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Extracellular Matrix Proteinases

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Received Date: 21-11-2021, **Accepted Date:** 10-01-2022, **Published Date:** 18-01-2022

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Abstract

Matrix metalloproteinases, known also as matrixins, cleave components of the extracellular matrix. They remodel collagen, elastin, gelatin and casein, and contribute to the MMP degradation. MMPs are secreted in latent forms (pro-MMP) and activated as zinc-dependent proteolytic enzymes in the extracellular compartment. MMPs are divided into 6 subgroups:

1. Collagenases that degrade triple-helical fibrillary collagens into $\frac{3}{4}$ - $\frac{1}{4}$ fragments
2. Gelatinases (A and B)
3. Stromelysins
4. Proteoglycanases
5. Matrilysins
6. Membrane-type MMPS, metalloelastase, enamelysin and others MMPs.

Four tissue inhibitors of matrix metalloproteinases (TIMP-1 to -4) have been identified. Enamel matrix of developing teeth MMP20 and KLK-4 were detected during the secretory stage of enamel. MMP20 null mice play role during enamel secretion, whereas KLK4 is crucial during the maturation stage. The additional roles of MMP are wound healing, cancer progression, and skeletal dysplasias. In addition, MMP inhibitors are useful in the prevention of caries progression.

Keywords

Matrix MetalloProteinases; Collagenases; Gelatinases; Stromelysin; Proteoglycanases; Matrilysins; Membrane-Type Mmps; Tissue-Inhibitors of Matrix Metalloproteinases (TIMP); Metalloelastase; Enamelysin (Mmp-20); KLK-4 (Enamel Maturation); Dental Caries

Introduction

Matrix metalloproteinases are members of a family of 28 secreted and membrane-bound zinc-dependent proteolytic enzymes [1]. They are also called matrixins and metzincin proteases. Members of the MMP family include the “classical” MMPs, the membrane-bound MMPs (MT-MMPs), the ADAMs (a disintegrin and metalloproteinase; adamlysins) and the ADAMTS. There are more members in the MMP and ADAMTS family including collagenases, gelatinases, stromelysins, elastases and aggrecanases. Adamlysins are membrane-bound MMPs that also degrade aggrecan. One member of the ADAM family is a tumor necrosis factor (TNF-Alpha)-Converting Enzyme (TACE) that activates pro-TNF-alpha. Most of the MMPs are synthesized as inactive latent enzymes. Conversion to the active enzyme is generally mediated by activator systems that include plasminogen activator or the pro-hormone convertase, furin. MMP activity is regulated by a group of endogenous proteins, called Tissue Inhibitor of Metalloproteinases (TIMPs) that bind to the activated pro-TNF-alpha. Significant advances have occurred in the understanding of the regulation of MMPs, ADAMs and ADAMTSs gene expression [2]. These proteinases are endopeptidases.

Up to now, 28 MMPs genes secreted and cell surface enzymes have been identified [3,4]. Their targets include other proteinases, proteinase inhibitors, growth factor-binding proteins, cell-cell adhesion molecules. These proteinases play important roles in tissue morphogenesis, development and remodeling. MMPs are secreted in latent forms (pro-MMP) and activated in the extra-cellular compartment. Their expressions and activities interact with specific Tissue Inhibitors of Metalloproteinases (TIMPs) [5]. They cleave cell surface receptors, apoptosis, release of apoptotic ligands and are implicated in chemokine/cytokine inactivation, carious lesions, cell migration, and differentiation.

MMP activity are controlled at least three levels: transcription, proteolytic activation of the zymogen form, and inhibition of the active enzyme by natural inhibitors. Numerous physical cellular interactions providing stimuli that can rapidly induce MMP expression.

In addition to craniofacial dysmorphisms caused by impaired intramembranous bone formation, the mice display dwarfism that may reflect defective endochondral ossification. Impaired endochondral ossification is the only developmental defect in MMP-9 null mice, suggesting that the non-redundant functions of MMP-9 during development are highly restricted. In contrast to MMP-9 null mice, MMP-14 null animals display numerous skeletal

defects. In addition to craniofacial dysmorphisms caused by impaired intramembranous bone formation, dwarfism may reflect defective endochondral ossification [6]. MMPs are also implicated in carious lesion development, immunolocalization and activity of the MMP-9 and MMP-2 in odontogenic region as well as pulp and peri-pulpal inflammation.

The aims of this paper are to review matrix proteinases and focusing at their role in carious lesion development.

