

Host Modulatory Agents in Periodontics the Valuable Innovation

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Abstract: Periodontitis is an extremely prevalent inflammatory disease induced by microbes leading to destruction of the tooth-supporting structures. Activation of host immune response by invading organisms results in the characteristic periodontitis. Most of the damage and the clinical signs of periodontitis are due to host inflammatory response. This modality of treatment is targeted to regulate immune and inflammatory response by maintaining the balance of pro-inflammatory and anti-inflammatory mediators. It could be applied both locally and systemically as adjunct to conventional treatment modalities. HMT can be used to lessen enzymes, prostanooids, cytokines. HMT can be used to control osteoclast function but shouldn't disturb normal tissue turnover. HMT are valuable innovation in periodontal disease management, aiming to reduce periodontal destruction, enhance wound healing and periodontal strength and permanence. Many agents are approved for management host dependent chronic inflammatory disease like rheumatoid arthritis and research is going on to administer it in periodontal disease management. Based on the clinical results, long-term studies are necessary to provide support for the adjunctive use of HMT in treatment of periodontal disease. As up to date the only FDA approved HMT agents is subantimicrobial dose doxycycline (SDD) although numerous agents are proposed and awaiting for approval.

Keywords: periodontitis, cytokines, host modulation therapy.

I. Introduction

Chronic periodontitis is defined as inflammation of the supporting tissues of teeth caused by microorganisms resulting in progressive destruction of periodontal ligament and loss alveolar bone with pocket formation, recession or both[1]. There are many risk factors which can modify host immune response and increase the susceptibility to periodontitis. Although bacteria initiates periodontal disease, host inflammatory response plays the major role in hard and soft tissue destruction in periodontitis[2]. Pro-inflammatory cytokines initiate inflammation stimulate osteoclast to proliferate and differentiate, they induce production of PGE2 that responsible for induction of MMPs so they play a key role in periodontitis. Since the destruction of periodontal tissue is caused by the host response; modulation of host response which aims to stop periodontal tissue destruction, stabilize or even regenerate is a promising approach to improve the therapeutic outcome of periodontal disease. Once pro-inflammatory cytokines are controlled MMPs, prostaglandins and osteoclasts will be controlled. This may be accomplished by different ways such as down regulation of proinflammatory cytokines, up regulation of anti-inflammatory cytokines. Other aspects of host modulation includes protein kinase inhibitors, arachidonic acid metabolites, bone remodeling, nitric oxide synthase inhibitors and antioxidants[3].

Cytokines

Cytokines are a large, diverse family of small proteins produced in response to activation and play an essential role in homeostasis by both modulating and regulating immune response. They play an essential role in both innate and adaptive immune responses, cell growth, differentiation, proliferation and directed migration, cell death, angiogenesis. developmental as well as repair processes and cell signaling [4]. The two principal producers of cytokines are helper T cells (Th cells) and macrophages, even though they can be induced and secreted by virtually all nucleated cells. Cytokines stimulate their target cells to release more cytokines. They can act synergistically or antagonistically[5]. Cytokines affect cells that express their receptors so they may affect neighboring cells or travel along distance through blood stream to function in an endocrine fashion. Binding to specific receptors on target cell leads to stimulation of cellular responses altering production of proteins. Cytokines are involved in normal biologic processes. They have many physiologic functions [4]. The cytokine network that facilitate the immune response includes pro-inflammatory, anti-inflammatory cytokines and cytokine receptors. It was evidenced that the T cell are the predominant cell in periodontal lesion, and the imbalance of T cells subsets ((Th 1, Th2 and Th17) are the basis beyond failure of periodontal disease treatment. Th1 cytokines arecellular and pro-inflammatory; while Th2 cytokines are associated with humoral immunity and present anti-inflammatory properties [6].

