# Role of MMPS in Periodontal Diseases

**Sachin Aditya B[1], K. R. Don[2], V. Vishnu Priya[3]**

*[1]Research Associate, [2]Reader, Department of Oral and Maxillofacial Pathology, Professor, Department of Biochemistry, Saveetha Dental College & Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai*

## Abstract

Matrix metalloproteinases (MMPs) belong to a family of structurally related zinc-dependent proteolytic enzymes that are known to play a key role in the catabolic turnover of extracellular matrix (ECM) components. Research studies to date have indicated that MMPs regulate the activity of several non-ECM bioactive substrates, including growth factor, cytokines, chemokines and cell receptors which determine the tissue microenvironment. Disruption of the balance between the concentration of active metalloproteinases and their inhibitors (TIMPS) may lead to pathological changes associated with uncontrolled ECM turnover, tissue remodeling, inflammatory response, cell growth and migration. This brief review presents some information on MMPs role in inflammatory, metabolic and cancer abnormalities related to the salivary glands, as well as MMP- related aspects that lead to the formation of human dentinal caries lesions. In oral diseases, the most relevant biological fluid commonly used for diagnosing periodontal diseases in saliva. Conventional treatment successfully reduces the levels of MMPs inhibits the progressive breakdown of gingival and periodontal ligament collagens.

***Keywords:*** *Matrix Metalloproteinases; Periodontal Diseases; Tissue Inhibitors.*

## Introduction

Periodontal disease is a common, complex, inflammatory disease characterised by the destruction of tooth supporting soft and hard tissues of periodontium, including alveolar bone and periodontal ligament[1]. Although the inflammation is initiated by bacteria, the tissues breakdown events that lead to the clinical signs if disease result from the host inflammatory responses that develop to combat the challenge presented by the subgingival biofilm.

Extracellular matrix (ECM) macromolecules play a key role in development and morphogenesis. Matrix metalloproteinases are also called matrixins, and are an important family of metal-dependent endopeptidases responsible for the degradation of ECM components. Expression of the 28 matrixins genes in humans is transcriptionally controlled by inflammatory cytokines, growth factors, hormones and cell-cell and cell-matrix interactions. Matrixins activities are also regulated by the activation of the precursor zymogens and inhibition by endogenous inhibitors, tissues inhibitors of metalloproteinases(TIMPs). Thus, the balance between MMPs and TIMPs are critical for the eventual ECM remodeling. Previously our team had conducted numerous original studies [2-9] and surveys [10-16], over the past 5 years. Now we are focusing on applying this knowledge to write the review on new advancements in the field.

### CLASSIFICATION OF MMPS

Based on the substrate specificity MMPs are classified into the following types [10,17] They are Collagenases-MMP-1, the substrates present in it are col-1,2,3,6,8,10 and gelatin, its specific role is over expression in the liver effectively attenuates fibrosis and causes hepatocyte proliferation. MMP-8, the col-1,2,3,7,8,10 and aggrecan, its specific role is promoted leukocyte infiltration in TNF- induced acute hepatitis. MMP-13, the substrate used are col-1,2,3,4,9,10 and gelatin, its specific role in liver diseases are acute liver injury and accelerates liver fibrosis. MMP-2, the substrates are

gelatin, col-1,2,3,4,7,10, its specific role is expressed during liver ischemia. MMP-9 , the substrates used were col-4,5 and gelatin, their role is expressed during Ischemia. Stromelysins are MMP-3, the substrate used are col-2,4,9,10 and gelatin, its specific role is expressed in hepatocellular carcinoma. MMP-10, the substrates are col-4,laminin, fibronectin and elastin, its specific role are hepatocellular carcinoma, MMP-11, the substrates are col-4, fibronectin, laminin, its specific functions are expressed in normothermic ischemia injury. MMP-19 the specific role of it is promoting TGF-p signalling in development of liver fibrosis. Matrilysins contains MMP-26 and MMP-7, its substrates are fibronectin, laminin, Col-4, gelatin and its function is expressed in biliary atresia fibrosis. Membrane type MMPs contain MMP-14, which has Gelatin and fibronectin as substrates and its role is shown in highly invasive hepatocellular carcinoma and MMP-15 and MMP-16 also contain the same substrates as MMP-14 but their role is expressed only on partial hepatectomy, MMP-17, MMP-24, MMP -25 are some of the membrane type MMPs. Other MMPs are MMP-12, MMP-20, MMP-22 and MMP 28.

