ejpmr, 2022,9(8), 113-116

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

MATRIX METALLOPROTEINASES: A LITERATURE REVIEW

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Article Received on 02/06/2022 **Article Revised on 23/06/2022** **Article Accepted on 13/07/2022**

ABSTRACT

Matrix metalloproteinases (MMPs) are a group of enzymes that are responsible for the degradation of extracellular matrix proteins during organogenesis, and in tissue turnover. The expression and activity of MMPs in adult tissues is ideally low, but increases during pathological conditions resulting in tissue destruction. The role of collagenases (MMP-8) in periodontitis and peri-implantitis is an example of the unwanted tissue destruction related to increased presence and activity of MMPs at the site of disease. There is evidence that indicates the role of MMPs in in dental caries and oral cancer. This review describes the presence and activity of various MMPs and its role in tissue destruction along with its other aspects that may facilitate the development of new means of diagnosis and treatment of oral diseases.

INTRODUCTION

Periodontal fibroblasts also secrete an active collagenase as well as a family of enzymes known collectively as matrix metalloproteinases. Matrix metalloproteinases (MMPs), are also known as **matrixins,** they function within the cells extracellularly, thereby degrading both the matrix and non-matrix proteins. These enzymes have the capacity to degrade the extracellular matrix. All of the metalloproteinases are secreted by fibroblasts in an inactive, precursor form and is effectively inhibited by a variety of tissue inhibitors. Thus, the balance between MMPs and TIMPs are critical for the eventual ECM remodelling in the tissue.[5] MMPs are also produced by some periodontal pathogens, such as A. actinomycetemcomitans and P. gingivalis, but the relative contribution of these bacterially derived MMPs to periodontal pathogenesis is small.

The MMP family is a group of calcium-dependent zinc-containing enzymes that are involved in the degradation of ECM.

MMPs can be divided into seven groups based on the substrate preference and domain organization: (1) collagenases, (2) gelatinases, (3) stromelysins, (4) matrilysins, (5) metalloelastases, (6) membrane-type MMPs (MT-MMPs), and (7) other MMPs.

Collagenases (MMP-1, MMP-8, MMP-13 and MMP-18) cleave interstitial collagens I, II and III into characteristic fragments but they can digest other ECM molecules and soluble proteins.

Gelatinases (MMP-2 and MMP-9) degrade gelatin with the help of their three fibronectin type II molecules that binds to gelatin/collagen. They also digest a number of ECM molecules including type IV, V and XI collagens, laminin.

Stromelysins (MMP-3, MMP-10 and MMP-11) have a domain arrangement similar to that of collagenases, but they do not cleave interstitial collagens.

Matrilysins (MMP-7 and -26) are synthesized by epithelial cells and is secreted apically. Besides ECM components it processes cell surface molecules such as pro-α-defensin, Fas-ligand, pro-tumor necrosis factor α, and E-cadherin.[21]

The predominant MMPs in periodontitis, MMP-8 and MMP-9, are secreted by neutrophils, and they are very effective at degrading type 1 collagen, which is present abundantly in the periodontal ligament. MMP-8 and MMP-9 levels increase with increasing severity of periodontal disease and decrease after treatment. The prolonged and excessive release of MMPs results in the significant breakdown of structural components of the connective tissues, thereby contributing to the clinical signs of disease.

Table 2. Matrix metalloproteinase family

Enzyme	Molecular weights (kDa)	MMP number	Substrates
Gelatinases			Denatures collagens
Gelatinase A	72	MMP-2	Native collagens IV, V, VII and X
Gelatinase B	92	MMP-9	Elastin and fibronectin
Collagenases			
Fibroblast-type CL	52	MMP-1	Collagen I, II, III, VII, VIII and X
PMN-type CL	75	MMP-8	
Stromelysins			
Stromelysin-1	55	MMP-3	PG core protein, fibronectin and laminin
Stromelysin-2	55	MMP-10	Collagen IV, V, IX, X and elastin
Stromelysin-3	61	MMP-11	
Metalloelastase	54	MMP-12?	Elastin
Matrilysin	28	MMP-7	Fibronectin, laminin and collagen IV PG core protein

Adapted from: Birkedal-Hansen H. Host mediated collagen destruction, metalloproteinases. In: Genco R, ed. Molecular basis for pathogenesis and molecular targeting in periodontal diseases. Washington, DC: ASM Publishers (in press), with permission.