Classification of MMPs and TIMPs- Roles in Dental Tissues

Classification of MMPS

MMPs are divided into 8 subgroups:

1. Collagenases (MMP-1, MMP-8, MMP-13) and MMP1 degrade triple-helical fibrillary collagens into $\frac{3}{4}$ - $\frac{1}{4}$ fragments
2. Gelatinases MMP-2, MMP-9 (gelatinases A and B)
3. Stromelysins, proteoglycanases MMP-3, MMP-10, MMP-11, MMP-12
4. Matrilysins (MMP-7 and MMP-26)
5. Membrane-type MMPS: (MMP 14, MMP-15, -16, -17, -24, -25) have a furin cleavage.
6. Other MMPs: MMP-11 stromelysin-3, metalloelastase, MMP-19, RASI-1
7. Enamelysin (MMP20)
8. Others MMPs (21, 23, 25, 26, 27, 28) [7-9]

MMPs are: 1. lytic for ECM components, 2. participate in membrane shedding, 3. alter the activity status of other proteases. According to Löffek et al., [10] the structure and function of MMPs and TIMPS (reviewed by Nagase et al., [9]) are implicated in atheroma, arthritis, cancer and chronic tissue ulcer. They are related to proenzyme activation, and mechanisms of inhibition by TIMPs. MMPs play role in the initial dentin mineralization [11]. Tooth germs were cultured for 10d in the presence of Marimastat (a general MMP inhibitor) or CT (1166) a selective inhibitor of gelatinase) [11-14]. Mineralization was impaired.

Stromelysin-1 KSPGs is implicated in predentin in the degradation of C4-S. DS-S, and therefore KS PG [12,15].

Immunofluorescence double labelling showed that MMP-2 colocalized with TIMP-2 mainly in odontoblasts. Their co-localization in predentin and circumpulpal dentin was faint because of the low immunoreactivity of TIMP-2. MMP activities are regulated by two major types of endogenous inhibitors: α -macroglobulin and TIMPs (Fig. 1).

Figure 1: Collagenase 1.

MMP-2

Mesenchymal cells dental papilla and dental follicle- Chromosomal location (16q13). Ectodermal cells produce the enamel organ. Bone tissue is formed around the developing tooth, trapped in a bony crypt. MMP-2 was observed in the dental germ cells, lamina propria, dental follicle ameloblasts, odontoblasts and bone cells [16]. MMP-2 may be important for the extracellular matrix rearrangement necessary for tooth development and secretion of its mineralized tissues.

MMP-9

Latent (pro)-MMP-9 (92 kDa) and active (82 kDa) bands implies a migratory role of cells through basement membrane. Chromosomal location: 20q11-2- q13.1.

Co-localization of MMP-9 and TIMP-1 could be identified in both the odontoblasts and deep dentin. The immunoreactivity of TIMP-1 was mainly located in the lumen of the dentin tubules, whilst that of MMP-9 was predominantly observed in the odontoblast processes and in the dentin matrix (Fig. 2).

Figure 2: MMP-2. MMP-9.

MMP-3 Stromelysin 1

Chromosomal location 11q23. Apart from the gelatinases, there are other MMPs present in the dentin, such as MMP-3, MMP-8 and MMP-20 allowing keratan sulphate proteoglycan concentration near the border where mineralization is initiated [5]. Chondroitin-4-sulphate/dermatan sulphate-containing proteoglycans participate in dentin matrix formation and its subsequent mineralisation [12] (Fig. 3).

Figure 3: Collagenase 3 (Stromelysin 1).

TIMPs

By precisely cleaving large insoluble ECM molecules, MMPs liberate bioactive fragments and growth factors. They change ECM architecture, influencing cellular behaviour [17]. TIMP-1 forms a complex with MMP-9, while TIMP-2 preferentially forms a complex with MMP [18].

Most pro-MMPs synthesized in the latent form are activated in situ by physiological mechanisms. They are inhibited by specific endogenous tissue inhibitor of MMPs (TIMPs 1 to 4) that play roles in the spreading of cancer and in angiogenesis.

MMP-20/enamelysin

MMP20 will also cleave the KLK4 propeptide to produce catalytically active KLK4. In addition, MMP20 is expressed in the odontoblasts of the pulp organ as is MMP2 and both MMP20. MMP20 and KLK4 of odontoblasts are responsible for dentin mineralization.

KLK-4 (kallikrein-related peptidase-4)

KLK-4 is expressed during the early maturation stage when the enamel proteins are reabsorbed from the hardening enamel. KLK4 cleaves amelogenin, and this resulted in the generation of twelve cleavage products which were characterized by N-terminal sequencing. The KLK4 genes of both mouse and human have 6 exons, the rest of which is noncoding [19].

ADAMs

The ADAMs are a fascinating family of transmembrane, secreted proteins with important roles in regulating cell phenotype via their effects on cell adhesion, migration, proteolysis and signalling [20]. ADAMs are also linked to pathological states when their functions are dysregulated, including cancer, cardiovascular disease, asthma, Alzheimer's disease [21]. Meprins, membrane-bound and secreted astracin metalloproteinases, are site-directed inhibitors of metzincin.