## STRUCTURE OF MMPS

MMPs are structurally similar but differ in substrate specifically. The following features are seen in the structure[18], they are single peptide, propeptide, Furin-cleavage site insert, catalytic domain, Fibronectin like repeats, hinge region, hemopexin domain and membrane insertion extension. While primary structures of these metalloproteinases domains have little homology among families, the overall protein folds are similar. A typical MMP consists of a propeptide of about 80 amino acids, a catalytic metalloproteinase domain of about 170 amino acids, a linker peptide of variable lengths (also called the 'hinge region') and a hemopexin (Hpx) domain of about 200 amino acids. Exceptions to this are MMP-7 (matrilysin 1), MMP-26 (matrilysin 2) and MMP-23; they lack the linker peptide and the Hpx domain and MMP-23 has a unique cysteine-rich domain and an immunoglobulin-like domain after the metalloproteinase domain. While the primary structures of these metalloproteinase domains have little homology among the families, the overall protein folds are similar. In 1994 3D structures of the catalytic domain of collagenases (MMP-1 and MMP-8) were determined by X-ray crystallography by several groups and subsequently crystal structures of proMMP-3 lacking the hemopexin domain and the active full-length MMP-1 in 1995. Since then, a large number of 3D structures of MMPs have been determined both by X-ray crystallography and by NMR spectroscopy including full-length proMMP-1, proMMP-2 and the proMMP-2–TIMP-2 complex.

## MODE OF ACTION

Mode of action of MMPs are as follows [18,19]

- MMPs may affect cell migration by changing the cells from an adhesive to non-adhesive phenotype and by degrading the ECM.

- MMPs may enter and alter the ECM microenvironment leading to cell proliferation, apoptosis or morphogenesis.

- MMPs may modulate the activity of biologically active molecules such as growth factor receptors by cleaving them or releasing them from the ECM [20.]

- MMPs may alter the balance of protease activity by cleaving the enzymes or their inhibitors.

## REGULAGION OF MMP ACTIVITY

The activity of MMP against extracellular matrix substrates is regulated at 4 gates [21]

1) Transcriptional regulation of MMP genes
2) Precursor activation
3) Differences in substrate specificity
4) MMP inhibitors

Alpha-2-macroglobulins, they capture the active MMP by a unique venus-fly trap mechanism activated by cleavage of a bond in the "bait" region. This cleavage leads to hydrolysis of a liable internal thio-ester bond and covalent cross-linking of a nascent glutamyl residue to lysyl side chains exposed on the surface of the attacking proteinase [22]

The first TIMP was described in 1975 as a protein, in the culture medium of human fibroblasts and in human serum, which was able to inhibit collagenase activity. The molecular weight of this protein was later shown to be 28.5kDa. Since then, three new TIMPs have been

discovered in different species, and have been designated TIMP-2,-3,-4, respectively

**MATRIX METALLOPROTEINASES AND BONE RESORPTION:**

The role of MMPs during bone resorption is not totally clear but new insights suggest that MMPs also play a key role during this event. Osteoclasts are unable to attach to the bone surface if the mineralised bone matrix is covered by an osteoid layer. Osteoid is composed of type 1 collagen, proteoglycans, glycoproteins and native types 4 and 9 collagens.

Osteoblast-derived collagenase (nMP-13) seems to be mainly responsible for degradation of non mineralised osteoid layers covering bone surfaces. MMP-13 is expressed in human breast carcinomas[23], articular cartilage from arthritic patients. Osteoblasts, periosteal cells and fibroblasts during human foetal bone development [24,25] and postnatally in bone remodelling[26]. MMP-13 is as efficient as MMP-1 and MMP-8 in digestion of type 1 collagenase [27,28]. Cleavage of collagen 1 by MMP-13 seems to be the initial step of the entire bone resorption process. Subsequent, denatured collagen fragments are also degraded by gelatinases MMP-2 and MMP-9, it cleaves acid insoluble type 1 collagen at 37 degree celsius and presents strong proteolytic activity against denatured type 1 collagen and type 4 collagen[27]. Other direct evidence of the inhibition of MMPs by chemically modified tetracyclines can prevent bone loss [29,30].

