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Anti- Cytokine Therapy in Periodontitis.

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ABSTRACT

Periodontitis is the destruction of the supporting structures of the teeth initiated by oral pathogenic bacteria. The bacteria stimulate the host inflammatory responses which primarily aim at killing the invading bacteria. In an endeavour to do so, the host releases toxic substances like cytokines which apart from helping the destruction of the microbe, also leads to a cascade of events that leads to the tissue destruction of the host itself. Inhibition of these toxic substances could lead to a beneficiary effect of preventing the host tissue destruction or periodontitis. In the present article we give an overview of the role of cytokines in periodontal therapy along with their possible effects as antagonists.

Keywords: Anti cytokine, periodontitis, host modulation.

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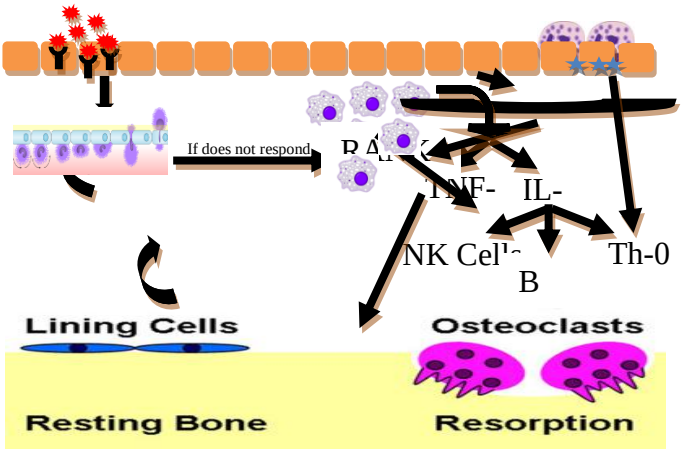
INTRODUCTION

Periodontitis is a chronic infectious inflammatory disease caused by microbes; however the presence of microbes is not enough for the cause of its complex nature of disease. Inflammation is the prime cause of periodontal disease. It commences with the aggregation of pathogenic microbes that induce the host to stimulate a cascade of inflammatory response reactions which in-turn leads to the destruction of the host tissues itself. There is a complex interplay of innate and adaptive immune responses which fights against the pathogens by direct interaction or by release of certain molecules including cytokines.

Cytokines are cell signalling molecules that aid cell to cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma. Cytokine biology reveals that there are some subsets of cytokines which are pro-inflammatory cytokines which stimulate the inflammatory responses and cause tissue destruction. The other subset is of anti-inflammatory cytokines which prevent an inflammatory response, hence arrests tissue destruction. Treatment strategies that aim to down regulate pro-inflammatory cytokines or up regulate anti-inflammatory cytokines can be aimed for periodontal therapy.

Role of Cytokines in the Pathogenesis of Periodontal Disease

Host response to the invading bacteria plays a major role in the periodontal tissue loss. There is established evidence concluding that deficient host response increases periodontal tissue destruction, at the same time too vigorous response also leads to periodontal diseases. [1] The first conclusive evidence that host response plays an important role was shown when treatment with a prostaglandin inhibitor flurbiprofen reduced the amount of bone loss in beagles. [2] As soon as the microbe attacks the gingival epithelium, there is complex interplay immune responses which begins with the release of a chemokine Interleukin-8 (IL-8). Chemokines are a class of chemotactic cytokines that stimulate the recruitment of relatively specific leukocyte subsets. [3] IL-8 is secreted by epithelial cells, macrophage, monocytes and fibroblasts and it is chemo-attractant to neutrophils. Subsequently, the inflammatory response sets therein. The innate immune response also contain tissue macrophages which contain toll like receptors (TLR) for microbes and upon binding, they release two most important cytokines which are IL-1 and Tumour Necrosis Factor- α (TNF-α). Both play a role in promoting tissue and bone destruction by promoting the RANK-RANKL-OPG pathway which stimulates osteoclastic bone destruction. [4] [Fig. 1] IL-1 also stimulates Th-0 subsets of cells which are mainly of 4 types- Th-1, Th-2, Th-17 and T-reg. [Fig 2]. In fig. 2, the red box denotes pro-inflammatory cytokines and the green box denotes anti-inflammatory cytokines. The aim of anti-cytokine therapy includes down-regulation of pro-inflammatory cytokines and up-regulation of anti-inflammatory cytokines.



