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REVIEW ARTICLE

Dynamics of Matrix Metalloproteinases in the Oral Environment

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ABSTRACT

Matrix metalloproteinases (MMPs) are an important family of zinc-dependent endopeptidases that mediate the extracellular matrix (ECM) degradation. The major component of the extracellular matrix, collagen, is catabolized. These enzymes have been implicated in oral pathologic processes, such as periodontal tissue destruction, root caries, tumor invasion, and temporomandibular joint disorders. The aim of this paper was to review of some general aspects of matrix metalloproteinases and discuss the role of these enzymes in normal physiology and pathology with emphasis on the oral environment. This process is important in a number of aspects of dentistry since matrix is constantly turning over. Although the members of the MMP family matrix possess different substrate specificities, they all possess similar structural and functional features and demonstrate similar mechanisms of proteolysis. The catalytic of the MMPs is regulated at multiple levels including transcription, secretion, activation and inhibition. The growth and repair of connective tissues is a delicately balanced process of ECM removal and replacement with significant control by primary MMPs and their natural inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). Dentists have a need to understand matrix turnover in the periodontal ligament and adjacent structures, embryology and development.

Keywords: Periodontitis, Matrix metalloproteinase, Collagenase, Gelatinase.

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INTRODUCTION

Mouth acts as a window to lot of systemic diseases and serves as a port of entry of the various infections that can alter and affect the immune status of the person. The oral cavity has the potential to harbor at least 600 different bacterial species and, in any given patient, more than 150 species may be present, surfaces of tooth can have as many as billion bacteria in its attached bacterial plaque and good oral hygiene is the fundamental for oral integrity as it greatly affects the quality of life.[1] Periodontitis is a destructive inflammatory disease of the supporting tissues of the teeth and is caused by specific microorganisms or a group of specific microorganisms resulting in progressive destruction of periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both.[2] Periodontitis is initiated by oral biofilm formation if untreated progress to gingivitis further leading to periodontal disease. The link between periodontal disease and systemic diseases has been scientifically proven over last two decades. The principle reason for this oral-systemic connection is dissemination of locally produced proinflammatory mediators, such as C-reactive protein, interleukin-1 beta (IL-1β) and IL-6 and tumor necrosis factor alpha.[3,4] The aim of periodontal therapy is to regenerate and restore the various periodontal components affected by disease to their original form, function and consistency.[5] The matrix metalloproteinase (MMP) corridor seems to be the most pertinent in periodontal disease. The purpose of the current review was to review the roles of MMPs on oral health.

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MATRIX METALLOPROTEINASE: THE CELLULAR ACTIVITY

Matrix metalloproteinase is a family of metal-dependent enzymes endopeptide.[6] In general, represent a class of enzymes that are responsible for the degradation of extracellular matrix (ECM). Reportedly has the ability to degrade virtually all ECM proteins,[7] such as collagen, laminin, fibronectin, elastin and proteoglycan core proteins.[8] The main components of ECM are proteins and polysaccharides are in gels that were hydrated. Macro molecules that build ECM are secreted on fibroblasts. If the matrix is more specific, such as cartilage or bone, the ECM will be secreted by higher level cells differentiation. An example is the bone-forming osteoblasts and chondrocytes which make cartilage. The variation in the combination of macro molecules in the matrix makes the emergence of differences in the formation of a tissue that can be adapted and this depends on the needs of its functions.[9]

The main role of matrix is to provide a framework matrix physically for all cells, also, function as a medium that regulate the identity, position, proliferation and cell fate. Interaction between the two components of both soluble and insoluble between extracellular cavity with cell surface is very vital for the overall development, integrity and function of tissue.[9] The cells within matrix that are able to modify its function depend on the relationship that made with ECM. This is generally through a cell adhesion molecule that crosses the cell membrane to connect with ECM molecules to the cell cytoskeleton.[10]

Up to now, it has been known for more than 20 of MMPs.[8] It is reported the number has reached more than 24 kinds that have been identified and classified successfully.[11,12] The enzyme showed a sequence homology consistent and generally comprises: a pre-domain peptide marker for secretion. Then the pro-domains are very important to maintain latency of properties. As well as the catalytic domain so high that serves to protect the bonding link, and further contains a domain that is shaped like hemopexin.[8] Inhibition of MMP activity performed by protease inhibitors, such as α2-macroglobulin and a group of specific tissue its tissue inhibitors of metalloproteinases called TIMPs.[8,13] Reported that when there is an imbalance between MMP and its inhibitory activity, the activity of MMP will play a critical role in the pathophysiologic process. Its activities known to be associated with several important diseases, such as joint damage in rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, acute myocardial infarction, gastric ulcer, fibrotic lung disease, and cancer.[14-17] In the cancer, the role of MMP is facilitating direct tumor cell invasion into the ECM.[8] Matrix metalloproteinase also participates in the normal remodeling processes, such as bone remodeling, ovulation and wound healing.[12] The purpose of this literature review is to understand some of the general aspects of the role of MMP in the oral environment both in normal and pathological conditions. It is expected that dentists, particularly those involved in basic research, will be better able to understand the function and activity of MMP and TIMP, turnover matrix of the periodontal ligament with adjacent structures as well as embryology and development.

