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ROLE OF MATRIX METALLO PROTEINASES IN PERIODONTAL DISEASES- A BRIEF OVERVIEW

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ABSTRACT

Periodontitis refers to the infectious diseases typified by specific immune-mediated obliteration of the supporting tissues of periodontium and tooth loss. Matrix metalloproteinases (MMPs) comprises of the zinc containing enzymes that degrades the specific extracellular matrix (ECM) components, thus, abolishing the matrix symmetry, balance and structural veracity. These molecules have several actions in tissues and basically produced by several host cells like fibroblasts, inflammatory cells, epithelial cells. An equilibrium between the production of MMPs and its inhibitors is of prime concern so as to preserve the normal physiologic structure of host tissues. The learning and growing interest in MMP has been shown to provide evidence signifying the extensive range of molecules that can be cleaved by them and the innumerable biological progressions that can be regulated by them. In this review, an outline of incipient evidence of MMPs and their role in the regulation of periodontal disease is portrayed briefly.

Key words:- Matrix Metalloproteinases, Perodontal disease, Extracellular matrix, Biomarker

INTRODUCTION

Matrix metalloproteinases (MMPs), aka 'matrixins', belongs to a large group of zinc-dependent proteases that are thought to be accountable for cleaving and reconstruction of the connective tissue components like collagen, elastin, gelatin and casein.[1] MMPs have an active role in the degradation of extracellular matrix (ECM) occurring through developmental stages like growth and morphogenesis. MMPs movement and activity can be witnessed in several diseases and pathological courses (like inflammation and cancer) especially involving the connective tissue degradation owing to their physiological functions. These enzymes do occur in various forms and alterations with varied location, substrate specificity and regulation, thus, playing vital roles within an organism.[2]

Periodontal disease refers to the common chronic pathological conditions affecting the periodontal tissues and surrounding structures involving the gingiva, periodontal ligament (PDL), radicular cementum and alveolar bone. Gingivitis occurs due to the interaction of the bacterial and host at the biofilm–periodontium boundary that triggers gingival inflammation. This further grows and progresses over time to the immune-mediated loss of the periodontal supporting tissues and structures resulting in the destructive form of the disease.[3]

The MMPs and their tissue inhibitors (TIMPs) facilitate the physiological tissue remodelling of the PDL. Nevertheless, due to certain disturbances of the equilibrium between MMPs and TIMPs can sometimes result in tissue breakdown leading to periodontal disease.[4,5]

MMPs- Structure, Histology Classification and Function

Jerome Gross and Charles Lapiere were the first to recognize an MMP with the help of biochemical approach. It was Ed Harris et al., 1980s, who were the first to suggest the name MMP to such molecules. Afterwards, the International Union of Biochemistry and Molecular Biology nominated the family with the exceptional name MMPs and allocated every single family member with a specific enzyme number.[6] MMPs are family of 24 enzymes consisting of analogous structure most of the time (approximate 40% cases). They are Zn-dependent endopeptidase, frequently released in an inactive form (except the membrane-associated MMPs or MT-MMPs). The principal structure of a single MMP can be divided into three main sections: N-terminal peptide, the catalytic segment (lined with a hinge), and C-terminal domain.[7] MMPs can be secreted by different host cells and bacteria like the fibroblasts, inflammatory cells, epithelial cells & bacteria such as P gingivalis and A actinomycetemcomitans.[8] MMPs can be classified into six groups depending upon their cleavage capability: **collagenases, gelatinases, matrilysins, stromelysin membrane-associated MMPs, and MMPs with no group designation**. Numbers are used to designate these MMP enzymes like- MMP-1 to MMP-28. Classification of MMP's is given in table 1. They have the ability to cleave the major and minor components of the ECM, (with certain exclusions like- MMP-11 and MMP-23). They also can lyse the ECM components and act as an activator for significant biological molecules. It is however, seen that the mode of action of different types of MMPs is importantly reliant on the group to which they belong. Examples of few of their functions can be enlisted as:-Collagenases (MMP-1, MMP-8, and MMP-13) helps to degrade the interstitial collagen (types I, II, and III). Gelatinases (MMP-2 and MMP-9), primarily cleave collagen type IV in basal membranes, and can also denature the collagen types V, VII, X, XIV, elastin, fibronectin, and aggrecan. Stromelysins can cleave the non-collagenous ECM (fibronectin, proteoglycans, laminin, and glycoproteins). MT-MMPs primarily facilitates the collagen degradation of the cell membrane. The macrophage elastase and other MMPs, mainly MMP-12, helps to cleave elastin, laminin, fibronectin, emalogenin, entactin, collagen, basal membrane, chondroitin sulfate etc.[9,10,11]