T cell subsets and their cytokines:

CD4 T-cells were initially subdivided into two subsets, designated Th1 and Th2, however new 2 subsets are added, namely, Th17 and Tregs (regulatory T-cells). Th1 is responsible for cellular immunity and protection against intracellular pathogens by yielding interleukin IL-1, IL-12, IL-2, interferon (IFN)- γ , and tumor necrosis factor (TNF)- α . IL-1 is known to be powerful cytokines with wide biological influence on many cell types and central role by its control on more than 90 genes during inflammation. Both IL-1 and TNF- α induce bone resorption by stimulating osteoclast [6]. IFN- γ is found to be predominant in severe and progressive periodontal lesions and it is related to donation of cytokines and inflammatory mediators [7]. Th17 produce IL-17 with the major function of producing the powerful proinflammatory cytokines like IL-1, IL-6, IL-8 and prostaglandin E2 (PGE2) and chief osteoclastogenic effects. Elevated level of GCF IL-17 is demonstrated in aggressive periodontitis. Th2 is responsible for humoral immunity and protection against extracellular pathogens by generating IL-3, IL-4, IL-5, IL-6, IL-10, IL-11 and IL-13. IL-4 & IL-10 are proved to be potent anti-inflammatory cytokines which counteract and lessen the proinflammatory cytokines. IL-10, the chief anti-inflammatory cytokine show vast immunoregulatory role by reducing IFN-gamma and IL-17, inhibiting bone resorption via counteracting RANK-RANKL connection [6].

Role of Cytokines in periodontitis:

Cytokines bind to receptors on the surface of target cell that triggers intracellular signaling cascades altering protein synthesis and leading to altered gene expression in the target cell, which lead to a biological effect. Nevertheless, unregulated or inappropriate production of particular cytokines lead to pathological consequences in autoimmune and inflammatory diseases [4]. By-products and enzymes released by invading organisms trigger release of pro-inflammatory cytokines like; interleukins (IL1), tumor necrosis factor- α (TNF- α), prostanooids (e.g. prostaglandin E2) and proteolytic enzymes like the matrix metalloproteinase (MMPs) [8]. IL-1 and TNF- α play a central role in periodontal tissue destruction by inducing expression of mediators that amplify the inflammatory response, lead to production of lytic enzymes and stimulate the production of chemokine. The pro-inflammatory effects of IL-1 and TNF- α , include stimulation of endothelial cell to express selectins that facilitate recruitment of leukocytes, activation of macrophages and induction of prostaglandin E2 (PGE2) by macrophages and gingival fibroblasts [9]. Bone and immune cells derive from same progenitors in the bone marrow, have the ability to differentiate into osteoclast. Some pro-inflammatory cytokines are considered osteoclastogenic and can modulate the receptor activator of nuclear factor kappa B (NF- κ B) ligand (RANKL), RANK, or osteoprotegerin. RANKL/RANK interaction is responsible for differentiation and maturation of osteoclast. Osteoprotegerin acts as a decoy receptor, produced by osteoblasts, which binds to RANKL and inhibits osteoclast development. Pro-inflammatory cytokines modulate osteoclastogenesis by boosting osteoclast differentiation, activation, life span and function [10]. Both IL-1 and TNF are potent stimulators of bone resorption they stimulate osteoclast proliferation differentiation and activate them yet the IL-1 is more potent. Both of them induce production of proteinases including MMPs which may contribute to connective tissue destruction [9]. IL-1 is produced primarily by activated macrophages or lymphocytes however it may be released by other cells. Bacterial lipopolysaccharides (LPS) is a potent activator of macrophage IL-1 and TNF- α production. TNF- α and IL-1 itself can activate macrophage IL-1 production. This upregulation caused by IL-1 is a significant augmentation mechanism.

These cytokines are balanced by anti-inflammatory cytokines and enzymes of the host immune system which function to eliminate microbial pathogens and protect the host. An inappropriate immune response in susceptible patient leads to overproduction of destructive enzymes and inflammatory mediators and causes periodontal disease [3].

