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Review Article

Periostat as a host modulating agent in the downregulation of matrix metalloproteinase {MMP} activity: A review

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ABSTRACT

Chronic Periodontitis is defined as the infection and the inflammation of the supporting tissues of the teeth with the progressive loss of attachment. As a result of this inflammation, the immune system gets activated leading to the release of various immunoinflammatory cells which in turn leads to release of cytokines which amplify the immune response leading to the clearance of infection. But if there is a release of cytokines over a longer period of time, it leads to the release of inflammatory mediators and one of such inflammatory mediators, is the matrix metalloproteinase, which leads to degradation of extracellular matrix. Periostat is one of the FDA approval host modulating agent which acts by downregulating the destructive aspect of matrix metalloproteinase and thus upregulate the protective aspect of host response.

1. Introduction

Among the dental diseases present in an individual, dental caries, gingivitis, and Periodontitis are the prevalent disease worldwide. Gingivitis, is a reversible disease which means, that if it is treated at proper time, it can lead to the restoration of normal features of gingiva. However if gingivitis not treated on a proper time, it can lead to the progression of gingivitis to periodontitis.[1] However this is also a proven fact that not at every time, gingivitis always progress to periodontitis. However periodontitis is always preceded by gingivitis. This conversion of gingivitis to periodontitis was initially believed to be because of microbes. But recent researches have evaluated that apart from microbes, one of the crucial factor that plays an important role in the conversion of gingivitis to periodontitis is the host response.[2]

2. Host Response

Host can be defined as an organism on which the parasite grows and obtain its nutrition. In the diseases of periodontium, that are initiated by bacteria, host can be defined as an organism which harbors these pathogens. Response is defined as the mechanism by which how the host cope up with that pathogens.[3] Gingivitis and periodontitis are caused initially by the microbes. The microbes initiate the disease process by means of their virulence factors such as lipopolysaccharide, gingipains, fimbriae. As a result of these virulence factors, immunoinflammatory response gets activated leading to the release of various immunoinflammatory cells like neutrophils, lymphocytes. These cells in turn release to a group of cell signaling proteins such as cytokines which amplify the immunoinflammatory response leading to the clearance of microbes. However this immunoinflammatory response acts a double edge sword, in the sense that the prolong release of these cytokines leads to the release of various mediators of inflammation and this forms the

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basis of host response in the sense that the host had responded to the immunoinflammatory response through the release of inflammatory mediators leading to destruction of extracellular matrix and bone resorption.[2]

3. Matrix Metalloproteinases (MMP'S)

Periodontitis is defined as an infection and inflammation of the supporting tissues of the teeth leading to destruction of the connective tissue with progressive attachment loss and bone loss. This destruction of the extracellular matrix along with bone resorption is due to the release of various mediators of immunoinflammatory response and one of this immunoinflammatory mediator is the matrix metalloproteinases (MMP'S) which causes extracellular matrix destruction. Matrix metalloproteinases encompasses a family of zinc depended membrane bound and secreted proteolytic enzyme. Their main function is to catalyze the breakdown of proteins in the cell plasma membrane or the extracellular matrix. The extracellular matrix consist of collagenous and non-collagenous proteins (glycoproteins and proteoglycans). For the collagen to be degraded by the collagenase, non collagenase proteins need to be degraded first and this initial degradation of non-collagenous proteins takes place by matrix metalloproteinases. Thus matrix metalloproteinases activation plays an important role in extracellular matrix degradation during periodontal tissue destruction.[4]

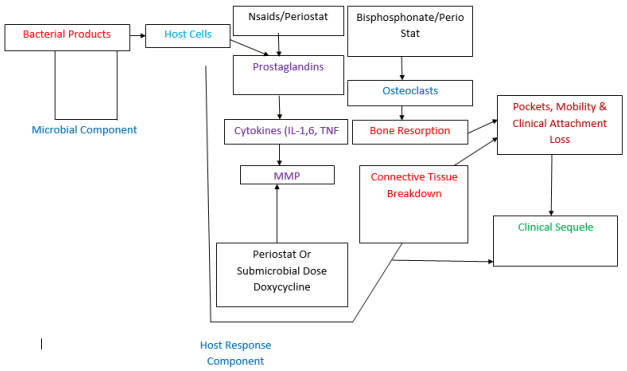

Fig. 1: Matrixmetalloproteinase effect on connective tissue breakdown

4. Periostat (Subantimicrobial dose doxycycline, SDD)

Approval: Only approved drug by U.S. food and drug administration to be used as a host modulating agent in the management of chronic periodontitis as an adjunct to scaling and root planning.[5]

Dosage: 20 mg twice daily for three to nine months[5]

Mechanism of action: Periostat has three mechanism of actions.[6]