REGULATION OF MMPS

The control of metalloproteinase activity in OA is complex, with regulation occurring at three different levels: synthesis and secretion, activation of latent enzyme, and inactivation by proteinase inhibitors.[8]

The activation may involve a mechanism called the 'cysteine switch' (**van Wart and Birkedal-Hansen, 1990; Springman et al., 1990)**, whereby an initial 'exogenous' proteolytic or free radical cleavage leads to a change in molecular conformation resulting from disengagement of a cysteine residue (near the amino terminus) from the zinc atom in the active site. This event can be initiated by three mechanisms:
1) Deletion of pro-domain by direct cleavage by another endoproteinase;
2) Allosteric reconformation of the pro-domain; and
3) Chemical modification of the free cysteine by reactive oxygen species or nonphysiological agents.[7]

The catalytic property of MMPs is regulated at four different levels: 1) gene expression with transcriptional and post-transcriptional regulation; 2) extracellular localisation of tissue or cell type of MMP release, termed as compartmentalisation; 3) pro-enzyme activation by removal of the pro-domain; and 4) inhibition by specific inhibitors, i.e. tissue inhibitors of matrix metalloproteinases (TIMPs), and by non-specific proteinase inhibitors, e.g. α2-macroglobulin.[6,7]

According to **Rosenblum et al** an alternative mechanism of zymogen activation is probably initiated by the intrinsic allostery of the MMP molecule. Therefore, domain flexibility of the modular domain organised MMP can contribute *via* promoting long-range conformational transitions induced by protein binding *via* exosites.[9]

TISSUE SPECIFICITY OF MMP'S

The physiological expression MMPs is normally low, with transiently higher levels in cases of homeostasis linked matrix remodelling or specific developmental events. However, distinct MMPs are differentially expressed in specific cell types or tissues.

TIMPs are produced by fibroblasts, macrophages, keratinocytes, and endothelial cells; they are specific inhibitors that bind to MMPs in a 1 : 1 stoichiometry**. (Perrera et al 2007).**

Turk et al stated that the prototype for true tissue specific expression is represented by MMP-20, which has been shown to be restricted to dental tissue, most likely driven by tooth-specific transcription factors.[10] According to **Illman et al**; MMP-28 expression seems to be restricted to developing germ cells as its transcription is mediated by the transcription factor Sox-5.[11]

Bioinformatic analysis done by **Munaut et al** on transgenic mice revealed RUNX-2 binding sites in an increasing number of MMP promoters, indicating that most MMPs do not have real tissue specificity. The gelatinases MMP-2 and -9 have been mainly associated with basement membrane degradation under pathological conditions since they are expressed by reactive epithelial and mesenchymal cells within in the skin.[12]

PHYSIOLOGICAL FUNCTIONS OF MMP

1. MMPs trigger bone growth and modeling

MMPs are critically important for osteoclasts at the resorption site, particularly for MMP-9 and MMP-14. MMP-14 is located within the ruffled borders of the osteoclasts, osteoblasts. The osteocytes express MMP-13, which is present in resorption lacunae and function to remove collagen remnants left over by osteoclasts**. (Perrera et al, 2007)**. MMPs also contribute to osteoclast recruitment and activity by releasing cytokines. MMPs are also important in osteoblastic bone formation, including MMP-2, MMP-9, MMP-13, and MMP-14. MMP-14 also contributes to normal bone homeostasis.