Epithelial cells, Invading microbes, Dendritic cell, Macrophage, TLR, Neutrophil

Fig. 1: Role of cytokines in Periodontal diseases

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Fig. 2.

Cytokines and Anti- Cytokine Therapy

Interleukin-1

IL-1 is one of the most important cytokines that plays a role in periodontal tissue destruction. It has 3 ligands- IL-1α, IL-1β, IL-1 Receptor Antagonist (IL-1RA). IL-1α and IL-1β have similar pre-inflammatory activities whereas IL-1RA acts as a competitive inhibitor to IL-1 and does not have an agonist activity.[5] IL-1α tends to remain associated to cell membranes whereas IL-1β is synthesises as an inactive pre-cursor after being processed post-translationally by a cystine asparagin protease. The focus on IL-1 for effective anti-cytokine therapy lies on lies on decreasing the levels of IL-1α and IL-1β whereas increasing the levels of IL-1RA.

Anti- IL-1 therapy

Strategies in the suppression of IL-1 have been based on the blockade of transcription, translation, secretion or receptor blockade. A unique anti-inflammatory mechanism for reducing the production and activity of IL-1 is found to be via the gp130 receptor family or the interferon (IFN) receptors, both utilizing the activation of the p91 nuclear factor which provides a negative signal. [6]

Anakinra (Kineret®) is the only FDA approved recombinant, non-glycosylated form of human IL-1RA. The drug claims that most clinical responses would be achieved on administration of 100mg of drug sub-cutaneously within 12 weeks of enrolment in Rheumatoid arthritis patients. Its role in periodontitis is however to be explored. Care should be taken for its administration as it may cause adverse reactions like infections, immunogenicity, malignancies and a decrease in the total white blood cell and platelet count.

Gemfibrozil (Gem), a lipid lowering drug has shown to upregulate IL-1RA in mouse by the inhibition of the PI3K-Akt pathway. Furthermore, it has been shown that Gem suppresses IL-1β mediated neuronal apoptosis via upregulation of IL-1RA. [7].

Tumor Necrosis Factor (TNF)

TNF is secreted by monocytes, macrophages, neutrophils, T- cells, Natural Killer cells (NK- cells) following their stimulation by bacterial lipo-polysaccharides. It exists in 2 forms- TNF-α and TNF-β. TNF-α is involved in normal inflammatory and immune response whereas TNF-β is a lymphotoxin. TNF-α is known to be a potent stimulator of bone resorption and inhibitor of bone formation. TNF-α also has been shown to up-regulate the production of other pro-inflammatory cytokines like IL-1β and IL-6. An attempt to decrease the levels of TNF-α would help to prevent bone resorption hence arrest periodontal tissue destruction.

Anti-TNF therapy

Anti- TNF drugs are a class of drugs that have been used for more than 10 years. They are used worldwide for the treatment of inflammatory conditions like rheumatoid arthritis, psoriatic arthriris, Crohn's colitis, ankylosing spondilitis. Since these drugs can reduce inflammation successfully in many inflammatory diseases, attempt can be made to incorporate these drug regimes for periodontitis which is an inflammatory disease. There are at present 5 FDA approved TNF drugs.

Infliximab (Remicade®)

Infliximab works by neutralizing the biological activity of TNF-α by binding with high affinity to the soluble and transmembrane forms of TNF-α, hence inhibits the effective binding of TNF-α with its receptors. Infliximab has been shown to halt periodontal inflammation and bone resorption in patients with rheumatoid arthritis who routinely have used 200mg of infusions. [8] Immunologic side effects have however reported in literature following infliximab infusions along with fatal blood disorders and serious infections. Also, severe allergic ractions like swelling of the lips, difficulty in breathing and lowered blood pressure are not uncommon.