PREVIOUS STUDIES

The two main components of macro molecules that build ECM is collagen and glycosaminoglycan and elastin molecules formed as an extension of the fiber tissue crosslinks. Elastin is seen clearly stands out among the structures, such as the periodontal ligament or other tissue that require elasticity when under pressure.[9] In the process of wound healing, the collagen is a major component in addition to epithelial cells. Physiology, naturally the process of going through phases: the inflammatory phase, the proliferative phase and remodeling or maturation phase. On the process of oral mucosa injury, the migration and proliferation of fibroblasts not only synthesize granulation tissue, but also has a very important role in ECM remodeling.[18]

Extracellular matrix remodeling needed during the process of cell migration in progress,[19] a process which is essential at a time of growth and development. At the time of development, there will be changes in the composition and configuration of ECM.[9] Protease is responsible for the turnover of ECM is likely implicated in some normal process of craniofacial development. During the process of tissue remodeling, cells should be separated from the local environment ECM, ECM components degrade and then migrate to the new position via proteolytic matrix modification.[20] Extracellular matrix remodeling is facilitated by several proteolytic enzymes include aspartyl, cystyl, metallo and serine-proteinase.[18]

Four large groups or families MMP (Table 1) has been identified as a group that interstitial collagenase I (MMP-1) that is secreted by fibroblasts[21] and polymorphonuclear leukocytes to MMP-8, 13 and MMP-18 (Xenopus).[22] Overview of the main activities of this group is their ability to divide or break up the interstitial collagenase I, II and III on region-specific tread third or fourth of the terminal N.[11] Group II is type IV collagenase called gelatinase A (MMP-2) and gelatinase B (MMP-9), which are both capable of breaking the gelatin. It has three fibronectin type II domain replicates that inserted on the catalytic domain and which are binding to gelatin, collagen and laminin.[23]

In general, MMP-3 has higher capable in terms of efficiency proteolytic than MMP-10.[24] Besides breaking the ECM components, the MMP-3 is also activates proMMP that some processing activities in part of proMMP-1 to make MMP-1 fully active.[25] Group IV is the so-called membrane-type MMP (MT-MMP). Members include MMP-14, 15, 16 and MMP-24 and MMP-called transmembrane, while 17 and MMP-25 called GPI anchor.

Other MMP is matrilysin with a loss characterization hemopexin domain.[26] Matrilysin 1 (MMP-7) and matrilysin 2 (MMP-26) also called endometase.[27] There are seven MMPs that are not classified in the group of the above categories. Metalloelastase (MMP-12) that is only expressed in macrophages[28] which are essential for the migration of macrophages.[29] Matrix metalloproteinase-19 was identified by cDNA cloning of the liver.[30] Enamelysin (MMP-20) breaks amelogenin especially at locations between the

Table 1: Group of matrix metalloproteinases[11]

Enzyme	*MMP*
Colagenase	
Colagenase interstitial, colagenase 1	MMP-1
Colagenase neutrophil, colagenase 2	MMP-8
Colagenase 3	MMP-13
Colagenase 3 (Xenopus)	MMP-18
Gelatinase	
Gelatinase A	MMP-2
Gelatinase B	MMP-9
Stromelysin	
Stromelysin 1	MMP-3
Stromelysin 2	MMP-10
Stromelysin 3	MMP-11
Matrilysin	
Matrilysin 1	MMP-7
Matrilysin 2	MMP-26
Membrane-type (MT)	
Transmembrane	
MT1-MMP	MMP-14
MT2-MMP	MMP-15
MT3-MMP	MMP-16
MT5-MMP	MMP-24
GPI anchor	
MT4-MMP	MMP-17
MT6-MMP	MMP-25
Other	
Macrophage elastase	MMP-12
No trivial name	MMP-19
Enamelysin	MMP-20
XMMP	MMP-21
CA-MMP	MMP-23
CMMP (Gallus)	MMP-27
Epilisin	MMP-28

newly formed tooth enamel. Outside to the other groups are MMP-22, 23 and MMP-28, commonly called epilysin. Epilysin is only expressed in keratinocytes.[31] Matrix metalloproteinases family members are organized on three basic components, namely propeptide amino-terminal, catalytic domain and domain of hemopexin shaped like carbon terminal.