TABLE 1 : CLASSIFICATION OF MMPs[2,11]

Sl No.	MMP	No of class	Enzyme	Substrate	kDa	Human Chromosome location
1.	MMP -1	Collagenases	Collagenase-1	Collagens (I–III, VII, VIII, and X), gelatin, aggrecan, L-selectin, IL-1β, proteoglycans, entactin, ovostatin, MMP-2, MMP-9	43	11q22-q23
2.	MMP-8	Collagenases	Collagenase-2/neutrophil collagenase	Collagens (I–III, V, VII, VIII, and X), gelatin, aggrecan, fibronectin	58	11q21-q22
3.	MMP-13	Collagenases	Collagenase-3	Collagens (I–IV, IX, X, and XIV), gelatin, plasminogen, aggrecan, perlecan, fibronectin, osteonectin, MMP-9	55	11q22.3
4.	MMP-18	Collagenases	Collagenase-4	Type I collagen		
5.	MMP-2	Gelatinases	Gelatinase-A	Gelatin, collagen IV–VI, X, elastin, fibronectin	66	16q13
6.	MMP-9	Gelatinases	Gelatinase-A	Collagens (IV, V, VII, X, and XIV), gelatin, entactin, aggrecan, elastin, fibronectin, osteonectin, plasminogen, MBP, IL-1β	92	20q11.2-q13.1

7.	MMP-3	Stromelysins	Stromelysin-1	Collagens (III–V, and IX), gelatin, aggrecan, perlecan, decorin, laminin, elastin, casein, osteonectin, ovostatin, entactin, plasminogen, MBP, IL-1β, MMP-2/TIMP-2, MMP-7, MMP-8,MMP-9, MMP-13	46	11q23
8.	MMP-10	Stromelysins	Stromelysin-2	Collagens (III–V), gelatin, casein, aggrecan, elastin, MMP-1, MMP-8	46	11q22.3-q23
9.	MMP-11	Stromelysins	Stromelysin-3	Unknown (casein)	44	22q11.2
10.	MMP-17	Stromelysins	Homology tostromelysin-2 (51.6%)			
11.	MMP-7	Matrilysins	Matrilysin (PUMP)	Collagens (IV, X), gelatin, aggrecan, decorin, fibronectin, laminin, elastin, casein, transferrin, plasminogen, MBP, β4-integrin, MMP-1, MMP-2, MMP-9, MMP-9/TIMP-1	20	11q21-q22
12.	MMP-26	Matrilysins	Matrilysin-2	Collagen IV, fibronectin, fibrinogen, gelatin, α (1)-proteinase inhibitor		11p15
13.	MMP-14	MT-MMP	MT1-MMP	Collagens (I–III), gelatin, casein, fibronectin, laminin, vitronectin, entactin, proteoglycans, MMP-2, MMP-13	54	14q11-q12
14.	MMP-15	MT-MMP	MT2-MMP	Fibronectin, entactin, laminin, aggrecan, perlecan; MMP-2	61	16q13-q21
15.	MMP-16	MT-MMP	MT3-MMP	Collagen III, gelatin, casein, fibronectin, MMP-2	55	8q21
16.	MMP-17	MT-MMP	MT4-MMP		54	12q24.3
17.	MMP-24	MT-MMP	MT5-MMP	Fibronectin, but not collagen type I or laminin	54	20q11.2
18.	MMP-25	MT-MMP	MT6-MMP	Progelatinase A		16p13.3
19.	MMP-12	Other enzymes	Macrophage metalloelastase	Collagen IV, gelatin, elastin, casein, fibronectin, vitronectin, laminin, entactin, MBP, fibrinogen, fibrin, plasminogen	45	11q22.2-q22.3