Etanercept (Enbrel®)

Etanercept is a fusion protein which is produced by recombinant DNA which fuses the TNF receptor to the constant end of the IgG1 antibody. Hence it has a potential to treat inflammatory diseases by inhibiting TNF-α. An experimental model of periodontitis in rats has shown that etanercept reduces the development of inflammation and tissue injury.[9] Hence human trials can be carried out to test its efficacy in periodontitis. However we need to watch out for its potential side effects like infections, hypersensitivity reactions and production of antibodies to etanercept.[10]

Adalimumab (Humira®)

Adalimumab is a recombinant human IgG1 monoclonal antibody used as a TNF inhibiting anti-inflammatory drug. It binds to the TNF-α, preventing it from activating TNF receptors.[11] It is currently FDA approved for rheumatoid arthritis. A study carried out in Japan recently has successfully proved decreased gingival index, bleeding on probing, periodontal pocket depth, decreased serum levels of TNF-α and IL-6 on giving adalimumab to patients with rheumatoid arthritis with a significance of <0.001. [12] This high significance value of this study opens up insights for clinicians to incorporate their periodontal management with adalimumab. The adverse effects of adalimumab includes susceptibility of rare serious infections , initiation of congestive heart failure, lupus like syndrome, medically significant neutropenias and pancytopenia. Hence care should be taken to prevent overdose before administration. [13] The safest prescribed dose according to FDA is 40mg every other week as a self administered subcutaneous injection.

Certolizumab (Cimzia ®)

Certolizumab is a monoclonal antibody directed against TNF-α. More precisely it is a PEGylated Fab fragment of a humanized TNF inhibitor monoclonal antibody. To the best of our knowledge, the use of certolizumab has not been reported in the literature for its effective use in periodontitis. It has however given significant effects in rheumatoid arthritis [14] and Crohn's Disease. [15] The side effects of Certolizumab reported when given for Croh's disease are bleeding, perianal/ perineal abscess. [16] The prescribed safe dose of Certolizumab according to FDA is 400 mg on week 0, 2 and 4 as a self administered cutaneous injection followed by 200 mg as a maintenance dose every other week.

Golimumab (Simponi ®)

Golimumab is another monoclonal antibody used as a TNF inhibitor that binds to the specific receptors of both trans-membrane and soluble TNF-α and blocks their action. It got its FDA approval in 2009 for its use in rheumatoid arthritis, psoriatic arthritis and ankylosing spondilitis. The use of Golimumab in the management of periodontitis is still at the animal stage. [17] The safety profile of golilumab is similar to that of other TNF-α inhibitors. [18]

c. Interleukin-6

Interleukin-6 (IL-6) is an important cytokine involved in the regulation of host response to tissue injury and inflammation. It is a pleotropic cytokine and is produced by many cells like monocytes, osteoblasts, fibroblasts, vascular endothelial cells in response to inflammation. It promots th differentiation of B-lymphocyte precursors into immunoglobulin secreting plasma cells as well as the differentiation of T-lymphocyte precursors to cytotoxic T lymphocytes. [19]
Anti IL-6 therapy

Since IL-6 is one of the most potent pro-inflammatory cytokine which leads to the periodontal destruction, an attempt can be made to reduce the levels of locally produced IL-6 to prevent periodontal tissue destruction. The effect of IL-6 receptor inhibition has been analysed by Kobayashi in patients with periodontitis and a significant decrease in the gingival index, bleeding on probing, probing depth was noted. [20]

CONCLUSION

In this era of molecular biology where we can get to the root cause of the disease and can make it possible to formulate pharmacological preparations that target to the root molecular cause of the disease, we must aim to incorporate such preparations for a better prognosis of our treatment. Since cytokines play a very important role in the pathogenesis of periodontal diseases, we can chose to incorporate the cytokine antagonists in our routine treatment strategies within the accepted safety profile norms.

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