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Short Communication

Matrix Metalloprotienases and its inhibitors: An insight

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Abstract:

Periodontal disease progression involves degradation of the collagenous matrix by a group of enzymes known as the matrix metalloprotienases. These matrix metalloprotienases are secreted by the polymorphonuclear leukocytes, macrophages, fibroblasts, bone, epithelial and endothelial cells. These molecules have involvement in both physiological and pathological processes. It is shown that periodontal disease occurs when there is an imbalance between the activated metalloprotienases and their endogenous inhibitors. These can be modified by exogenous inhibitors like bisphosphonates, tetracyclines, etc.

Key Words: Collagenous matrix, matrix metalloprotienases, periodontal diseases

Introduction

Periodontal disease progression during active phase is the consequences of breakdown of the collagenous fibres and the extracellular matrix.

There are various pathways for the metabolic degradation of extracellular matrix:

1. Plg-dependent pathway
2. MMP pathway
3. PMN serine protienase pathway
4. Phagocytic pathway
5. Osteoclastic pathway

Role of Matrix Metalloprotienases

These endopeptidases share several characteristics. All are secreted in precursor form that requires activation and all are inhibited by tissue inhibitors of metalloprotienaes (TIMPS). They share structural features and amino acid sequences. All family members degrade one or more components of extracellular matrix.

Major classes of MMPs are Collagenases, Gelatinases, Stromelysin and Matrilysin Pump. Their substrates are mainly collagen type I, II, III and X, collagen type IV, V, VII, X, XI, proteoglycan core proteins and type IV collagen(X links), stromelysin and elastin respectively.

Structure

Structurally there is a high degree of similarity between the amino acid sequences in each group and between groups.[1] All MMPs may be regarded as derivatives of a 6 domain prototype structure, formed either by addition or deletion of regulatory domains.[2]

Domain 1

All the metalloprotienases have a propeptide of about 80 residues containing a region of homology with a conserved cystine that has importance in preserving latency of proform.

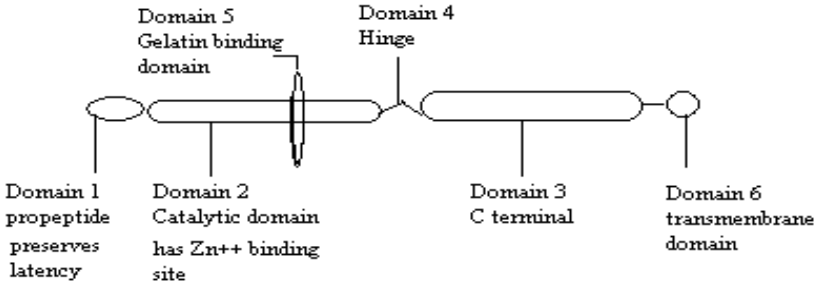

Figure 1: Basic structure of Matrixmetalloprotinase showing the six domains.

Domain 2

The catalytic domain, it has conserved Zn++ binding site with 8 histidine residues, contained within a Zn++ and Ca++ region about 160 residues.

Domain 3

- C terminal domains of 200-300 residues are found in all MMPs except matrilysin,
- they contain a disulfide bridge. This domain in collagenase constitute a four bladed
- beta propeller structure, that interacts with substrates.

Domain 4

Except matrilysin all MMPs have a proline rich hinge region that connects domain2 with domain3.

Domain 5

The gelatinases alone have a domain associated with the catalytic domain, resembling motifs in the fibronectin molecule, and there is an additional insert in gelatinase beta with homology to type V collagen (Figure 1).

Domain 6

In the case of the membrane bound group there is an additional short charged region at the C terminus and a putative membrane-spanning motif (Figure 1).

It seems likely that the catalytic domain of metalloprotienases is sufficient alone for substrate cleavage but that the c terminal regions have much influence on specific substrate interactions.

Activation of MMP precursors

The latency of MMP precursors appear to be maintained,at least in part by a coordinate bond which links an unpaired cystine residue in the propeptide to the active site Zn ++in the catalytic domain.[3]

Disruption of this Cys- Zn++bond may be achieved in different ways:

1. by interaction or modification of the cystiene residue by organomercurials, metal ions, thio; reagents and oxidants(HOCL)
2. by conformational change of the polypeptide backbone induced by certain chaotropic agents(KI,NaSCN) and detergents(SDS)
3. by excision of a portion of propeptide by proteolytic enzyme s like trypsin, plasmin, chymotrypsin, neutrophil elastase, cathepsin B and plasma kallikrein.