There are many anti-inflammatory cytokines that antagonize effects of pro-inflammatory cytokines. These include IL-11, IL-4 and IL-10 [6]. IL-11 exerts its anti-inflammatory effects by inhibition of TNF- α and other proinflammatory cytokines and stimulation of tissue inhibitor of metalloproteinase-1 (TIMP-1) [11]. IL-4 suppresses IL-1 β synthesis and enhances the expression of IL-1 receptor antagonist. IL-10 is the central anti-inflammatory cytokine secreted by CD4⁺ Th2 cell, Treg, monocyte, and macrophage cells of the immune system. It exerts its effect by suppression of expression of proinflammatory cytokines, chemokine, adhesion molecules, antigen-presenting and costimulatory molecules, attenuation of TNF-receptor expression and promotion of its shedding into systemic circulation as well as inhibition of the up-stream NF- κ B transcription factor, an essential secondary messenger required for inducing proinflammatory cytokine gene expression [12].

Host Modulation

Treatment of periodontitis could be focused on three aspects: eradication of invading organism, reduction of risk factors and host response modulation. Host modulation is a new concept in dental vocabulary. Host is defined as an animal or plant that harbors and provide sustenance for another organism whereas modulation can be defined as the functional and morphological fluctuation of cell response to a stimulus or changing environmental

conditions [11]. Ultimately, it is the host's reaction to the presence of the bacteria that leads to tissue destruction. Since the destruction of periodontal tissue is supposed to be due to the host response, it is logical to consider therapeutic approaches that modulate the host response in addition to antibacterial approaches in the management of periodontitis. It is a recent therapeutic approach in periodontal disease [13]. A number of host modulatory agents have been investigated for example the nonsteroidal anti-inflammatory drugs (NSAIDs), subantimicrobial-dose doxycycline (SDD), and bisphosphonates and many other examples. The development of knowledge and understanding the role of host response in periodontal disease pathogenesis led to the development of Host Modulatory Therapies (HMT). The concept of host modulation was first introduced to dentistry by Williams in 1990 and Golub et al. in 1992 and later on expanded by many researchers. Host modulation therapy aims to reduce periodontal tissue destruction and regenerate it by down regulating the destructive immune response or up regulating the protective ones. In other words it aims to restore the balance of pro-inflammatory and anti-inflammatory mediators. It could be administered both systemically and locally [14]. It is very effective in improving therapeutic outcomes, slowing the progression of disease, allowing for more predictable management of patients, and possibly even working as preventive agents against the development of periodontitis [15].

Modulation of Matrix Metalloproteinase (MMP):

MMP is an enzyme (proteinase) produced by bacteria and many cell types during tissue homeostasis, but its manifestation appears to be high during inflammation. During active periodontal diseases, periodontal pathogens increase both the production and activity of MMP. Some of the HMT is directed against this proteinase, many techniques are tested but the only accepted method is tissue inhibitor of matrix metalloproteinase (TIMP's) which competitively bind MMP active site. MMP inhibition is accomplished by tetracycline and its derivatives doxycycline, subantimicrobial-dose doxycycline (SDD), which has the competency of being anti-inflammatory and bone sparing agent. Tetracycline based host modulating agent, i.e. sub-antimicrobial dose of doxycycline SDD (Doxycycline hyclate 20 mg (Periostat) has been approved by Food and drug administration (FDA) to have highly predictable results as a host modulating agent in periodontal diseases and also an effective adjunctive therapy in various diseases of periodontium [13].