**MMP IN PERIODONTAL DISEASES:**

In periodontal disease, MMPs play a key role in degradation of ECM, basement membrane and protective serpins as well as in the modification of cytokine action and activation of attachments apparatus is the hallmark of periodontal diseases [31,32]. Organisms like porphyromonas gingivalis and aggregatibacter actinomycetemcomitans do produce collagenases for the breakdown of ECM but they do not help much in periodontal collagen degradation and resident gingival and periodontal ligament fibroblasts produce collagenases that are thought to be involved in normal tissue turnover. The inflammatory reaction associated with periodontitis may damage the surrounding cells and connective tissue structures, including alveolar bone, causing tooth loss[32,33]. Inflammatory cells such as neutrophils and macrophages produce MMPs, with neutrophils being the major source of collagenase and gelatinase in inflammatory diseases such as periodontitis[31]. MMP-3 is effective at degrading proteoglycans and fibronectin. Epithelial cells can also produce elevated levels of these enzymes, which may facilitate the apical migration and lateral extension of the junctional epithelium and the subsequent loss of connective tissues attachment. Inflammatory cells, particularly neutrophils, are thought to play a particularly important role in MMP- mediated PDL destruction [34,35]. Epithelial cells can also produce elevated levels of these enzymes, which may facilitate the apical and lateral extension of junctional epithelium[36].

**ESTIMATION OF MMP IN PERIODONTAL DISEASES:**

Matrix metalloproteinases can also process various bioactive non matrix substrates, such as cytokines, chemokines, growth factors and immune mediation, thereby mediating both anti and pro-inflammatory processes. Therefore, the levels of matrix metalloproteinases should not be interpreted solely as surrogate markers of time destruction but also as part of physiological or anti-inflammatory defence[37]. Based on these biochemical or immunological findings, the oral fluids have been a target for extensive research on diagnostic utilisation of MMPs and their regulators as potential candidates for PDL diseases. Various proteomic techniques are being used to estimate the levels of these MMPs.

**ROLE OF MMP INHIBITORS IN PERIODONTAL DISEASES:**

Inhibiting MMPs can be an effective adjunctive treatment in the management of periodontitis as they are important mediators in the connective tissue breakdown in periodontitis. Inhibitors fall into three categories:

1) Collagen peptidomimetics and nonpeptidomentics- a. Peptidomimetic MMP inhibitors, b. Batimastat, C .Marimastat, d. Non peptidic MMP inhibitors. E. BAY 12-9566, f. AG3340, g. BMS-27529, h.CGS-27023A.

2) Tetracycline derivatives - a. Doxycycline, b. Col-3(metastat)

3) Bisphosphonate.

A disturbed balance between MMPs and TIMPs might contribute to the disease process in degenerative diseases. In some cases, the occurrence of MMPs and TIMPs in body fluids such as saliva, gingival cervical fluid(GCF) or serum provides additional information about the progression of the disease. In health periodontal tissue, TIMP levels are generally higher than in inflamed periodontal tissues, in which MMP levels exceed TIMP levels. The more severe the information the higher the concentration of MMP. The inhibition of MMP expression or activity, or increased TIMP expression might reduce tissue destruction in periodontitis.

Different inhibitors include

a. Alpha -2- macroglobulins

b. Tissue inhibitors of metalloproteinases

c. Inhibiting antibodies

d. Synthetic inhibitors

During inflammation, however, the later high molecular weight protein may escape the vasculature and also function in the extracellular matrix. Multiple synthetic peptides have been formulated in an attempt to synthesise more specific chelators including hydroxyzine acid derivatives.

## Conclusion

MMPs are important components in many biological pathological processes because of their ability to degrade ECM compounds. The use of a host modulatory agent such as MMP inhibitor can assist with conventional treatment for periodontitis and, when used adjunctively, can enhance and make clinical therapeutic responses more predictable in more susceptible patients.