Matrix Metalloproteinase activity and periodontal disease

In periodontal disease, matrix metalloproteinase's play key role in the degradation of the extracellular matrix, basement membrane and protective serpins as well as in the modification of cytokine action and activation of osteoclasts.[4]

Some bacteria associated with periodontitis are capable of producing bacterial collagenases ex) Porphyromonas gingivalis and Actinobacillus Actinomycetumcomitans, these proteinases are however not believed to be of major importance in periodontal collagen breakdown.The differentiating factor between mammalian and bacterial collagenases is their different modes of collagenolysis, mammalian collagenases (MMP-1) cleaves the undenatured triple helical collagen molecule at a single site resulting in characteristic ¾ and ¼ fragments, where as the bacterial collagense attacks the collagen substrate at multiple sites resulting in more than 200 peptide fragments.

The extracellular matrix not only consists of collagen fibrils but also their associated proteoglycan and fibronectin which must be removed first in order for the collagenase to have access to the collagen substrate. MMP -3

Table 1: Classification of Matrix Metalloprotienases.

ENZYME	NOMENCLATURE	MATRIX SUBSTRATE
Interstitial collagenase		
Fibroblast type	MMP – 1	Collagens I, II, III, VII, VIII, X, gelatin
PMN type	MMP – 8	Same as MMP -1
Gelatinase		
72 KDa	MMP – 2	Gelatin, collagenIV, V, VII, X, XI, elastin, Fibronectin
92 KDa	MMP – 9	Gelatin, CollagenIV, V, elastin
Stromelysin - 1	MMP – 3	Proteoglycan core, fibronectin, CollagenIV, V, IX, X, elastins
Stomelysin - 2	MMP – 10	like MMP-3
PUMP - 1	MMP – 7	fibronectin, laminin, collagen, gelatin, PG core protein II

(stromelysin) is effective at degrading proteoglycans and fibronectin (Table 1).

Both resident gingival and periodontal ligament fibroblasts produce collagenases that are involved in normal tissue turnover.[5] Inflammatory cells also produce MMPs mainly neutrophils which is a major source in periodontitis. The loss of delicate balance between the MMPs and its inhibitors results in periodontal disease.[6, 7]

Genetic studies suggested that (MMP-1 and TIMP-1) transcript levels were higher in periodontitis affected gingival compared to healthy gingival. No difference in MMP-8 (neutrophil derived collagenase) transcript levels was found.

Matrix metalloproteinase inhibitors

The inhibitors can be:

Endogenous –Tissue inhibitors of MMPs(TIMPs) and α-2 macroglobulins

or 2. Exogenous- Zn ++ and Ca++ chelating agents EDTA

Phosphorous containing peptides

Sulphur based inhibitors

Hydroxamic acid derivatives- Bisphosphonates

Drugs like tetracyclines, Cyclosporin A[8] and phenytoin

Inhibition of Matrixmetalloprotinase function means inhibition of periodontal disease progression, therefore the use of exogenous inhibitors can be of significant importance in treatment of periodontal disease.

Discussion

To summarize MMP's play a significant role (mainly fibroblast derived collagenases) in the periodontal disease process. The estimation of these proteinases and their inhibitors in saliva and GCF would help in distinguishing periodontal health and disease. Unfortunately, however at present no methods exist that would be sufficiently specific and sensitive and yet at the same time practical in clinical situations. The development of such an assay would probably be a n important addition to the diagnosis and management of periodontal diseases.

Conclusion

To conclude, with the understanding of the role of matrix metalloprotienases in health and as well as in disease we can modulate the factors that induce MMP production and activity. The levels of these indicators in saliva, gingival crevicular fluid and gingival tissues may help us diagnose the type of periodontal disease, their likely response to treatment, the need for additional therapeutic agents and also to monitor the progress of the disease.

References:

1. Reynolds JJ, Meikle MC. Mechanisms of connective tissue matrix destruction in periodontics. Periodontol 2000 1997;14:144-57.
2. Birkedal-Hansen H. Role of Matrix metalloprotienases in human periodontal disease. J Periodontol 1993;64:474-84.
3. Birkedal-Hansen H, Moore WG, Bodden MK, Windsor LJ, Birkedal-Hansen B, DeCarlo A, Engler JA. Matrix metalloprotienases- A Review. Crit Rev Oral Biol Med 1993;4(2):197-250.
4. Reynolds JJ, Hembry RM, Miekle MC. Connective tissue degradation in health and periodontal disease and roles of matrix metalloproteinases and their natural inhibitors. Adv Dent Res 1994;8(2):312-8.
5. Alvares O, Klebe R, Grant G, Cochran DL. Effects of growth factors on the expression of collagenase and TIMP-1 in periodontal ligament cells. J Periodontol 1995;66:552-8.
6. Kinane DF. Regulators of tissue destruction and homeostasis as diagnostic aids in periodontology. Periodontol 2000 2000;24:215-25.
7. Ryan ME, Golub LM. Modulation of matrix metalloproteinase activities in periodontitis as a treatment strategy. Periodontol 2000 2000;24:226-38.
8. Bolzani G, Della Coletta R, MartelliJúnior H, MartelliJúnior H, Graner E. Cyclosporin A inhibits production and activity of matrix metalloproteinases by gingival fibroblasts. J Periodont Res 2000;35:51-8.