Modulation of Arachidonic Acid (AA) metabolites:

Arachidonic acid can be metabolized via cyclooxygenase (COX) or lipoxygenase (LOX) pathways. The final products of the COX pathway include prostaglandins, prostacyclin, and thromboxane. Prostaglandins are an important mediator of bone loss in periodontitis. Nonsteroidal anti-inflammatory drugs inhibit the formation of prostaglandin and AA metabolites. And the application of NSAIDs in periodontitis models are proved to lower bone loss and lessen inflammation by inhibiting prostanoids (PGE₂) [3]. The use of NSAIDs (systemic flurbiprofen, Indomethacin, and others) daily for three years showed diminished alveolar bone resorption, but has a major disadvantage of rebound effect in addition to the need of daily administration for years. NSAIDs side effects ranging from gastrointestinal hemorrhage to renal and hepatic damage. Based on the clinical results to date, additional long-term studies are necessary to provide support for the adjunctive use of NSAIDs in the treatment of periodontal disease [13]. Topical application of selective NSAIDs which selectively inhibit COX-2 was attested to be with little unwanted reactions. Triclosan also proved to inhibit AA metabolite by its anti-inflammatory properties, its addition to dentifrices reduced sites with bone loss, attachment loss and deep pockets [16].

Agents promoting resolution:

These agents are involved in resolution phase rather than inhibit inflammation, they stimulate resolution programs via many methods. Best examples are Lipoxin and Resolvin. Lipoxin are members of eicosanoid family produced by Lipoxygenase (LO) pathway having important role on neutrophils chemotaxis and phagocytosis regulation; which on high level could be destructive. On presence of Lipoxin neutrophils chemotaxis is inhibited and monocytes are attracted with non-destructive role. Lipoxin may be promising strategy to reduce neutrophil mediated periodontal damage but more studies are needed. Resolvin proved to have anti-inflammatory role as they promote defense and clear inflammatory metabolites [13].

Modulation Of Bone Remodeling:

Bone resorption is crucial characteristics of periodontal tissue break down. Aiming host modulation via Modulation of bone remodeling, was achieved by changing osteoclast differentiation or reducing their half-life. RANKL/osteoprotegerin ratio was found to be high in patients with periodontitis, therefore osteoprotegerin/RANKL/RANK axis was targeted for the treatment of bone resorption-related diseases and so periodontal disease [10]. Bisphosphonate are the compounds used in modulation of bone remodeling using its character of being bone-sparing drug. It is used in management of systemic bone diseases. Its action extends over tissue level, molecular and cellular levels. It can hamper osteoclast differentiation, impede their attachment to

bone, accelerate their apoptosis etc. As well as it down regulate matrix metalloproteinase activity. Many clinical trials assessed the bisphosphonates (namely Alendronate) on treatment of moderate and severe periodontitis as additional treatment to conventional periodontal debridement and approved to inhibit bone resorption and maintain periodontal bone bulk. The shortcoming of prolonged use bisphosphonates was that they may impede bone remineralization, change in white blood cell counts and lead to jaw necrosis [17].

Estrogen And Selective Estrogen Receptor Modulators (ESRMs):

Estrogen hormone play vital role in osteoclast differentiation and resorption inhibition as well as it regulate pro and anti-inflammatory mediators. Estrogen deficiency in post-menopausal osteoporosis is related to bone resorption, which is reversed by estrogen supplementation. And it could be protective treatment modality in periodontal diseases. ESRMs appear to offer the benefits of estrogen with less side effects [3].

Modulation of Nitric Oxide Synthase (NOS) activity:

nitric oxide (NO) is a highly sensitive free radical which is important in small amount for tissue homeostasis and host defenses, but it was found in excess amount in many inflammatory diseases which make it toxic & may lead to cytokine release, DNA and protein damage. Animal experiments that tested the inhibition of the isoenzyme nitric oxide synthase (NOS) by group of drugs e.g. mercapto ethyl guanidine (MEGs); reduce inflammation, and bone loss. NOS inhibitors prevent alveolar bone resorption in experimental periodontitis. However further studies are needed to validate its beneficial effects in periodontal diseases [13].

Nutrients: Down regulation of reactive oxygen species* using Antioxidants (AO's) can be accomplished by using nutrients as modulators of inflammation through three separate mechanisms namely: hunt free radicals, reprocess them to other molecules, seize their metal ion. Major extracellular antioxidants e.g. vitamin C, vitamin E, carotenoids, and omega 3 [18].