1. Matrix metalloproteinases are the zinc and calcium dependent proteolytic enzyme, this means that the active component through which matrix metalloproteinases causes extracellular matrix destruction in periodontitis are the zinc and calcium ions which are present in matrix metalloproteinases. Periostat after binding to these Matrix metalloproteinases results in chelation with these zinc and calcium ions thus inactivating these metallic ions resulting in inability of these matrix metalloproteinases to cause extracellular matrix degradation.
2. During inflammatory response there is a release of reactive oxygen species by neutrophils. The use of Periostat result in destruction of these reactive oxygen species through the scavenging action of periostat, and thus this scavenging action results in reduction of tissue proteinase activity by the protection of a1-proteinase inhibitor.
3. Periostat downregulates the activity of matrix metalloproteinases by reduction in cytokines level, thus stimulating osteoblastic activity hence enhancing new bone formation and upregulating the collagen synthesis and henceforth preventing the extracellular matrix degradation.

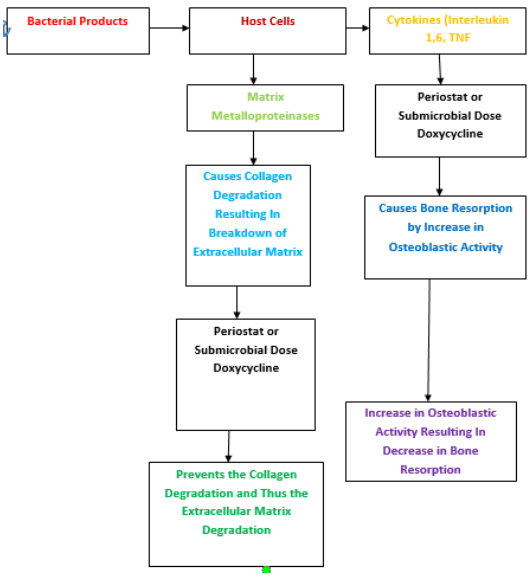

Fig. 2: Mechanism of action of Periostat on the Matrix

5. Metalloproteinases

5.1. Contraindications

Periostat is contraindicated in following situations.[5]

1. Persons having allergy or hypersensitivity to tetracyclines.

2. Preganent or lactating women as it may cause discoloration of child teeth.
3. Patients having gingival or periodontal abscess or in the conditions when antibiotics are indicated.

5.2. Sequencing prescription of periostat with periodontal treatment:[5]

Periostat is indicated as an adjunct to mechanical periodontal therapy and should never be used as a standalone therapy. Periostat should be prescribed to coincide with the first episode of scaling and root planing and is prescribed for 3 months upto a maximum of 9 months of continuous dosing. Modification of any risk factors such as smoking, nutrition, stress, and poor diabetic control can also be addressed at this time.

5.3. Clinical studies on pharmacologic modulation of matrix metalloproteinases

In a study by Golub et al in 1994, and Thomas et al (2000), a subantimicrobial dose of Periostat (20mg) twice daily with the period of long term administration was given in the patients suffering from chronic periodontitis was introduced and the result was the downregulation of collagenase activity without the emergence of periostat resistant microorganism or typical adverse events.[7]

Golub et al in 1997, conducted a study on the use of periostat as an adjunct to scaling and root planing and found that the use of periostat as an adjunct to scaling and root planing resulted in significant reduction in matrix metalloproteinases-8,11 levels in gingival crevicular fluid.[8]

Gapski et al in 2004, conducted a study in which periostat was given bid for 6 months as an adjunct to open flap debridement and was compared with the open flap debridement alone. The results of this study showed that periostat group showed significant probing pocket depth reduction as well as enhanced wound healing as compared to controls.[9]

6. Conclusion

Periodontitis is a disease entity that will result in inflammation and destruction of periodontium. The main etiological factor responsible for the causation of gingivitis and periodontitis is the dental plaque, but it can be modified by the other factors such a host response. Host response refers to how the host cope up with this disease entity. But this host response is not always in favor of host, and hence host modulation is a concept that came into existence in the year 1994 by golub et al. Host modulation is defined as the alteration of the coping up mechanism of the host so that there is an enhancement in host survival of the entire dentition on a long term basis. Periostat also known subantimicrobial dose doxycycline (SDD) is the only food and drug administration (FDA) approval drug for the host modulation. This periostat mainly acts on the matrix metalloproteinases which play and important role in periodontal pathogenesis. The main reason behind using Periostat as a host modulating agent lies in the fact that it acts through chelation, scavenging action which leads to the matrix metalloproteinases inactivation and thus preventing the breakdown of extracellular matrix. Periostat is given as 20 mg bid for a period of three to nine months. Thus host response and its modulation forms an essential criteria in the management of periodontitis for the prolong survival of entire dentition.

7. Source of Funding

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8. Conflict of Interest

The authors declare no potential conflicts of interest concerning the authorship and publication of this article.

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