(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 3, Page No: 330-337
May-June 2021

Double edged sword - Matrix Metalloproteinases: A Review

[1]Selvaraj Silviya, [2]Vijayarangan Anitha M.D.S *, [3]Muthukali Shanmugam M.D.S [4]Balachandran Ashwath M.D.S., [5]Elumalai Agila M.D.S., [6]Durai Aishwarya M.D.S

[1]Post Graduate, [2]Professor and Head, [3,4]Professor, [5]Reader, [6]Senior Lecturer
Department of Periodontology, Chettinad Dental College and Research Institute Rajiv Gandhi Salai, Kelambakkam, Chengalpet, Tamilnadu

***Corresponding Author:**
Vijayarangan Anitha M.D.S
Department of Periodontology, Chettinad Dental College and Research Institute Rajiv Gandhi Salai, Kelambakkam, Chengalpet, Tamilnadu

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

ABSTRACT

Matrix metalloproteinases belongs to one of the four proteinase systems which are responsible for degradation of all components of extracellular matrix particularly the versatile protein – Collagen. Collagen is responsible for the framework of the supporting periodontal tissues. MMP has a dual role both in physiology and pathology. When the balance among the factors which maintain homeostasis is disturbed tissue destruction occurs by activation of MMP. This review focuses on the history, classification, regulation, physiological and pathological role of MMP.

Keywords: Extracellular matrix, Matrix metalloproteinases, Periodontitis, Wound healing.

INTRODUCTION

Extracellular matrix (ECM) macromolecules are important during the development and morphogenesis of tissues and serves as a scaffold for normal biological functions. The synthesis, breakdown and remodelling of the ECM are critical events in normal physiological processes like embryonic development, wound healing and angiogenesis [1]. Remodelling of the ECM is carried out by four different protease systems - cysteine proteases, serine proteases, aspartic proteases and metalloproteinases (MMP). MMPs are referred to as metzincins superfamily. They have important roles in physiological and pathological processes, as they regulate various cell behaviours [2].

Periodontitis is an inflammatory disease which causes destruction of the supporting tissues of the teeth. The microorganisms associated with the disease will initiate the disease and the progression is influenced by the host immune response [3]. The disease progression involves a network of interacting molecular pathways made of pro-inflammatory mediators like cytokines, growth factors, reactive oxygen species, an MMP, and their inhibitors and regulators [4]. MMPs form the most important group of proteinases responsible for the degradation of matrix proteins during periodontitis, and imbalance between MMPs and their inhibitors may trigger the degradation of ECM, basement membrane, and alveolar bone [5].

Matrix metalloproteinases are large family of zinc and calcium dependent endopeptidase which are responsible for tissue remodelling and degradation of extracellular matrix including collagens, elastins, gelatin, matrix glycoproteins and proteoglycan [6].

II. HISTORICAL BACKGROUND

The initial milestone for the discovery of matrix metalloproteinases was achieved by **Woessner in**

1962 [7]. He discovered a protein enzyme which is present in mammalian tissue is responsible for degradation of collagen. Later in the same year **Jerome Gross and Charles M Lapiere** [8] cultured fragments of resorbing tadpole tail on reconstituted collagen gels. A collagenolytic enzyme that could attack native collagen fibrils was recovered from the culture medium. Within a short time these studies were extended to show a similar activity in a wide variety of tissues, that the collagen molecule was cut into three-quarter and one-quarter length fragments, and that the enzyme activity was dependent on metal ions.

III. CLASSIFICATION OF MMP

Matrix Metalloproteinase comprise a family of around 28 members which are broadly categorized into six groups which are involved in various physiological and pathological conditions [9]. MMP are classified based on their pre-synaptic region on chromosomes and their various substrate specificity.

Members of mmp family and their classification [10]

Collagenases: MMP-1, MMP-8, MMP-13, MMP-18

Gelatinases: MMP-2, MMP-9

Stromelysins: MMP-3, MMP-10, MMP-11

Matrilysins: MMP -7, MMP-26

Membrane type MMP:

- Transmembrane MMP: MMP-14, MMP-15, MMP-16, MMP-24
- GPI Anchor MMP: MMP-17, MMP-25

Others: MMP-12, MMP-19, MMP-20, MMP-21, MMP-23, MMP-27, MMP-28

IV. STRUCTURE OF MMP

MMPs consist of four distinct domains and a signal peptide, the N-terminal prodomain (propeptide), catalytic domain, linker region, and C-terminal hemopexin-like domain. The membrane-type (MT) MMPs contain an additional transmembrane (TM) domain that anchors them to the cell membrane [11].

Exceptions are:

1. MMP-7 and MMP-26 (matrilysins) lack the linker region and Hemopexin (HPX) domain and thus are referred to as “minimal MMPs”.
2. MMP-2 and MMP-9 possess three repeats of fibronectin type II-like motifs within the CAT domain.
3. MMP-17 and MMP-25 are type I TM enzymes anchored to membranes through a C-terminal glycosyl phosphatidyl inositol (GPI) residue.
4. The N-terminal MMP-23 pro-domain contains a type II TM domain that anchors the protein to the plasma membrane.
5. Instead of the C-terminal HPX domain common to other MMPs, MMP-23 contains a small toxin-like domain (TxD) and an immunoglobulin-like cell adhesion molecule (IgCAM) domain [12].

V. REGULATION OF MMP

MMPs are the important regulators for tissue homeostasis due to multidirectional communication within tissues and cells and their widespread spectrum of substrate.