Periodontal Immunization methods:

Immunization is induction of immunity by active, passive or genetic immunization. Immunization methods are done via generation of protective antibodies to prevent Periodontitis [19]. Periodontitis is a microbial infection, so preparing a vaccine against particular pathogen has shown convenient clinical results, although further research for a comprehensive vaccine is warranted. The organism that is targeted for immunization is *P. Gingivalis*. The pathological parts used are outer membrane protein, gingipains, fimbriae and heat shock protein [18]. Studies of immunization procedures with immunoglobulin G against *P. Gingivalis* decreased bacterial load in subgingival plaque, prostaglandin E2 and slows bone loss. Immunization methods showed good clinical results but periodontal disease is a polymicrobial disease and the vaccination is against single pathogen; therefore to formulate a wide spread vaccine more research is needed [19]. Active immunotherapy against TNF i.e. anti-TNF- α vaccination, using TNF kinoids (TNF-K); is under study for management of many TNF- α -dependent chronic inflammatory diseases [20].

Modulation Of Immune And Inflammatory Responses

Host Modulating Agents Acting On Cytokines:

The potential role of inflammatory cytokine in periodontal disease pathogenesis is mentioned earlier. down regulation of proinflammatory and/or upregulation of anti-inflammatory cytokines will be good treatment modality for treatment of periodontal diseases. IL-1 and TNF have the major element in the pathological process of periodontal disease, though obstructing IL-1/TNF activity reduce inflammatory mediators and block the procedures for bone destruction. This is accomplished by several different, but highly specific, strategies. These strategies include:

Cytokine Receptor Antagonist:

receptor antagonist binds cytokines receptors and prevent cytokines from binding their receptor (competition). e.g. IL-1 receptor antagonist (IL-1ra), which is commercially available as Kineret (Anakinra) used in treatment of rheumatoid arthritis (100 mg daily). However the tough periodontal lesions environment may abolish soluble cytokine antagonists before their full action which may dictate repeated injections [21].

Anti-cytokine antibodies:

Examples for anti-cytokine antibodies. Infliximab neutralizes the biological activity of TNF- α by binding with high affinity to the soluble and transmembrane forms of TNF- α . Etanercept is a fusion protein which is produced by recombinant DNA which fuses the TNF receptor to the constant end of the IgG1 antibody. adalimumab, certolizumab and golimumab are monoclonal antibodies used as a TNF inhibiting anti-inflammatory drugs [22].

Other offered anticytokines antibodies are; anti-IL-6 antibody (Tocilizumab), anti-IL-15 antibody (AMG714), anti-IL-12 and IL-23 antibody (Ustekinumab), anti-IL-17 antibody (AIN457) [18]. These drugs are successfully used in treatment of rheumatoid arthritis. Periodontal disease and rheumatoid arthritis share many pathological events together with proinflammatory cytokines playing major role in their pathogenesis. so the administration of anti- cytokine therapy in periodontal therapy need to be investigated. Application of cytokine antagonist will be good treatment modality to improve periodontal disease prognosis, within the known safety standards. However the problem of the need of repeated application and rebound effect need to be solved [22].

Soluble cytokine receptors:

bind to cytokines in solution (liquid form) and prevents signaling of proinflammatory cytokines receptors of IL1, TNF, IL6 [18].soluble protein delivery of antagonists to IL-1 and TNF in animal studies showed potential for halting periodontal attachment damage and defeat bone loss [23].Soluble receptors must be administered in large amounts and repetitively because of rapid clearance in vivo. These disadvantages can be overcome either by using cytokine traps [24]or gene transfer [25].

Administration of anti-inflammatory cytokines:

Cytokines implicated in suppression of the destructive inflammatory response include IL-4, IL-10, IL- 1 INF- γ 1, [26][27], and Transforming growth factor (TGF- β). Both IL-4 and IL-10 can target macrophages and inhibit the release of IL-1, TNF, reactive oxygen intermediates, and nitrous oxide However these agents can be abolished before their action being taken fully and repeated application is required [28].