Tissue inhibitors of metalloproteinases (TIMP), which consists of TIM-1, 2, 3, and TIMP-4 have sized between 21 and 28 kDa. Is a multifunctional protein that regulates the function of MMP either at the level of activity and its ability to hydrolyze a substrate in particular. Tissue inhibitors of metalloproteinase-1 is more effective than TIMP-2 in its function in the inhibition of MMP-1 and MMP-3. In general, MMP-9 secreted in the cell as a complex with TIMP-1, TIMP-2, while associated with MMP-9.[6] The experiment showed that TIMP-2 has more than 10× compared the effectiveness of TIMP-1 in inhibiting the activity of MMP-2.[32] Matrix metalloproteinases production by TIMP balance shows an important condition for maintaining homeostasis of ECM.[6]

DISCUSSION

Matrix metalloproteinases reportedly been implicated in a wide variety of normal processes physiology including bone remodeling, implantation trophoblast, abnormal angiogenesis and wound healing.[33] When MMP showed its excesses, it has been known that MMP participate in acceleration of ECM breaking which is associated with several diseases, including periodontitis,[34] arthritis, atherosclerosis, tissue ulceration, tumor cell invasion and metastasis.[7] As a large group, the MMP is naturally capable break down or decompose all structural components of the ECM in normal pH. Maintaining the integrity of the ECM main function seems to be the goal. The other research evidence found that MMP activity could have an effect on cell adhesion. Reported that an increase in human melanoma cell adhesion was significantly with increased TIMP-2, and a reduction in adhesion is also obtained with a reduced level of TIMP-2.[35] The study also proved that the balance of MMP-2 is activated by the level of TIMP-2 is an important event for cell adhesion and motility among ECM. When the ECM attachment is too strong, then the cells are not able to move into the ECM. Conversely, if the ECM too tenuous bound then appears there is a possibility that the migration of cells can be achieved.

Most of the MMP not be constitutive expressed by cells *in vivo*. Expression varies according to the speed as a result of the response to exogenous substances including cytokines, growth factors and hormones. However, TIMP and α2-macroglobulin (α2M) and α1-antiproteases remain a cause expression of MMP. It is known that TIMP regulate MMP activity on the tissue or on the edge of the cell, whereas α2M regulate the interstitial fluid.[22] Matrix metalloproteinases catalytic activity is regulated at several levels, including transcription, secretion, and inhibition activity.[22,36] Some MMPs can activate other members of the MMP; e.g. MMP-14, 15, and 16 can activate MMP-2, MMP-3 while already demonstrated its ability to activate MMP-9.[37] Similarly, collagenase MMP-1 can be activated by MMP-3 and MMP-10. Latent form of MMP-13 can be activated by MMP-2, 3, 10, and MMP-14 and can activate MMP-2 and MMP-9. Thus, the ability of MMP to activate each other has created a network of proteases in the pericellular cavity.[38]

Connective tissue growth and repair is a process that is balanced from the turnover of the ECM are significantly controlled by MMP and TIMP. Research shows that both MMP and TIMP are an important part in various disciplines science when studying the turnover of ECM.[9] Another evidences showed that polymorphisms on MMP genes seem to relate to the spread of disease levels that were characterized by the degradation of ECM.[6]

Some evidences have been supporting the fundamental role of MMPs during development and oral-tissue remodeling. Matrix metalloproteinases needed to replace email matrix proteins during the email maturation, this generates high remineralized tissue.[39] Matrix metalloproteinase plays an important role in the breakdown of collagen at the time of the destruction of periodontal tissue.[40] It had been reported that the gingival fibroblasts, keratinocytes, resident macrophages and PMN all have the ability to express MMP-1, 2, 3, 8 and 9 MMP,[41] inflammatory cytokines and growth factors that increase the transcriptional regulation of MMP.[6] Increasing the number of high MMP periodontal tissues causing imbalance and degradation of collagen which then would lead to loss of tooth. In patients with periodontitis had significantly proved of gelatinase that the amount is higher than healthy people and then appeared to decrease after treatment. Both gelatinases activities also plays an important role in the dentine damage by caries. The role also stands out as a potential enzymes for the degradation of ECM by activating of collagenase 3 (MMP-13) and neutrophil collagenase.[6] Gelatinase is suspected in humans also plays an important role in osteogenesis.[42]

In the inhibitation activity against MMP, TIMP then also have other biological functions. TIMP-1 and TIMP-2 could potentially activated erythroid[43,44] as well as cell growth promoting activity.[45,46] Excessive expression of TIMP-1, 2 and TIMP-3 had reduced tumor growth.[47] Also reported that TIMP-2 has been potentially inhibit endothelial cell growth induced by bFGF (basic fibroblast growth factor).[48] In addition, TIMP-2 could form specific complexes with MMP-2 latent.[36] Tissue inhibitor of metalloproteinase-2 has a characterization not shared by the other of TIMPs which is the ability to diffuse freely into the ECM. Tissue inhibitors of metalloproteinase-2 could also regulate the activity of MMP-2 by activating MMP-2 latent when linked with the MT-1-MMP.[49] So far, the role of TIMP-4 in the oral cavity has not been specifically disclosed.

CONCLUSION AND SUGGESTION

This review study introduces the outline some of the important functions of MMP and TIMP activity as inhibiting. The role of some MMP and TIMP in the oral cavity is very important to be understood by the dentist considering this enzyme implicated both in normal and pathological state of the oral cavity as periodontium tissue damage, dental caries, tumor invasion and temporomandibular joint disease. The dentist is involved in basic research must understand the role of matrix turnover in the periodontal ligament with adjacent structures, embryology and development. This complex area is always constant change and was instrumental in several research disciplines. For future studies should be considered and developed inhibiting factors that are useful not just to increase the role of MMP biology but also for the development of therapeutic intervention diseases associated with an imbalance of ECM degradation.

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