INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

www.ijabpt.com Volume-3, Issue-3, July-Sept-2012 Coden : IJABPT Copyrights@2012 ISSN : 0976-4550

Received: 15th May-2012 *Revised: 17th May-2012* *Accepted: 21st May-2012*

Review article

HOST MODULATION AND HOST MODULATING AGENTS IN PERIODONTAL THERAPY

[1]Dr. Amit Bhardwaj, MDS, Senior Lecturer, Department of Periodontics, SGT Dental College, Gurgaon, Haryana, 122001.

[2]Dr. Shalu Verma Bhardwaj, Dental Surgeon, Gurgaon, Haryana, 122001.

ABSTRACT: Specific microorganisms initiate the immune-inflammatory processes that destroy tissue in periodontitis. Recent work has demonstrated, in addition to bacterial control, that modulation of the host immune-inflammatory response is also capable of controlling periodontitis. The concept of host modulation is fairly new to field of dentistry but is universally understood by most physicians who routinely apply the principles of host modulation in the management of various chronic progressive disorders. In dentistry the term was introduced by William and Golub and later on expanded by others in dental profession. This article gives an overview of host modulation and host modulation agents.

Keywords- Host modulation, host modulation agents, periodontal diseases.

INTRODUCTION

Plaque biofilm and associated host responses are involved in the pathogenesis of periodontitis. Current data suggest that a small group of predominantly Gram negative, anaerobic bacteria within the biofilm are often associated with disease initiation and progression. The microbial challenge consisting of antigens, lipopolysaccharides (LPS) and other virulence factor stimulate host responses, which result in disease, limited to the gingiva or initiation of periodontitis. Protective aspect of the host response includes recruitment of neutrophils, production of protective antibodies and possibly the release of anti-inflammatory cytokines. The determination that periodontal tissue destruction is primarily due to the host response has created area of research directed at altering an individual's reaction to bacterial challenge. Various host modulating therapeutics have been developed or proposed to block pathway responsible for periodontal tissue breakdown.

Host modulation in periodontal diseases

Modulation of host cytokines

Cytokines, literally 'cell proteins' in etymology, transmit information from one cell to another via autocrine or paracrine mechanism. Following specific binding to their complementary receptor pro-inflammatory cytokines like interleukin-1 (IL- 1) and tumor necrosis factor (TNF) trigger intercellular signaling events and catabolic cell behaviors. To counter balance catabolism and maintain homeostasis both IL -1 and TNF have endogenous inhibitors. IL -1 receptor antagonist is structurally related to IL -1. It binds to receptor without trigger signal transduction. The type 2 IL -1 receptor and the extracellular domain of TNF receptor-1 & -2 can occur in soluble forms as competitive antagonist (Nungavaram SR, et al., 2002).

IL-1 receptor and TNF receptor antagonist have been reported to inhibit allergen-induced inflammation, ocular inflammation, LPS induced acute pulmonary inflammation and toxic endotoxin. Both IL - 4 and IL -10 can target macrophage for the release of IL-1, TNF, reactive oxygen intermediates and nitric oxide and IL-10 plays a major role in suppressing immune and inflammatory response produced by T cell, B Cell, monocytes and macrophages. Other cytokines, which are involved in the suppression of the destructive inflammatory response, include IL-11.

In a ligature induced canine model, recombinant human IL-11 shown to reduce disease progression by it inhibitory action of production of TNF-µ, IL -1 and nitric oxide (Graham E, Racheal JW, 1994).

Coden : IJABPT Copyrights@2012 ISSN : 0976-4550

Nitric Oxide

Nitric oxide (NO) is a free radical with important physiological functions including CVS, nervous system and immune homeostasis. Nitric oxide activates MMP in cultured chondrocytes. Functions as a second messenger mediating the effects of the pro-inflammatory cytokine IL-1b in articular chondrocytes. High local cover of nitric oxide and peroxynitrite (product of NO + superoxide) are cytotoxic to bacteria, fungi protozoa and tumor cells may also cause deleterious host effects such as DNA damage, lipid peroxidation, protein damage and stimulation of inflammatory cytokines. The inhibition of inducible nitric oxide has been associated with decrease carragernan induced inflammation depressed hemorrhagic shock in animal models

Nitric oxides inhibitors

1) L-NG- monomethyl arginine inhibits both inducible and constitutive nitric oxide forms.
2) L-arginine methyl ester inhibits both inducible and constitutive nitric oxide forms.
3) Merecaptoethylguanidine act as selective inhibitor of inducible nitric oxide forms. Mercaptoethlguanidine blocks inducible NOS scavenge peroxynitrite and inhibit cycloxygenase pathways.
4) N-iminoethyl-L-lysine act as selective inhibitor of inducible nitric oxide forms.
5) Reduces MMP activity in cartilage, decrease production of IL-1b by synvium (Dennis EL, et al., 1993).