Natural T regulatory cells (nTreg):

are the corner stone immunoregulatory groups, and play an important role in the suppression of autoimmune responses and maintaining homeostasis. the position of nTreg in the periodontal disease pathogenesis is expanding.Upregulation of regulatory T lymphocytes (Tregs) may actually help to balance the proinflammatory response possibly through expression of IL-10 [29]. Treg cells which are present in periodontal tissue represent a protective Th subset by their anti-inflammatory and anti-resorptive properties. However more research are indicated to assess the role of nTreg in periodontal health and disease[30]. Gene transfer: Gene transfer therapy involves the transfer of a therapeutic or working gene copy into specific cells of an individual in order to repair a faulty gene copy or to introduce a new gene whose function is to cure or to favorably modify the clinical course of a condition[20].

Gene transfer:

in periodontics replace the enigma of administering growth factors in large quantities with its unwanted effects by delivering gene encoding the needed growth factor. This inspire new tissue engineering strategy in periodontal regeneration. But still more work is needed to find a save, cost effective and efficacious submission system[31].

Modulation of the level of inflammatory mediators by Targeting signaling pathway:

in this strategy the destructive inflammatory mediators would be obstructed at the level of cell-signaling pathways needed for transcription factor activation and vital for their gene expression or mRNA stability[10]. In periodontal disease the most important pathways include the mitogen activated protein kinase (MAPK), nuclear factor kappa B (NF- κ B), p38 and janus tyrosine kinase-signal transducer and activator of transcription (JAK/STAT) mediators.However modulation of one signaling pathway may affect expression of more than one inflammatory mediator and alter the whole cytokine network[32].

Another approach to modulate cytokines is achieved by usingnanoparticles:

either to suppress cytokines like TNF or to induce synthesis of anti-cytokines [33]

Cytokine traps:

They have very high affinity to cytokines compared with other soluble receptors.Consist of fusion proteins between the constant region of IgG and the extracellular domain of two distinct cytokine receptor components involved in cytokine binding. And by potently binding to cytokines can act as innovative therapeutic modality for cytokine dependent diseases [24]

recombinant human IL - 11:

subcutaneous injection of (rh IL-11)anti-inflammatory cytokine on animal induced periodontitis reported slows the injury and loss in both bone and attachment [28]

Locally Administered Host Modulation Therapy

in addition to the systemic host modulatory therapy there are several agents administered locally to reestablish all the constituents of the periodontium. Its function as regenerative material rationalize its role as a host modulating agent. Example of these agents are bone morphogenic protein, Enamel matrix proteins, Platelet derived growth factor, nuclear factor kappa Beta. Some of the agents administered systemically can also be applied locally with benefit of reducing the unwanted effect of systemic distribution. Example of these agents are bisphosphonate and NSAIDs (ketorolac mouth wash, and S-ketoprofen tooth paste) [3].

Since periodontal destruction has enormous variety of pathogenic pathways, polypharmaceutical approaches may be developed that modify a number of different pathways associated with inflammation and tissue destruction. Although these modalities of host modulation are promising, proinflammatory cytokines play a major role in many physiological processes and inhibition of them could result in adverse effects [34] [35]. The adverse effects include susceptibility to infections and cancer when anti proinflammatory drugs are used in large quantities [36]

II. Conclusion

The basis of periodontal disease management is mechanical debridement but host modulatory therapy is equally essential and vital. Host modulation constitutes a logical therapeutic strategy to improve the outcome of periodontal therapy especially for high risk and susceptible patients. HMT strategies are simple, and easy to apply. Incorporation of HMT preparations into our routine practice is promising but challenged by its potential adverse side effects. Further multicenter research and trials are needed to formulate new preparations that achieve the desired therapeutic outcome, overcome the adverse side effects and make the promise of prevention of periodontal disease destruction applicable and save.

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