20.	MMP-19	Other enzymes	RASI 1	Type I collagen		12q14
21.	MMP-20	Other enzymes	Enamelysin	Amelogenin, aggrecan, COMP		11q22.3
22.	MMP-21	Other enzymes	MMP identified on chromosome 1			
23.	MMP-22	Other enzymes	MMP identified on chromosome 1			11q24
24.	MMP-23	Other enzymes	From human ovary cDNA			1p36.3
25.	MMP-28	Other enzymes	Epilysin			17q11.2
26.	MMP-29	Other enzymes	Unnamed			

PATHOPHYSIOLOGY OF MMPs

Most MMPs own dissimilar chief structures but consists of common modules called protein domains. They contain numerous different functional domains like N-terminal signal peptide or pro-domain that guides the synthesis of MMP within the cell and is removed before secretion; the pro-domain that maintains the enzyme in an inactive state; a catalytic domain comprising of a conserved Zn-binding region and a conserved methionine, determining substrate specificity of MMP; a hinge or linker domain linking catalytic domain to hemopexin domain; and the hemopexin domain binding the TIMPs and certain substrates and helps in membrane activation and few proteolytic activities. MMPs are typically formed in dormant non-active forms, hence, activation with a cysteine switch is obligatory for the enzyme function. Activation can take place either in extracellular or in intracellular space depending on MMP structure. MMP proenzyme comprises of unmatched cysteine sulfhydryl groups, that gets cleaved proteolytically or non-proteolytically for its activation. Several proteolytic enzymes like serine protease plasmin, bacteria proteases along with oxidative stress, and other MMPs helps in proteolytic activation. Non-proteolytic activation can be attained in vitro by SH-reactive agents, using mercurial compounds, detergents, gold compounds, or by oxidation. The extracellular proteolysis occurring via MMP needs to be controlled in a specific manner in order to maintain equilibrium. Endogenous inhibitors like TIMP (from human cells) and exogenous inhibitors like α-2 macroglobulin (synthesized as therapeutic agents) have the potential to inhibit the activity of MMPs.[12]

ROLE OF MMP IN ORAL ENVIRONMENT

The physiological and pathological activities in the oral cavity entails the diverse functions of MMPs, wherein, it has been seen to be isolated from samples of GCF, enamel, saliva and periodontal tissues. Various major events of the oral cavity like enamel formation, cell migration, tissue remodelling, wound healing, and organogenesis involve the actions of MMPs. They are proven to have a role in the remodelling of the organic matrix of dentin and bone during the formation and repair of the oral tissue. There are certain events like immune response, inflammation and ECM remodelling that demands the role of MMPs specifically. The production, activation, and inhibition of these MMPs are all strongly controlled in health and it is only when uninhibited dysregulation of MMPs occurs, certain destructive actions supervene.[13,14]

ROLE OF MMP IN PERIODONTAL DISEASE

Chronic or aggressive periodontal disease is considered to be a continuing chronic inflammation and tissue destruction resulting in pocket formation and severe bone loss. The process of destruction is principally associated with bacterial actions leading to over expression of defense mechanism like MMPs and other mediators. These are thought to be formed by infiltrating neutrophils, macrophages, and the resident cells of periodontium. There exists ample amount of evidence incriminating the fundamental function of MMPs in periodontal diseases.[7]

MMPs play essential role in the dilapidation and destruction of the ECM, basement membrane and defensive serpins and in the alteration of cytokine action and initiation of osteoclasts.

- Collagenases are thought to be produced by the resident gingival and periodontal ligament fibroblasts that plays an essential role in normal tissue turnover.
- Neutrophils produce collagenase and gelatinase that causes periodontitis.
- The apical migration and lateral extension of the junctional epithelium along with loss of connective tissue attachment is facilitated by enzymes produced by epithelial.
- Fibroblast collagenase (FIB-CL) is released by the osteoblasts when provoked by bone-resorbing agents. It is documented that osteoclastic bone resorption is started by the osteoblastic reaction to resorptive signals [parathyroid hormone (PTH)], involving the expression of FIB-CL and other MMPs thus, causing dissolution of the unmineralized collagenous osteoid layer.
- MMP (including MMPs-1,2,3,7,8,and 9), are thought to be seen in greater proportion in the GCF and saliva samples retrieved from periodontitis patients that elicits direct correlation with initiation and progression of periodontal disease.
- MMP-13, and MMP-14, with the help of pro-MMP-9, also causes periodontal tissue destruction by synchronized actions along with other proteinases.