Nuclear factor kappa B

It is an important transcription factor complex that appears to play a fundamental role in regulating inflammation. Occurs inactively in the cytoplasm of most inflammatory cells but is activated and released in response to pro-inflammatory stimuli. Free nuclear factor kappa B diffuses across the nuclear membrane, binds to DNA and stimulates cytokine gene expression and release (Graham E, Racheal JW, 1994).

Antagonist for endothelial cell adhesion molecules

E selection an ICAM-1 expressed on endothelial cell membranes that are responsible for the rolling and tethering of leukocytes during extravagation events. Agents such as tepoxatin, sodium cromoglycate, BMS-190394 and Kappaopoid PD 117302 show promising results in inflammation models.

Modulation of arachidonic acid metabolism

The arachidonic acid (AA) metabolites include a variety of fatty acid derived components that are enzymatically produced and released in response to local tissue injury. These metabolites have been collectively implicated in a wide range of events that are associated with disease, such as platelet aggregation, vasodilatation, vasoconstriction, neutrophil chemotaxis and increase vascular permeability. Its concentration increases in diseased periodontal sites in range of 10 to 20 times. One proposed approach to modulate the host response is inhibition of enzymes responsible for the release of these destructive products. NSAIDs may be of therapeutic value in treating periodontal disease because of their abilities to interfere with AA metabolism and thereby the inflammatory process.

Host modulation agents in periodontal diseases

Subjects who received adjunctive antibiotic therapy exhibited equipment gains in CAL when compared with subjects receiving either ibuprofen or placebo. Adverse effect of prolonged administration of non-selective Cox-1 and Cox-2 NSAIDs includes gastric upset and hemorrhage, renal and hepatic impairment Recently selective NSAIDS called Cox-2 inhibitors have been developed that selectively block isoenzyme associated with inflammation rather than that associated with homeostasis.

Lipoxins

Lipoxins are series of archidonic acids derivatives formed by interaction between individual lipoxygenases and appear to function as endogenous anti-inflammatory agent. Lipoxins are potent counter regulatory signals in-vitro and in-vivo endogenous pro-inflammatory mediators, including lipids (leukotrines, PAF) and cytokines (TNF-a, 1L-6) resulting an of leukocyte dependent inflammation. It has compensatory or protective role to limit PMN activity and PMN mediated damage.

LxB4 stimulates proliferation & differentiation of granulocyte-monocyte colonies from human mononuclear cell. (Jan P and Jim T, 2000).

Coden : IJABPT Copyrights@2012 ISSN : 0976-4550

Triclosan

Phenol derivative (2, 4, 4 tricoloro 2-hydroxyl diphenyl ether) is a non-ionic antimicrobial agent. Used as mouthwashes and in tooth pastes. It has both an
antibacterial and anti inflammatory agent actions: -

1. Acts on microbial cytoplasmic membrane inducing leakage of cellular constituents and thereby causing bacteriolysis.
2. Also inhibits cycloxygenase and lipoxygenase and thus may interfere with the production of AA metabolites. Use of dentifrice containing sodium fluoride (0.243%) and triclosan (0.3%) with 2.0% PVM/M copolymer (polyvinyl methyl ether malaeic acid copolymer) reduced the frequency of deep periodontal pockets and the number of sites exhibiting attachment and bone loss in patients deemed
highly susceptible to periodontitis.

Matrix metallo proteinase inhibition

MMPs are a family of Zn+ and Ca+ dependent endopeptidases secreted or released by variety of inflammatory cells. Belong to a family proteolytic enzyme that degrades extracellular matrix molecules such as collagen, gelatin, and elastin. These are secreted by various cell types. One mechanism of MMP activation involves the proteolytic cleavage of a portion of the latent enzyme. Example, chymotrypsin like protease produced by T. denticola, Neutrophil Cathepsin-G. The role of inhibitors is particularly important because it is an imbalance between the activated MMPs and their inhibitors that leads to pathological breakdown of the extracellular matrix to disease such as periodontitis and arthritis. Compensating for the deficit in the naturally accruing inhibitors or TIMPs to block or retard the proteolytic destruction of connective tissue is of therapeutic significance. Tetracycline, which may modulate many of these matrix protective mechanisms, have been found to be effective of MMPs mediated connective tissue destruction in variety of pathological processes. (Maria E, Ryan LE, 2000).