Gelatinase B (MMP-9) null mutants are characterised by delayed long bone growth and development due to

impaired vascular invasion in skeletal growth plates**. (Mosig et al).**[13]

2. MMPs in angiogenesis and vascular development

The mechanism by which the MMPs contribute to the regeneration of neovessels is via degrading type I collagen. Active MMP-2 itself can regulate sprouting of newly formed vessels by the release of cytokines and growth factors.[14] Importantly, MMPs not only promote angiogenesis but also generate anti-angiogenic peptides: MMP-3, -7, -9, -13 and -20, for example, have been shown to generate the anti-angiogenic endostatin by processing type XVIII collagens **(Egeblad et al)**.[15]

3. MMPs in the immune response and innate immunity

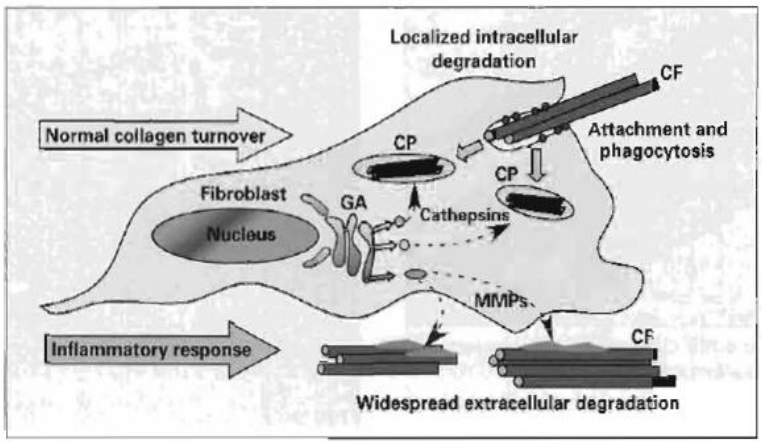
In agreement with the expression pattern of the MMPs -8, -2 and -9 in innate immune cells, such as monocytes, activated macrophages, alveolar macrophages and neutrophils, these enzymes have been linked to pathologies associated with innate immune dysregulation. MMP-2 and -9 participate in immune cell recruitment by providing a chemokine gradient of both the CC- (e.g. CCL7) and the CXC-motif (e.g. CXCL12, CXCL6 and CXCL8) ligands thereby having both pro- and anti-inflammatory effects.[11,14]

4. MMPs have essential roles in wound healing and cell migration

In vivo as well as in vitro data have demonstrated the importance of many secreted and membrane bound MMPs that contribute either directly or indirectly to the process of wound healing and neovascularisation. Upon injury most, if not all, MMPs are induced and expressed in almost any involved cell types, including mesenchymal, epithelial and immune cells. Another recently identified role of MMP activity in wound healing is the recruitment of immune cells since neutrophil recruitment requires the presence and activity of MMP-7 and MMP-8 **(Gutierrez et al)**.[16]

5. Intracellular collagen degradation

The periodontal fibroblasts are responsible for collagen degradation in addition to synthesising and secreting proteins as opposed to the view that degradation was essentially an extracellular event involving the activity of proteolytic enzymes such as collagenases. The main evidence which indicates that the periodontal fibroblasts are also **'fibroclastic'** is the presence of organelles termed as **intracellular collagen profiles**. The time taken to degrade collagen intracellularly is not known, although about 30 minutes has been suggested (a time similar to that required for synthesis).[7]



Degradation of collagen fibrils (CF) via the intracellular and extracellular pathways.

Tencate and Deporter (1975) indicate a cellular basis for the connective tissue remodeling which takes place during physiologic tooth movement. The fibroblast is capable of synthesizing and degrading collagen simultaneously and, utilizing this ability, the orderly control of collagen remodeling within the periodontal ligament is possible.[17]

Trelstad and Hayashi(1979) suggest that the intracellular collagen profiles are not merely intracellular but invaginations of the cell membrane, and that they may, in a part, relate to the way the collagen is secreted in a deeper cellular invagination so that its orientation can be better controlled.[18]

Cho and Garant(1981) suggested the possibility of internal polymerization of collagen before secretion wherein the number of profiles increased after the administration of microtubule agent, colchicine.[19]

CONCLUSION

Most MMP activity in the periodontal tissues is derived from infiltrating inflammatory cells. In addition to fibroblasts, metalloproteinases and other enzymes that destroy periodontal tissues are also produced by keratinocytes and tissue macrophages. Evidence suggests that, biochemically, the internal degradation of collagen does not involve matrix metalloproteinase (MMP-1) but acid phosphatase and cathepsins. In addition, cell surface located alkaline phosphatase and MMPs may be involved in the process of internalising a collagen fibril from the extracellular matrix.