**Acknowledgement:** The author extends gratitude to the institution for their support.

**Conflict Of Interest:** No conflict of interest declared.

**Ethical Clearance:** It is taken from "Saveetha Institute Human Ethical Committee" (Ethical Approval Number- SDC/SIHEC/2020/DIASDATA/0619-0320)

## References

1. Sorsa T, Golub LM. Is the excessive inhibition of matrix metalloproteinases (MMPs) by potent synthetic MMP inhibitors (MMPIs) desirable in periodontitis and other inflammatory diseases? That is: "Leaky" MMPIs vs excessively efficient drugs [Internet]. Vol. 11, Oral Diseases. 2005. p. 408–9. Available from: http://dx.doi.org/10.1111/j.1601-0825.2005.01160.x
2. Palati S, Ramani P, Shrelin HJ, Sukumaran G, Ramasubramanian A, Don KR, et al. Knowledge, Attitude and practice survey on the perspective of oral lesions and dental health in geriatric patients residing in old age homes. Indian J Dent Res. 2020 Jan;31(1):22–5.
3. Prasanna GE, Gheena S. A study of empathy across students from 4 health disciplines among 1st years and Final years [Internet]. Vol. 9, Research Journal of Pharmacy and Technology. 2016. p. 1472. Available from: http://dx.doi.org/10.5958/0974-360x.2016.00286.9
4. Uma PK, Ramani P, Sherlin HJ, Others. Knowledge about Legal Aspects of Medical Negligence in India among Dentists--A Questionnaire Survey. Medico Legal Update. 2020;20(1):111–5.
5. Palati S, Ramani P, Herald. J. Sherlin, Gheena S, Don KR, Jayaraj G, et al. Age Estimation of an Individual Using Olze's Method in Indian Population-A Cross-Sectional Study [Internet]. Vol. 13, Indian Journal of Forensic Medicine & Toxicology. 2019. p. 121. Available from: http://dx.doi.org/10.5958/0973-9130.2019.00179.8
6. Gunasekaran G, Abilasha R. TOOTH SENSITIVITY AMONG RESIDENTIAL UNIVERSITY STUDENTS IN CHENNAI [Internet]. Asian Journal of Pharmaceutical and Clinical Research. 2016. p. 63. Available from: http://dx.doi.org/10.22159/ajpcr.2016.v9s2.13228
7. Harrita S, Santhanam A. Determination of Physical Height Using Clinical Crown Height of Deciduous Teeth [Internet]. Vol. 13, Indian Journal of Forensic Medicine & Toxicology. 2019. p. 23. Available from: http://dx.doi.org/10.5958/0973-9130.2019.00255.x
8. Sukumaran G, Padavala S. Molar incisor

hypomineralization and its prevalence [Internet]. Vol. 9, Contemporary Clinical Dentistry. 2018. p. 246. Available from: http://dx.doi.org/10.4103/ccd.ccd_161_18