Tetracycline

Mechanisms by which tetracycline inhibits connective tissue breakdown are following-

A. Mediated by extracellular mechanisms

1. Direct inhibition of active MMPs dependent on Ca2+ and Zn2+ binding properties of tetracycline.
2. Inhibition of oxidative activation of pro-MMP independent of cation binding properties of tetracycline.
3. Tetracycline disrupt activation by promoting excessive proteolysis of into enzymatically inactive fragments, dependent on cation binding of tetracycline.

B. Mediated by cellular regulation

1. Tetracycline decreases cytokines, inducible nitric oxide synthase, phospholipase A2 and prostaglandin synthesis
2. Effect on protein kinase C, calmodulin.

C. Mediated by Pro anabolic effects

1. Increased collagen production.
2. Osteoblastic activity and bone formation (McCauley LK and Rahime MN, 2002).

Chemically modified tetracycline

The antimicrobial and anticollagenase properties of tetracycline reside in different parts of the drug molecules. The carboxyl and hydroxyl groups at C-11 and C-12
respectively might be essential for the anticollgenase property.

CMT, have devoid of antimicrobial activity but retains their anticollagenase activity pathologically elevated collagenase activity both in-vivo and in-vitro.

Bone resorption in-vitro / in-vivo at concentration of 5-10 mg/ ml. This inhibition was reversible, removal of tetracycline after 48 hrs resulted in resumption of bone resorption.

Mechanism of action:

1. Prevent the oxidative activation of latent pro-MMPs.
2. Decreased levels of pro-inflammatory cytokines.
3. Prevent the formation of multinucleated osteoclast like cells from tartrate resistant and phosphatase-stained cells of
The osteoclast lineage.

Coden : IJABPT Copyrights@2012 ISSN : 0976-4550

4. Bind to the osteoclast sensor (i.e. calcium sensor or ryanodine receptor on its plasma membrane) & diminishes cells functions i.e. matrix adhesion, cell spreading, podosomes expressions, enzyme secretion & bone resorption.
5. CMTs may also bind to the ryanodine reception on the nuclear membrane, alter the nucleoplasmic calcium influx and consequently affect osteoclast gene expression and apoptosis. (Fierro IM and Serhan CN, 2001).

Subantimicrobial dose doxycycline (sdd)

Doxycycline Hyclate (Periostat):- Available as 20-mg capsule, prescribed twice daily for use. Approved by U.S Food and Drug Administrator for the adjunctive treatment of periodontitis. It acts by suppression of the activity of collagenase, particularly that produced by PMNs. It does not exhibit antimicrobial effects but can effectively lower MMP level.

Evidence indicates that LDD regimens can

1) Inhibit the pathologically elevated collagenase actively in the gingival tissues and in the GCF of patient with adult periodontitis.
2) Reduce the typical side effect produced by commercial available dose regimens of tetracyclines presumably because the peaks or maximum serum level is reduced by about 90% compared to regular dose doxycycline regimens.
3) Prevent the progression of periodontitis assessed by measuring attachment loss.

Bisphoshonates

These are analogs of pyrophosphate in which the carbon atom replaces the linking oxygen atom in the pyrophosphate molecule. There are completely resistant to
enzymatic hydrolysis (alkaline phosphatase, pyrophosphatase) and are extremely stable. Bind to the hydroxyappatite crystals of bone and prevent both their growth and dissolution. Substitution of different side chains for hydrogen at locations R1 and R2 changes the potency and side effect profile of the compound.

Mechanism of action

A) Tissue level
- Decrease bone turnover due to decrease bone eruption.
- Decrease number of new bone multicellular units.
- Net positive whole body bone balance.

B) Cellular level
- decrease osteoclast recruitment
- increase osteoclast apoptosis
- decrease osteoclast adhesion
- decrease depth of resorption site
- decrease release of cytokines by macrophages
- Increase osteoblasts differentiation and number.

C) Molecular level
- Inhibits mevalonate pathway (can result in perturbed cell and induction of apoptosis.
- Decrease post-transitional prenylation of GTP blinding proteins.

Contra indications for use:

1 Sensitivity to phosphate.
2 GI upset

Drawbacks:

1 Chronic administration over long periods to be effective.
2 High cost and accessibility.
3. A full body irradiation that would occur since these agents have to be administered IV. (Howard CT, et al., 2002).

Estrogen and Selective Estrogen Receptor Modulators (SERMS)

Estrogen deficiency is associated with large increase in bone resorption, with osteoclast formation and activity and reduced osteoclast apoptosis. Treatment with estrogens clearly inhibit bone loss as well as bone turnover and increase bone mineral density. The estrogens inhibit both osteoclast activity and differentiation by regulating production of stimulating and inhibitory by cytokines by osteoblasts and monocytes.