REFERENCES

1. HASSELL, T. M. *Tissues and cells of the periodontium. Periodontology*, 1993; *2000; 3(1): 9–38*. doi:10.1111/j.1600-0757.1993.tb00230.x
2. Tencate's oral histology – Development, Structure and function -7th edition.
3. Orban's oral histology and embryology-
4. McCulloch CA. Progenitor cell populations in the periodontal ligament of mice. *Anat Rec*., 1985; 211(3): 258–262. doi:10.1002/ar.1092110305
5. Hideaki Nagase, Robert Visse, Gillian Murphy, Structure and function of matrix metalloproteinases and TIMPs, Cardiovascular Research, February, 2006; 69(3): 562–573. https://doi.org/10.1016/j.cardiores.2005.12.002
6. Overall CM, Lopez-Otin C. Strategies for MMP inhibition in cancer: innovations for the post-trial era. Nat Rev Cancer, 2002; 2: 657–672.
7. Ra HJ, Parks WC. Control of matrix metalloproteinase catalytic activity. Matrix Biol., 2007; 26: 587–596.
8. Gary S. Firestein, Ralph C. Budd, Sherine E. Gabriel, Iain B. McInnes, James R. O'Dell, Kelley and Firestein's Textbook of Rheumatology (Tenth Edition), Elsevier, 2017; 1115-1166.e7,
9. Sela-Passwell N, Rosenblum G, Shoham T, et al. Structural and functional bases for allosteric control of MMP activities: can it pave the path for selective inhibition? Biochim Biophys Acta, 2010; 1803: 29–38.
10. Turk BE, Lee DH, Yamakoshi Y, et al. MMP-20 is predominately a tooth-specific enzyme with a deep catalytic pocket that hydrolyzes type V collagen. Biochemistry, 2006; 45: 3863–7.
11. Illman SA, Keski-Oja J, Lohi J. Promoter characterization of the human and mouse epilysin (MMP-28) genes. Gene, 2001; 275: 185–194.
12. Munaut C, Salonurmi T, Kontusaari S, et al. Murine matrix metalloproteinase 9 gene. 5′-upstream region contains cis-acting elements for expression in osteoclasts and migrating keratinocytes in transgenic mice. J Biol Chem., 1999; 274: 5588–5596.
13. Mosig RA, Dowling O, DiFeo A, et al. Loss of MMP-2 disrupts skeletal and craniofacial development and results in decreased bone mineralization, joint erosion and defects in osteoblast and osteoclast growth. Hum Mol Genet, 2007.
14. S. Löffek, O. Schilling, C-W. Franzke Biological role of matrix metalloproteinases: a critical balance European Respiratory Journal, Jul, 2011; 38(1): 191-208. DOI: 10.1183/09031936.00146510
15. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. Nat Rev Cancer, 2002; 2: 161–174.
16. Gutierrez-Fernandez A, Inada M, Balbin M, et al. Increased inflammation delays wound healing in mice deficient in collagenase-2 (MMP-8). FASEB J., 2007; 21: 2580–2591.
17. Tencate AR, Deporter DA, Freeman E. The role of fibroblasts in the remodeling of periodontal ligament during physiologic tooth movement. *Am J Orthod*, 1976; 69(2): 155–168. doi:10.1016/0002-9416(76)90194-
18. Trelstad RL, Hayashi K. Tendon collagen fibrillogenesis: intracellular subassemblies and cell surface changes associated with fibril growth. *Dev Biol*., 1979; 71(2): 228–242. doi:10.1016/0012-1606(79)90166-0
19. Cho MI, Garant PR. An electron microscopic radioautographic study of collagen secretion in periodontal ligament fibroblasts of the mouse: I. Normal fibroblasts. *Anat Rec*., 1981; 201(4): 577–586. doi:10.1002/ar.1092010402.
20. Singer II. The fibronexus: a transmembrane association of fibronectin-containing fibers and bundles of 5 nm microfilaments in hamster and human fibroblasts. *Cell*., 1979; 16(3): 675–685. doi:10.1016/0092-8674(79)90040-0