These activated MMPs help to stimulate the synthesis and production of other signaling molecules (cytokines and chemokines), that further facilitates the regulation of the progression of periodontal disease. Studies have shown that management of periodontitis (especially scaling and root planing) decreased the level of different MMPs (MMPs-1,2,3,8,9,12, and13). Phase 1 therapy including the abolition and control of the causative and predisposing factors tends to reduce the MMP levels and increases the ratio of TIMPs. MMP-8 and MMP-1 isolated from GCF proves to be essential biomarkers to differentiate between different types of periodontal lesions and also monitors the maintenance phase.[3,5,6]

DEGRADATION OF THE PERIODONTIUM

MMPs assist in the degradation of ECM components and facilitates cell migration, wound healing and tissue remodelling. They are related to arthritis, periodontitis, hepatitis, glomerulonephritis, atherosclerosis and cancer cell invasion. They activate the latent form of pro-inflammatory mediators like interleukin (IL)-1β, TGF- β1, membrane bound tumour necrosis factor (TNF)-α and dissimilar MMPs. These MMPs get secreted in latent, inactive pro-enzyme forms wherein plasmin and other MMPs acts as activators. Their activity is additionally controlled by the TIMPs 1,2,3 and 4.[15]

Production of MMP by cytokines and growth factors

The various cells like polymorphonuclear leukocytes, fibroblasts, keratinocytes, macrophages and endothelial cells, when activated by different cytokines, arachidonic acid metabolites and growth factors, helps in the production of MMPs. Osteoblasts gets activated by PTH, vitamin D3, IL-1, TNF-α, prostaglandin E2 and endotoxin and Osteoclasts produce and synthesize the MMPs. MMP-13 or collagenase-3 (activated by membrane-type matrix metalloproteinase or MT1-matrix metalloproteinase or MMP-14) is found to be connected with degradation of collagen during bone resorption.[16]

Gingival MMP & alveolar bone loss

Collagenase and gelatinases have been detected in GCF and in inflamed gingiva that exhibits positive associations between MMPs and the chronicity of periodontal disease. MMP-8 (main interstitial collagenase) is present in gingival extracts and GCF. MMP-13 is seen in the GCF of periodontitis patients and it seems chiefly accountable for the degradation of non-mineralized osteoid layer on the bone surface thus revealing the mineralized matrix to osteoclasts. MMP-1,8 and 13 facilitates the digestion of type I collagen which is regarded as the early step of the process of bone resorption. Denatured collagen fragments also gets degraded by gelatinases MMP-2 and MMP-9 (assists cathepsin K in osteoclastic bone resorption).[16,17]

The regulation of MMP involves the following steps:-

a) ***Transcriptional regulation of MMP expression:*** It has been documented that the secretion of MMP s increase on demand in the tissues. The neutrophils store MMP-8 and other MMPs subcellularly and releases them speedily (selective degranulation). At the transcriptional level MMP expression is controlled by several growth factors and cytokines, oncogenes, hormones. AP-1(activator protein-1) transcription factor complexes get activated by extracellular stimulus and binds to the AP-1 binding site in the MMP gene thus stimulating the secretion of MMP.[8]
b) ***By precursor activation:*** MMP needs to get converted to the active form that is obligatory for enzyme function with the help of the interaction between cysteine residue and zinc ion. During this activation,

the opening of the Cys-Zn^{2+} bond releases Zn^{2+} ions that reacts with H_2O to sustain the open form of MMP that in turn needs to pass through numerous other structural changes be totally active.[8]

c) ***Substrate specificity:*** it is known that enzymes consist of overlapping substrate specificities although notable differences of the collage cleavage especially if major concern here.[8]

d) ***Inhibition inhibitors of MMP:*** they help to prevent the overproduction of MMP, thus, avert the tissue destruction. These MMP inhibitors depicts therapeutic role of MMPs and can prevent its overproduction, thus, evading tissue destruction and pathological condition.[8]

MMP INHIBITORS

TIMPs that bind MMPs in a 1:1 stoichiometry is considered to be endogenous inhibitors. They consist of four types named TIMP 1–4 whose expression and secretion is monitored and controlled during development and tissue remodeling.[12]

❖ ***Exogenous:-***[18]

MMPs inhibition proves to be an efficient adjunct treatment in treating periodontitis since they are important mediators of the connective tissue breakdown. They are of 3 categories:-

