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Metalloproteinase (MMPs) As Prognostic and Diagnostic Tool in Periodontics – A Review

KEYWORDS: Matrix metalloproteinase, Periodontitis, Tissue inhibitors of Matrix metalloproteinase (TIMPs), extracellular matrix (ECM).

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ABSTRACT *Matrix Metalloproteinase (MMPs)are group of enzyme that in concert are responsible for the degradation of most extracellular matrix proteins during organogenesis,growth and normal tissue turnover. The expression and activity of MMPs in adult tissue is normally quite low, but increases significantly in various pathological condition that may lead into unwanted tissue destruction,such as in inflammatory disease,tumor growth and metastasis. MMPs have a marked role in tissue destructive oral disease.the role of collagenase,especially MMP-8 in periodontitis and peri-implantitis is the best known example of unwanted tissue destruction related to increased presence and activity of MMPs at site of disease.*

INTRODUCTION

Matrix metalloproteinases (MMPs) (also called matrixins) are a large family of calcium dependent zinc-containing endopeptidases, which are responsible for tissue remodeling and degradation of extracellular matrix including collagen,elastin,gelatin,matrix glycoprotein and proteoglycans.. They are distinguished from other endopeptidases by their dependence on metal ions as cofactors, their ability to degrade extracellular matrix (ECM), and their specific evolutionary DNA sequence. Members of the family of metalloproteinases are mainly but not exclusively synthesized by connective tissue cells. Metalloproteinases can also be synthesized by hemopoietic cells, including monocytes and macrophages, keratinocytes, endothelial cell.

MMPs And Their Classification

On the basis of substrate specificity and homology, MMPs can be divided into 6 groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs (MT-MMPs), and other MMPs (Table 1).

No.	MMP No	Class	Enzyme
1	MMP-1	Collagenases	Collagenase-1
2	MMP-8		Neutrophil collagenase
3	MMP-13		Collagenase-3
4	MMP-18		Collagenase-4
5	MMP-2	Gelatinases	Gelatinase-A
6	MMP-9		Gelatinases-B
7	MMP-3	Stromelysins	Stromelysin-1
8	MMP-10		Stromelysin-2
9	MMP-11		Stromelysin-3
10	MMP-27		Homology to stromelysin-2 (51.6%)
11	MMP-7	Matrilysins	Matrilysin (PUMP)
12	MMP-26		Matrilysin-2
13	MMP-14	MT-MMP (membrane type)	MT1-MMP
14	MMP-15		MT2-MMP
15	MMP-16		MT3-MMP
16	MMP-17		MT4-MMP
17	MMP-24		MT5-MMP
18	MMP-25		MT6-MMP
19	MMP-12	Other enzymes	Macrophage metalloelastase
20	MMP-19		RASI 1
21	MMP-20		Enamelysin
22	MMP-21		MMP identified on chromosome 1
23	MMP-22		MMP identified on chromosome 1
24	MMP-23		From human ovary cDNA
25	MMP-28		Epilysin
26	MMP-29		Unnamed

Matix metalloproteinases are inhibited by tissue inhibitors of Matix metalloproteinases(TIMPs). They may be both endogenous and exogenous. The endogenous metalloproteinases are TIMPs. Exogenous MMP inhibitors include hydroxamic acid derivatives such as batimastat (BB-94), marimasta (BB-2516),116 and SM-25453. MMPs are inactivated by TIMP-1, TIMP-2, TIMP-3, and TIMP-4, which act by forming a 1:1 complex with the catalytic zinc in the MMPs site. TIMPs may be either secreted as soluble proteins (TIMP-1, TIMP-2, and TIMP-4) or bound to ECM components (TIMP-3).

Metalloproteinases And Tissue Inhibitors Of Metalloproteinases In Periodontitis

A relationship has been established between latent and active forms of collagenase extracted from gingival tissues and inflammation[2]. Collagenase activity has been identified not only in gingival explant culture supernatants but also in gingival crevicular fluids at levels that correlate with disease activity: collagenase activity can be found in the crevicular fluid of patients with periodontitis in much larger amounts than in control subjects[3]. This collagenase seems to be only partly tissue derived and mostly from polymorphonuclear leukocytes in the inflammatory infiltrate. Gelatinase B (MMP-9) is prominent in crevicular fluid and gingival tissue specimens from patients with periodontitis.

