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A Review On Matrix Metallo Proteinases And Its Role In Periodontal Diseases

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ABSTRACT

Matrix metalloproteinases (MMPs) are a family of nine or more highly homologous Zn(++)-endopeptidases that collectively cleave most if not all of the constituents of the extracellular matrix. This review article discusses in detail the types of MMPS, its biological actions and role in periodontal disease. The regulation of MMP activity at the transcriptional level and at the extracellular level (precursor activation, inhibition of activated, mature enzymes) is also discussed.

Key words: matrix metalloproteinases, collagenases, periodontal destruction, periodontitis

I.Introduction

The matrix metalloproteinases (MMPs) are a family of structurally and functionally related endoproteinases that are collectively capable of degrading most of the components of the extracellular matrix [1,2].They are calcium dependent, zinc-containing endopeptidases, which are involved in tissue remodelling and the degradation of ECM, including collagens, elastins, gelatin, matrix glycoproteins and proteoglycans.Connective tissue and pro-inflammatory cells secreting MMP'S are fibroblasts, osteoblast, endothelial cells, macrophages, neutrophils and lymphocytes. Expressed as zymogens, they are further processed by other proteolytic enzymes such as serine proteases, furin, plasmin and others and forms active forms.

II. Formation and activation of matrix metalloproteinases

The MMPs are secreted as latent enzymes and hence require activation. They are produced as zymogens with a signal sequence and propeptide segment that must be removed during activation. Proteolysis is tightly regulated to prevent tissue damage.

III. Structure of MMP

A short chain sequence is followed in order by a propeptide which endows the virgin enzyme with catalytic latency, a catalytic domain which contains the active site and the catalytic machinery, a proline rich hinge region and apexin-like COOH- terminal domain which plays a role in determining substrate specificity.

The propeptide domain contains a cysteine residue that binds zinc in the active site to form the cysteine switch. The binding of cysteine in the catalytic domain blocks the active zinc site, maintaining the latent or inactive state[3].All MMP's structural organization present a prepeptide sequence that directs their secretion in the extracellular environment and a propeptide domain that maintains them in their zymogenic form.The propeptide keeps the

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enzyme in an inactive/ latent state through the interaction of a cysteine residue with the catalytic zinc.

MMP's are able to degrade practically all ECM components and can be classified according to their substrate specificity as collagenases, gelatinases, stromelysins and matrilysins. Collagenase degrade triple helical fibrillar collagens, main components of bone and cartilage.Gelatinases degrade molecules in the basal lamina around capillaries, facilitates angiogenesis and neurogenesis and contribute to instigating cell death.Stromelysins[MMP-3, MMP-10, MMP-11 and MMP-7] are small proteases that degrade components of the ECM, although not the triple helical fibrillar collagens.

Table 1- Classification of MMPs[4]

Collagenases	Gelatinases	Stromelysins	Membrane type MMPs
MMP 1 MMP 8 MMP 13	MMP 2 MMP 9	MMP 3 MMP 10 MMP 11	MMP 14 MMP 15 MMP 16 MMP 17 MMP 24 MMP25
Others	Inhibitors	Matrilysins	Enamelysins
MMP 19 MMP 22 MMP 23	TIMP 1 TIMP 2 TIMP 3 TIMP 4	MMP 7	MMP 20
Mettaloelastase			
MMP 12			

IV. Biological action of MMPs

The substrate specificity of the MMPs is not yet fully characterized. Known substrates of the ECM components (fibronectin, vitronectin, laminin, entactin, tenascin, aggrecan, myelin basic protein, etc.). The collagen (Types I, II,III,IV,V,VI,VII,IX,X,XIV) have all been shown to be the substrates for different MMP's with greatly different efficacies.Proteinase inhibitors such as α1- proteinase inhibitor, antithrombin- III and α2-macroglobulin are selectively cleaved by MMP's.