Enamel MMPs

MMP20 and KLK4 are necessary to clear proteins from the enamel matrix of developing teeth. MMP 20 is crucial during the secretory-stage matrix, whereas KLK4 was essential during the maturation-stage and there is only limited functional redundancy for these enzymes [22].

MMPs have been suggested to play an important role in the destruction of dentin organic matrix and, therefore, in the control or progression of carious decay. Host-derived MMPs can originate both from saliva and from dentin. They may be activated by an acidic pH brought about by lactate release from cariogenic bacteria. Once activated, they are able to digest demineralized dentin matrix after pH neutralization by salivary buffers. Furthermore, the degradation of SIBLINGs (Small Integrin-binding Ligand N-linked Glycoproteins) by the caries process may potentially enhance the release of MMPs and their activation.

Emmprin

Emmprin (Basigin, CD147) [23,24]: the acronym name for Extracellular Matrix Metalloproteinase Inducer (EMMPRIN) has four isoforms (basigin -1 to -4). Emmprin KO mice display delayed enamel deposition [25]. Emmprin/CD 147 deficiency disturbs ameloblast-odontoblast cross-talk, and delays enamel mineralization [25]. It has also been suggested that EMMPRIN, through the induction of proteases, orchestrate the epithelial-mesenchymal cross-talk necessary for tooth formation, enabling cleavage of the basement membrane and direct cell-cell interactions. At more advanced stages, EMMPRIN can also facilitate enamel

maturation by inducing proteases such as MMP-20 that are capable of cleaving matrix components [26]. EMMPRIN deficiency results of decreased in MMP-3 and MMP-20 expressions.

MMPs and Carious Lesion

Salivary (collagenase-2) and TIMP-1 levels are located in dentinal carious lesions [27].

Cysteine cathepsins activate latent MMPs

MMP-8 is one of the most promising biomarkers for early diagnosis of periodontitis. Caries increase the level of endogenous MMP-2. Acidic pH during the carious process may induce MMP production by odontoblasts as well as their activation. MMP-2, MMP-20 and cathepsin B fluid further contributes to peritubular dentin degradation. Odontoblasts secrete gelatinase A (MMP-2), gelatinase B (MMP-9), collagenase 2 (MMP-8), collagenase-3 (MMP-13), and enamelysin (MMP-20). MMPs participate in dentinal caries development and progression. Cathepsins are present in intact dentin. The consistent detection of cysteine cathepsin activity displays in carious as well as in intact dentin. Significant levels indicate that dentinal cysteine cathepsins have an important role in dentinal caries pathogenesis.

The downregulation of MMP-8 can be a factor leading to reparative dentin formation, since it is essential for modulating tissues during normal dentin formation. Thus, the MMPs expressed by odontoblasts may have a role in reparative dentin formation and the growth factors can act as MMP regulators, as well as collagen synthesis regulators. Taking into consideration the enhanced site of carious lesion, together with the fact that the level of MMPs diminishes, and accompany the spreads of the carious dentin pathology [28].

Host-derived MMPs can originate both from saliva and from dentin. They may be activated by an acidic pH brought about by lactate release from cariogenic bacteria. Once activated, they are able to digest demineralized dentin matrix after pH neutralization by salivary buffers. The different available MMP inhibitors, natural or synthetic, were explored, and suggest that MMP inhibition by several inhibitors, particularly by natural substances, may provide a potential therapeutic pathway limiting caries progression in dentin [29].

Conclusion

MMPs and TIMPs regulate the proteins from the extracellular matrix. Matrix metalloproteinases, known also as matrixins, cleave components of the extracellular matrix. They remodel collagen, elastin, gelatin and casein, and contribute to the MMP degradation. MMPs are secreted in latent forms (pro-MMP) and are activated as zinc-dependent proteolytic enzymes in the extracellular compartment. MMP-2 and -9 play roles in dentin and enamel formation. Mmp20 and KLK-4 were detected during the secretory stage of enamel. MMP20 null mice play important role during enamel secretion, whereas KLK4 is crucial during the maturation stage. MMP activity is tightly controlled at the level of pro-peptide activation and inhibition by TIMPs. In addition, MMP inhibitors are useful in the prevention of caries progression.

Conflict of Interest

The author declares no conflict of interest.

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Goldberg M | Volume 3, Issue 1 (2022) | JCMR-3(1)-045 | Review Article

Citation: Goldberg M. Extracellular Matrix Proteinases. *Jour Clin Med Res*. 2022;3(1):1-10.

DOI: <http://dx.doi.org/10.46889/JCMR.2022.3101>

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