1. Collagen peptidomimetics and non-peptidomimetics

- ✓ Peptidomimetic MMP inhibitors
- ✓ Batimastat
- ✓ Marimastat
- ✓ Nonpeptidic MMP inhibitors
- ✓ BAY 12-9566
- ✓ AG3340
- ✓ BMS-27529
- ✓ CGS-27023A

2. Tetracycline derivatives

- ✓ Doxycycline
- ✓ Col-3 (metastat)

3. Bisphosphonates

ROLE OF MMP INHIBITORS IN PERIODONTAL DISEASE (PARMAR)

A distressed and upset equilibrium between MMPs and TIMPs might lead to the degenerative matrix degradation and disease process. The presence of MMPs and TIMPs in saliva, GCF, or serum delivers supplementary evidence about disease progression. TIMP levels are usually seen to be higher than in inflamed conditions (MMP levels > TIMP levels). Thus, presence of active MMPs is directly proportional to the severity of inflammation. It is found that MMP-1, -2, -3, and -9 are markedly elevated while, TIMP-1 and -2 are pointedly reduced. Hence, MMP inhibition or augmented TIMP expression, can decrease periodontal tissue destruction. Examples of inhibitors are:-Alpha 2- macroglobulins, Tissue inhibitors of metalloproteinases, Inhibiting antibodies, Synthetic inhibitors. [6]

❖ ***Endogenous or natural inhibitors***[18]

MMP tissue inhibitors and Alpha 2-macroglobulin bind non-covalently to members of the MMP family. TIMPs regulated the MMP activities pericellularly, while, Alpha 2-macroglobulin regulates body fluids. TIMPs might seep through the vasculature and act in the ECM owing to its high molecular weight during inflammation. Several synthetic peptides are being articulated so as to produce accurate chelators involving phosphorus containing peptides, sulfur-based inhibitors and peptidyl hydroxamic acid derivatives (mostly used). They are of 3 categories:-

a) Collagen peptidomimetics (Batimastat, Marimastat) and non-peptidomimetics (BAY 12–9566, AG3340, BMS- 275291, CGS-27023A)

b) Tetracycline derivatives- Doxycycline, Col-3 (metastat)

c) Bisphosphonates

Therapeutic considerations

MMP inhibition can be achieved by targeted therapy that can serve as potential therapeutic stratagem for the treatment of periodontitis. This can act as an adjunctive therapy along with routine clinical therapy (scaling and root planing) that would advantageous to improve prognosis of the disease. Modified tetracyclines, as approved by FDI are the MMPIs that are used in periodontal disease management. Chemical modification of the molecules of tetracycline family wherein, separation of the antibiotic and protease inhibitory activities are conducted have also been used to produce inhibitors. Such antibiotics without the actual antibiotic properties proves beneficial owing to the absence of gastrointestinal side effects, toxicity or increased plasma concentrations for long time. *Doxycycline hyclate,* is a low-dose tetracycline analogue without any anti-microbial activity is constructively used for treating periodontal diseases. This facilitates the inhibition of MMP-8 and MMP-13 protease mechanisms and due to the modulation of the host response. Tetracyclines (used along with standard mechanical therapy of scaling and root planning), tend to inhibit MMP activity due to its cationic binding proteins.

Certain chelating agents including EDTA, EGTA, or 1,10 phenanthroline has an inhibitory action on MMPs. Few MMPs can also be inhibited by chlorhexidine. Hence, the use of targeted therapy with regards to MMP acts as a useful aide to scaling and root planing procedures in periodontal diseases.[12]

CONCLUSION

It has been documented through previous studies that MMPs have a significant role in inflammation and immune response regulation. They are proficient to facilitate the cross-activation and auto-activation cascades, and also regulate the accessibility of numerous inflammatory signaling molecules especially in periodontally inflamed cases. MMPs have the potential to increase or decrease the bioavailability of signaling molecules with the help of various complementary mechanisms resulting in extensive loss of periodontal supporting tissue and initiating inflammation. Hence, it can be concluded that MMPs belonging to the endopeptidases family, are proficient enough to degrade the ECM, collagen fibers and basement membrane resulting in periodontal diseases. Thus, adequate recognition and lessening of these levels are imperative for inhibition of the progressive lesions.

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