Sorsa et al[4] demonstrated that the major collagenase in periodontitis was human collagenase-2, MMP-8, accompanied by MMP-9. These findings have been confirmed and extended by the studies utilizing a wide range of RNA-

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and protein analyzing techniques specific for MMPs and TIMPs. Tissue inhibitors of metalloproteinase levels could be measured only in healthy individuals or in clinically healthy sites.

In recent clinical studies, Lee et al.[5] showed a good correlation between active MMP-8 and disease activity, whereas Hayakawa et al.[6] found significantly lower TIMP-1 levels in whole saliva in diseased subjects compared with healthy normal subjects. Thus, it seems that periodontal disease activity does indicate an imbalance of proteinases over inhibitors.

Proteinases And The Phagocytic Pathway For Collagen Breakdown

Everts et al.[7] studied degradation of collagen in the bone-resorbing area underlying the osteoclast. This degradation clearly involved both metalloproteinases and certain cysteine- proteinases. Studies show that specific inhibitors of a cysteine proteinase (cathepsin B) and metalloproteinases (collagenase and gelatinases A and B) can block bone resorption in vivo[8].

Gelatinase-B has been implicated along with collagenase as of importance in osteoclastic bone resorption. In situations where there is a high turnover of matrix (such as inflammation), the metalloproteinases are especially important in a mainly extracellular pathway of degradation.

Immunolocalization Of Metalloproteinases In Periodontal Disease

On histological and morphological examination it was found that MMPs may be synthesized by both fibroblastic cells and macrophages. Cells secreting metalloproteinases and TIMP- 1 were often observed in sites with connective tissue remodeling. The report of collagenase immunolocalization in human gingival biopsy specimens of periodontitis patients[9] suggested that MMPs are associated with inflammatory cells. Collagenase, gelatinase **A,** stromelysin- 1 and their specific inhibitor TIMP-1 can be immunolocalized from gingival tissues of patients with periodontitis and patients undergoing crown lengthening.

Balance Of Metalloproteinases And Tissue Inhibitors Of Metalloproteinases In Tissue Remodeling

A study showing reduction in tissue inhibitor of MMP synthesis compared with MMP in synovial explants from a rabbit model arthritis and later from studies of human rheumatoid synovium in culture gave the first evidence that tissue destruction in this process might result from imbalance in MMP over TIMP. Iintial destruction is by specific attack on matrix macromolecules by MMP. This would further facilitate extracellular degradation and add to any intacellular degradation by phagocytosis.

Future Prospects

With a wealth of information provided in this field over the last few years we have begun to understand the significance of matrixins in biology and pathology. The actions of matrixins *in vivo* are complex and diverse; they are not restricted to simple breakdown of ECM, but they may reveal cryptic biological functions of ECM macromolecules. Both concepts need to be taken into consideration for our understanding of the timely alteration of cellular environments required in normal development and morphogenesis. Detailed structural and functional analyses of MMPs led to the development of numerous potent synthetic inhibitors of matrixins, and some are in clinical trials to treat patients with cancer, arthritis, periodontal disease, and corneal ulceration. Such agents may be of great therapeutic value, but concerns remain about the consequences of inhibiting biologically functioning matrixins and related ADAMs. Alternative approaches may be tissue-targeted gene therapy with TIMPs or TIMP variants that selectively inhibit specific metalloproteinases. We also anticipate the discovery of many more new MMPs, which will introduce further complexity in tissue matrix catabolism. Such discovery would reveal more precise mechanisms of tissue matrix turnover. The further gain of knowledge about the mechanisms of cell/tissue-specific regulation of MMP gene expression and their signal transduction pathways may also lead to the rational design of inhibitors that perturb the production of MMPs in a particular cell type without affecting other cells. Such agents will be of great value not only for understanding of the basic biology of matrix and its turnover but also for intervention of diseases resulting from aberrant ECM degradation

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