway and leukotrienes and other hydroxyl eicosatetraenoic acids of LO pathways play a vital role in inflammation.[8]

PGE2 and AA metabolites in increased levels are found in gingival crevicular fluid and periodontal tissues in patients with periodontal disease. Host modulation therapy can be achieved by modulating the release of these destructive products. NSAIDs is one of the approach by which these metabolites can be regulated.

1. **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) blocks cyclo-oxygenase pathways and reduce PGE2 synthesis leading to inhibition in progression of periodontal disease and further bone resorption.(8) Indomethacin, first proved the host modulatory effect by inhibiting the progression of periodontal disease in a ligature-induced canine periodontitis model.

NSAIDs can delivered both topically and systemically and have been proved efficacious in both forms for treatment of periodontal disease. The systemic delivery of Flurbiprofen has been found to have inhibitory effect on progression of periodontal disease. However, their systemic use counters few adverse effects like gasto-intestinal upset and heamorrhage.

The local application of NSAIDs is also a method to deliver these agents. NSAIDs are lipophilic and readily gets absorbed by the periodontal tissues. Few NSAIDs that are administered topically include ketorolac trimethamine rinse and S-ketoprofen dentrifice.

2. **Lipoxins:** Lipoxins are secreted by neutrophils and most commonly seen in elevated levels in patients suffering from aggressive periodontitis. Lipoxins are believed to be arachidonic acid derivatives formed by Lipooxygenase pathway and are potent inflammatory mediators. Lipoxins are also found to be secreted in increased quantities in gingival crevicular fluid.[9]

The approach in reducing the levels of Lipoxins would be beneficial in inhibiting the progression of periodontal disease by lowering down the inflammatory process or pathway.

4. **Triclosan:** Triclosan is an anti-inflammatory and anti bacterial agent. It is a non-ionic antimicrobial agent. Triclosan is believed to inhibits both cyclo-oxygenase and lipo-oxygenase pathways.

4. **Steroids:** Steroids are found to inhibit Phospolipase A2 enzyme by stimulating the excessive production of annexins/lipocortins. They stabilize the lysosomal membranes and suppress the cellular degranulation. Steroids like dexamethasone cause degradation of preexixting mRNAs for IL1β, TNFα thereby dampening PGE2 release.[10]

5. **Antioxidants:** Antioxidants like Vitamin C and E, Green tea catechins and other herbal products are believed to prevent oxidation of these arachidonic acid metabolites by molecular oxygen and subsequent hydrolysis to form PGE2.

C. Regulation of Matrix Metalloproteinases

(MMPS): MMPs are the enzymes which belong to the family of calcium and zinc dependant endopeptidases. They are secreted by neutrophils and macrophages, along with some resident cells like fibroblast, osteoblast, osteoclast, epithelial cells of periodontium.(11)

MMPs degrade the extracellular matrices like collagen, gelatin, proteoglycan, fibronectin at neutral PH levels. The pathogenesis of periodontal disease is directly proportional to the MMP activity. The bacterial plaque stimulates the resident cells of the periodontium, directly or indirectly, to release theses MMPs and thereby initiating connective tissue remodeling.

Polymorphonuclear leukocyte type collagenase (MMP-8) and gelatinase (MMP-9) are the most potent and are usually seen with increased activity during periodontal tissue destruction. In addition, MMP-13 (collagenase-3) is believed to be a mediator of bone resorption and cartilage destruction and has been identified in GCF from chronic periodontitis patients.

Some of the MMP inhibitors which could help in reducing the disease activity are as follows:

1. **Hydroxamic acid derivatives:** Galardin designed for topical use in non-healing corneal ulcers., Batimostat for breast cancer (parenterally administered) and Marimastat administered for cancer including ovarian, prostatic, pancreatic and gastrointestinal malignances, are the derivatives known to inhibit MMPs.

However, these derivatives may not have sufficient specificity to prevent unwanted toxicity, and includes adverse events including joint pain and stiffness.

2. **Tetracyclines:** Tetracycline belongs to the group of antibiotics which are most extensively investigated MMP inhibitors. Apart from the antimicrobial property, tetracycline appears to inhibit MMP activity drastically. Tetracyclines thereby inhibit extracellular matrix destruction by multiple non-antimicrobial mechanisms (e.g. chelation, inhibition of activation of pro-MMP molecules).(5)

Mechanism of action:

a. mediated by extracellular mechanisms:

- active MMP inhibition

- inhibition of oxidative activation of pro-MMPs

- disrupts activation by promoting excessive proteolysis of pro MMPs into inactive fragments

- inhibition of MMPs protects α1-PI

b. mediated by cellular regulation

- inhibits inflammatory cytokines, iNOS, PLA2, PGE2

- inhibits protein kinase C

C. mediated by pro- anabolic effects

- increases collagen production and bone formation

The reduced dose of doxycycline (20mg bid) is considered as one of the potent HMT agent. This low dosage of doxycycline may not exhibit antimicrobial effects, but can effectively lower MMP levels, hence, referred to as Sub-Antimicrobial Dose Doxycycline (SDD).

Chemically Modified Tetracyclines

CMT 1 – 4 dedimethyl aminotetracycline are also believed to inhibit MMP activities. CMTs 1,3, 6, 7, 8 are effective inhibitors of which CMT 3 is the most potent compound. CMTs 2 and 4 affects MMP8 but not MMP 13. CMT 5 is ineffective.

D. Modulation of Bone Remodelling: Bone is a dynamic tissue under constant remodeling with active formation and resorption. Disruption of balance in this leads to either increased bone formation as in osteopetrosis or increased bone resorption as in osteoporosis, osteopenia, periodontal disease etc.(8)

The effects of osteoporosis and periodontal disease predominantly after the age of 35 and have common risk factors that may interfere with healing (e.g. smoking and influence of disease or medications). Thus, therapeutic strategies used to prevent and manage osteoporosis and osteopenia may also inhibit periodontal bone loss.

1. **Bisphosphonates:** Bisphosphonates are known to manage osteoporosis in an effective way. The beneficial effects of bisphophonates are used nowadays for treatment of periodontal disease.

Bisphosphonates are non-biodegradable analogs of pyrophosphate. They have a high affinity for calcium phosphate crystals and that inhibit osteoclast activity. These compounds also appear to inhibit MMP activity through a mechanism that involves the chelation of cations.

They are classified into three generations of drugs:

First generation drugs with alkyl side chain: Etidronate

Second generation drugs with amino side chain: Alendronate. Pamidronate, zoledronate

Third generation drugs with cyclic side chains: Risedronate

Other drugs that can be used to modulate bone metabolism include,

2. Anti-inflammatory agents
3. Osteoprotegrin
4. Anti RANKL
5. Selective Estrogen Receptor Modulators (SERMs)
6. CMTs
7. Anti- integrins

Conclusion

The variety of known host modulation therapy helps clinicians to modulate the periodontal disease initiation and progression in an effective way. The use of these agents has led to avoid of advanced surgical approaches to treat such periodontal conditions. The prevention of periodontal disease at the host level is a promising strategy.

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