9. Sheriff KAH, Ahmed Hilal Sheriff K, Santhanam A. Knowledge and Awareness towards Oral Biopsy among Students of Saveetha Dental College [Internet]. Vol. 11, Research Journal of Pharmacy and Technology. 2018. p. 543. Available from: http://dx.doi.org/10.5958/0974-360x.2018.00101.4
10. Hema Shree K, Ramani P, Sherlin H, Sukumaran G, Jeyaraj G, Don KR, et al. Saliva as a Diagnostic Tool in Oral Squamous Cell Carcinoma - a Systematic Review with Meta Analysis. Pathol Oncol Res. 2019 Apr;25(2):447–53.
11. Abitha T, Santhanam A. Correlation between bizygomatic and maxillary central incisor width for gender identification [Internet]. Vol. 22, Brazilian Dental Science. 2019. p. 458–66. Available from: http://dx.doi.org/10.14295/bds.2019.v22i4.1775
12. Krishnan RP, Ramani P, Sherlin HJ, Sukumaran G, Ramasubramanian A, Jayaraj G, et al. Surgical Specimen Handover from Operation Theater to Laboratory: A Survey. Ann Maxillofac Surg. 2018 Jul;8(2):234–8.
13. Hannah R, Ramani P, Herald. J. Sherlin, Ranjith G, Ramasubramanian A, Jayaraj G, et al. Awareness about the use, Ethics and Scope of Dental Photography among Undergraduate Dental Students Dentist Behind the lens [Internet]. Vol. 11, Research Journal of Pharmacy and Technology. 2018. p. 1012. Available from: http://dx.doi.org/10.5958/0974-360x.2018.00189.0
14. Sarbeen JI, Insira Sarbeen J, Gheena S. Microbial variation in climatic change and its effect on human health [Internet]. Vol. 9, Research Journal of Pharmacy and Technology. 2016. p. 1777. Available from: http://dx.doi.org/10.5958/0974-360x.2016.00359.0
15. Ahad M, Gheena S. Awareness, attitude and knowledge about evidence based dentistry among the dental practitioner in Chennai city [Internet]. Vol. 9, Research Journal of Pharmacy and Technology. 2016. p. 1863. Available from: http://dx.doi.org/10.5958/0974-360x.2016.00380.2
16. Manohar J, Abilasha R. A Study on the Knowledge of Causes and Prevalance of Pigmentation of Gingiva among Dental Students [Internet]. Vol. 10, Indian Journal of Public Health Research & Development. 2019. p. 95. Available from: http://dx.doi.org/10.5958/0976-5506.2019.01859.x
17. Koromantzos PA, Makrilakis K, Dereka X, Offenbacher S, Katsilambros N, Vrotsos IA, et al. Effect of Non-Surgical Periodontal Therapy on C-Reactive Protein, Oxidative Stress, and Matrix Metalloproteinase (MMP)-9 and MMP-2 Levels in Patients With Type 2 Diabetes: A Randomized Controlled Study [Internet]. Vol. 83, Journal of Periodontology. 2012. p. 3–10. Available from: http://dx.doi.org/10.1902/jop.2011.110148
18. Birkedal-Hansen B, Pavelic ZP, Gluckman JL, Stambrook P, Li Y-Q, Stetler-Stevenson WG. Oral and Maxillofacial Pathology: MMP and TIMP gene expression in head and neck squamous cell carcinomas and adjacent tissues [Internet]. Vol. 6, Oral Diseases. 2008. p. 376–82. Available from: http://dx.doi.org/10.1111/j.1601-0825.2000.tb00130.x
19. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression [Internet]. Vol. 2, Nature Reviews Cancer. 2002. p. 161–74. Available from: http://dx.doi.org/10.1038/nrc745
20. Uma PK, Ramani P, Sherlin HJ, Others. Knowledge about Legal Aspects of Medical Negligence in India among Dentists--A Questionnaire Survey. Medico Legal Update. 2020;20(1):111–5.
21. Incerti M, Crascì L, Vicini P, Aki E, Yalcin I, Ertan-bolelli T, et al. 4-Thiazolidinone Derivatives as MMP Inhibitors in Tissue Damage: Synthesis, Biological Evaluation and Docking Studies [Internet]. Available from: http://dx.doi.org/10.20944/preprints201710.0200.v1
22. Djuric T, Zivkovic M. Overview of MMP Biology and Gene Associations in Human Diseases [Internet]. The Role of Matrix Metalloproteinase in Human Body Pathologies. 2017. Available from: http://dx.doi.org/10.5772/intechopen.70265
23. Lim SC. Expression of c-erbB receptors, MMPs and VEGF in head and neck squamous cell carcinoma [Internet]. Vol. 59, Biomedicine & Pharmacotherapy. 2005. p. S366–9. Available from: http://dx.doi.org/10.1016/s0753-3322(05)80080-0

24. Lee Y-A, Ji H-I, Lee S-H, Hong S-J, Yang H-I, Yoo MC, et al. The role of adiponectin in the production of IL-6, IL-8, VEGF and MMPs in human endothelial cells and osteoblasts: implications for arthritic joints [Internet]. Vol. 46, Experimental & Molecular Medicine. 2014. p. e72–e72. Available from: http://dx.doi.org/10.1038/emm.2013.141