V. Up regulators of MMP[5]

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The up regulators of MMP's includes IL-1β, Tumor necrosis factor-α, Epidermal growth factor, Platelet derived growth factor (PDGF) and Transforming growth factor-α

VI. Down regulators of MMP[5]

The down regulators of MMP's includes Interferon, TNF-β and Glucocorticoids

VII. Regulation of MMPs

Controlled at various levels:

Transcription(by cytokines)[6,7,8,9,10,11]

It is performed by cytokines. Cytokines are the chemical messengers that affect the surrounding or the distant cells by up-regulating or down-regulating the protein synthesis by these cells. Genes for MMP synthesis are activated when remodelling of ECM is required or under pathological conditions during inflammation. MMP-2 is an exception- synthesized and secreted in low quantity in tissues and is identifiable in healthy tissue.Synthesis of MMP-13 is upregulated by osteoblasts when stimulated by IL-1β and TNF-1α, also upregulated by IL-6, TGF-β.TGF-β downregulates MMP-1 and MMP-3 genes. IL-8- potent chemoattractant for neutrophils, stimulates the release of MMP-9 stores in the tertiary granules of the neutrophils in the extracellular environment.

Proteolytic activation of the zymogen form(via plasmin-dependent or MMP-dependent pathway)

Inhibition of the active enzymeα-macroglobulins

They are potent inhibitors of MMP activity.They capture active MMP's by a unique venus fly trap mechanism activated by a cleavage of a bond in the bait region.Cleavage leads to hydrolysis of a labile internal thiol-ester bond and covalent cross linking of a mascentglutamyl residue to lysyl side chain exposed on the surface of the attacking proteinase. The rapid capture rates, particularly with collagenase suggest particularly α2-M, play an important role in the regulation of MMP activity in human periodontal diseases.[12]

VIII. Role of MMPs in periodontal diseases

The microbial etiology of periodontal diseases is well defined. LPS derived from bacteria have the capacity to activate junctional epithelial cells to release potent cytokines such as interleukin-1, interleukin-8, tumor necrosis factor-α, prostaglandins and proteases.These chemoattractant signals lead to the transmigration of leukocytes and monocytes/macrophages.These inflammatory cells further stimulate the resident ligament cells, such as fibroblasts, macrophages, osteoblast, keratinocytes and endothelial cells to produce cytokines and MMPs.[13]

Under normal physiological conditions, the activities of MMPs are precisely regulated at the level of transcription, activation of the precursor zymogens, interaction with specific ECM components, and inhibition by endogenous inhibitors. [14,15]However under pathological

conditions they play an important role in connective tissue degradation. BIRKEDAL-HANSEN et al (1993)[15] have provided the following evidence to prove the involvement of MMPs in periodontal diseases: cells isolated from normal and inflamed gingiva are capable of expressing a wide variety of MMPs in culture; Several MMPs can be detected from the gingiva in vivo andMMP-8 and MMP-3 are readily detected in the gingival crevicular fluid from gingivitis and periodontitis patients.

Furthermore, the authors proposed the following mechanisms responsible for periodontal destruction based on MMPs and TIMPs interaction. Imbalance between MMPs and TIMPs causes irreversible connective tissue breakdown.MMP-8 (neutrophil collagenase) exists in elevated amounts in the GCF collected from inflamed periodontal pockets and is converted to the active form by plaque, host and microbial derived proteases.Periodontal ligament collagen fibres attached to the root surface are destroyed by MMPs, which favors the apical migration and lateral extension of the pocket epithelium i.e attachment loss.

Studies have shown that high concentrations of natural tissue inhibitor of MMPs (TIMPs) are found in the gingival crevicular fluid of healthy gingiva.[16] (Page,1997-PERIO 2000). Collagen type I is the main ECM component of gingiva, PDL and alveolar bone and its destruction is the key factor in uncontrolled destructive lesion.[17,18]The major collagenolytic MMPs associated with the severity of periodontal inflammation and disease are collagenase-2 (MMP-8) and collagenase-3 (MMP-13), whereas collagenase-1 (MMP-1) is related to the physiological periodontal tissue turnover.[19,20]

IX. Conclusion

MMPs are important components in many biological and pathological processes because of their ability to degrade ECM components. Considerable advancements have been made in the understanding of biochemical and structural aspects of MMPs and their mechanical inhibition by TIMPs. They can act as biomarkers for periodontal disease. Studies have shown the use of MMP-8 are a clinically useful oral fluid biomarker in periodontal and periimplant disease. Further research is required to understand the role of MMPs in periodontal diseases and how it can be controlled or modified to prevent connective tissue destruction.

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