The effect of steroid hormones as metabolic mediators of the expression of cytokines may be plausible explanation for the protective effect of estrogen supplementation against periodontal disease.
The discovery of the agents able to exert full or partial estrogen effects on various tissues led to the development of a new class of drug known as SERMs. The mechanism by SERMs inhibit bone resorption is likely to be the same as estrogens mechanism, by blocking production of cytokines that promote osteoclast differentiation and by promoting osteoclast apoptosis. SERMs appear to offer many of the benefits of estrogen with fever adverse effects. SERMs have noted to improve blood cholesterol level. Raloxifen is the first drug in this class approved for the treatment of osteoporosis. Taxonifen is another drug of this class used in
follow up treatment of some women with breast cancer

Anti-integrins

A Key early event in the bone resorptive process is the attachment of the osteoclast to the bone matrix. This matrix attachment is mediated by integrin primarily μvb3, and result in the intimate contact of the osteoclast with the matrix to be resorbed and formation of the sealing zone that enables the osteoclast to isolate a micro-environment beneath it to facilitate resorption. Blocking the adhesion of osteocalsts to their target matrix through the use of agents that disrupt integrins has been reported to inhibit bone resorption and may provide viable option after clinical investigation.

Periodontal vaccines

Vaccination is a process that induces specific immune resistance to bacterial or viral infectious diseases. The key features of a successful vaccine are safety, effectiveness, stability, a long shelf life and relatively low cost.
Vaccination can be accomplished by two methods-
1. Active immunization- Individuals immune system is stimulated by administrating killed or live attenuated bacteria or virus components or attenuated products derived from micro-organism.
2. Passive immunization - Antibodies formed in one individual are transferred to another. The complexity of periodontopathic bacteria might be a problem in determining of antigen for vaccine against periodontal disease. Among >500 species, 5-7 species have been implicated in the etiology of periodontitis. But species like, P.gingivalis and B. forsythus might play an important role as primary pathogen. The development of vaccine against periodontitis might be possible and the utilization it could be an effective method for control and prevention of periodontal disease.

DNA Vaccines

These are developed based on viral and bacterial peptides and plasmid vectors. They might induce immunity to numerous agents including periodontopathic bacteria, following confirmation of their safety.
Advantages:
1. Manufactured more easily than vaccines consisting Host modulation of an alternated pathogen, an outer or internal proteins or recombinant proteins.
2. Since DNA is stable by nature and resistant to extremes of temperature storage, transport and distribution it might be highly practical.
3. The simplicity of changing the sequence encoding antigenic proteins by means of mutagenesis and of adding hetrologous epitopes by basic molecular genetics framework.

CONCLUSION

Host response modulation has emerged as a valid treatment concept for the management of periodontal disease and represents a significant step forward for clinicians and patients. To date, only sub antimicrobial dose doxycycline has been approved specifically as a host response modulator. Further research is necessary to evaluate the efficacy of sub antimicrobial dose doxycycline in primary care, and also to focus on very long-term outcomes, such as prevention of tooth loss.

Coden : IJABPT Copyrights@2012 ISSN : 0976-4550

REFERENCES

Dennis EL, Charles ES, Neal VP. (1993).Humoral immunity to stress protein and periodontal disease J Periodontol ; 64: 819-27.

Fierro IM and Serhan CN. (2001).Mechanisms in anti-inflammation and resolution: the role of lipoxins and aspirin-triggered lipoxins. Braz J Medical Biol Res ;34: 555-60.

Graham E, Racheal JW. (1994). Connective tissue elements as diagnostic aids in Periodontology. J Am Dent Assoc; 125: 163-69.

Howard CT, Avi S, Bruno G, Ron Z, Peter CF. (2002). Biphosponates and periodontics J Periodontol 2002; 73: 813-22.

Informational paper: Modulation of host response in periodontal therapy. J Periodontol; 73: 460-470.

Jan P and Jim T. (2000). Role of bacterial proteinase in matrix destruction and modulation of host response. Perio 2000; 24: 226-52.

Maria E, Ryan LE. (1999-2000). Modulation of matrix mettaloproteinase activity in periodontitis as a treatment strategy Perio;14: 144-57

McCauley LK and Rahime MN. (2002). Mediators of periodontal osseous destruction and remodeling: Principles and implications for diagnosis and therapy. J Periodontol; 73: 1377-91.

Nungavaram SR, Barry RR, Robert AG, Xu J,Liu Y, Turner G et al. (2002). Inhibition of mettaloproteinase mediated periodontal bone loss in rats: A comparison of 6 chemically modified tetracycline. J Periodontol; 73: 726-34.