25. Kim K-S, Lee Y-A, Kim K-Y, Kim S-S, Hong S, Song R, et al. AB0048 The role of adiponectin in the production of il-6, il-8, vegf, and mmps in human endothelial cells and osteoblasts: implications for arthritic joints [Internet]. Vol. 72, Annals of the Rheumatic Diseases. 2013. p. A800.2–A800. Available from: http://dx.doi.org/10.1136/annrheumdis-2013-eular.2371

26. d'Ortho M-P. MMPs, inflammation and pulmonary arterial hypertension [Internet]. Matrix Metalloproteinases in Tissue Remodelling and Inflammation. 2008. p. 81–97. Available from: http://dx.doi.org/10.1007/978-3-7643-8585-9_6

27. Prahasanti C, Nugraha AP, Saskianti T, Suardita K, Riawan W, Ernawati DS. Exfoliated Human Deciduous Tooth Stem Cells Incorporating Carbonate Apatite Scaffold Enhance BMP-2, BMP-7 and Attenuate MMP-8 Expression During Initial Alveolar Bone Remodeling in Wistar Rats (). Clin Cosmet Investig Dent. 2020 Mar 24;12:79–85.

28. Statement of Retraction: Regulation function of MMP-1 downregulated by siRNA on migration of heat-denatured dermal fibroblasts. Bioengineered. 2020 Dec;11(1):558.

29. Berens C. Interactions of tetracyclines with RNA [Internet]. Tetracyclines in Biology, Chemistry and Medicine. 2001. p. 177–96. Available from: http://dx.doi.org/10.1007/978-3-0348-8306-1_7

30. Blackwood RK. Structure Determination and Total Synthesis of the Tetracyclines [Internet]. The Tetracyclines. 1985. p. 59–136. Available from: http://dx.doi.org/10.1007/978-3-642-70304-1_3

31. Salivary Biomarkers (PGE2, MMP-8, ALP Levels) and Clinical Periodontal Parameters for Segregation of Periodontal Health and Diseases [Internet]. Vol. 3, International Journal of Advanced Research in Biological Sciences (IJARBS). 2016. p. 27–36. Available from: http://dx.doi.org/10.22192/ijarbs.2016.03.09.004

32. Kasuma N, Oenzil F, Darwin E, Sofyan Y. The analysis of matrix metalloproteinase-8 in gingival crevicular fluid and periodontal diseases. Indian J Dent Res. 2018 Jul;29(4):450–4.

33. Thompson DM, Lee H-M, Stoner JA, Golub LM, Nummikoski PV, Payne JB. Loss of alveolar bone density in postmenopausal, osteopenic women is associated with circulating levels of gelatinases. J Periodontal Res. 2019 Oct;54(5):525–32.

34. Nokhbehsaim M, Eick S, Nogueira AVB, Hoffmann P, Herms S, Fröhlich H, et al. Stimulation of MMP-1 and CCL2 by NAMPT in PDL cells. Mediators Inflamm. 2013 Aug 22;2013:437123.

35. Ateia IM, Sutthiboonyapan P, Kamarajan P, Jin T, Godovikova V, Kapila YL, et al. Treponema denticola increases MMP-2 expression and activation in the periodontium via reversible DNA and histone modifications. Cell Microbiol [Internet]. 2018 Apr;20(4). Available from: http://dx.doi.org/10.1111/cmi.12815

36. Song S-E, Choi B-K, Kim S-N, Yoo Y-J, Kim M-M, Park S-K, et al. Inhibitory effect of procyanidin oligomer from elm cortex on the matrix metalloproteinases and proteases of periodontopathogens. J Periodontal Res. 2003 Jun;38(3):282–9.

37. Yan M, Noguchi K, Ruwanpura SMPM, Ishikawa I. Cyclooxygenase-2-dependent prostaglandin (PG) E2 downregulates matrix metalloproteinase-3 production via EP2/EP4 subtypes of PGE2 receptors in human periodontal ligament cells stimulated with interleukin-1alpha. J Periodontol. 2005 Jun;76(6):929–35.