The activity of MMP has to be tightly regulated since uncontrolled MMP activity can easily become destructive and lead to breakdown of homeostasis. The catalytic activity of MMPs is strongly controlled at four different levels [13]:

1) Gene expression with transcriptional and post-transcriptional regulation

2) Removal of the pro-domain by pro-enzymatic activation

3) Compartmentalisation - Extracellular localisation and tissue or cell type of MMP release

4) Inhibition by specific inhibitors.

1) *Modulation of MMP gene expression*

Gene expression of MMP is primarily regulated at the transcriptional level. MMPs are co-regulated by various inductive stimuli, like growth factors and cytokines (TNF-á, IL-1, EGF,

bFGF and PDGF) , and may also be co-repressed by glucocorticoid hormones,parathormone, progestrone and retinoids [14].

2) *Cysteine switch mechanism*

MMPs are usually synthesised as zymogens (inactive pro-forms) with a pro-domain. The pro-domain has

Volume 4, Issue 3; May-June 2021; Page No 330-337

a conserved ‘‘cysteine switch’’ sequence near the border zone of the catalytic domain, whose free cysteine residue interacts with the catalytic zinc ion. The interaction is to maintain enzyme latency and prevent binding and cleavage of the substrate [15]. For a Pro-MMP to become catalytically active, interaction between the thiol of the conserved prodomain cysteine residue and the zinc ion of the catalytic site must be disrupted. The thiol-Zn^{2+} interaction can be broken and a latent MMP can gain catalytic activity - by three mechanisms:

a) Direct cleavage of the pro-domain by another proteinase

b) Reduction of the free cysteine by reactive oxygen species or by nonphysiologic reagents such as alkylating agents, heavy metal ions, and disulfides

c) Allosteric reconformation of zymogen [16]

3) Compartmentalisation

The regulation of MMP proteolysis starts early on with their secretion. The localization of MMPs in the pericellular space and the extracellular environment generally have a strong impact on their inactive pro - form activation [17].

Secreted MMPs which are often associated to the cell membrane, focuses their activity to specific substrates in the pericellular space. Examples for cell surface substrate recruitment are binding of MMP-1 to α2β1 integrin, which depends on interaction of α2 integrin with both linker plus hemopexin-like domain of MMP-1, MMP-9 binding to CD44. Cells use surface receptors, like integrins to inform themselves what protein in the cell periphery has been encountered and consequently, which type of enzyme is needed and where it has to be released.

4) *Inhibitors of MMP*

Matrix Metalloproteinases act on the surface of the cells or in the extracellular space. The matrix metalloproteinases activities are controlled by a combination of zymogen activation and inhibition by endogenous inhibitors like tissue inhibitors of metalloproteinases (TIMPs) and α2-macroglobulin.

TIMPS

TIMPs are the key inhibitors in tissue. TIMPs have been found in Drosophila and Caenorhabditis elegans. In humans four TIMP have been identified. These secreted proteins will regulate the MMP activity during tissue remodelling process. All four mammalian TIMPs are basically similar, but they have distinctive structural features and biochemical properties. The three-dimensional structure of TIMP has a wedge-shaped appearance. The TIMPs have molecular weights of ~21 kDa. Mammalian TIMPs are two-domain molecules, having N-terminal domains which has 125 amino acids and a smaller C-terminal domain having 65 amino acids, the each domain were stabilized by three disulphide bonds [18].

Although different TIMPs bind tightly to most MMPs [19], there were some differences in inhibitory properties between different TIMPs.

1. TIMP-2 and TIMP-3 are effective inhibitors of the membrane-type MMPs (MTMMPs). TIMP-2 binds tightly to the zymogen of MMP-2 (proMMP-2) forming a complex that is important in the cell-surface activation of proMMP- 2
2. TIMP-3 is a good inhibitor of tumor necrosis factor-K converting enzyme (TACE) [20], a metalloproteinase that is not a member of the matrixin family. TIMP-3 is appears to bind strongly to ECM components
3. TIMP-1 forms a specific complex with proMMP-9.
4. TIMP-4 also binds to the C-terminal domain of proMMP-2.

α2-macroglobulin

α2-macroglobulin is a large plasma protein found in blood. It act as an antiprotease and will inhibit variety of proteinases. It can be regarded as the major plasma inhibitor of metalloproteinases. It is synthesised mainly in the liver by hepatocytes, but it is also produced by macrophages and fibroblasts. α2-macroglobulin can almost universally inhibit endoproteinases, including the MMPs and the ADAMs. Inhibition is mainly by the cleavable ‘bait’ region that, once proteolytically cleaved, causes a conformational change that entraps the proteinase, which becomes covalently anchored by transacylation. α2-macroglobulin is the largest major non-immunoglobulin protein in human plasma [21].

VI. PHYSIOLOGICAL ROLE OF MMP

Volume 4, Issue 3; May-June 2021; Page No 330-337

Matrix metalloproteinases have various physiological roles in mammary development, Apoptosis, cell migration, Immune response, Bone formation, Angiogenesis and Wound healing.

MMP function during implantation

Development of the placenta starts with the invasion and migration of trophoblast cells into the maternal tissue to establish connection with the maternal circulation [22]. The trophoblasts express high levels of MMP-9. Inhibition of MMP-9 decreases migration and degradation of ECM by trophoblasts. Ets-2 is a member of the Ets family of transcription factors that regulate the transcription of MMPs. When the activity of MMP-9 is insufficient it cause Ets-2 deficiency. The Ets-2-deficiency leads to defective development of the placenta.

MMPs in mammary development

During embryonic period, the mammary gland develops by the budding of an epithelial tube into the mammary fat pad and subsequently the terminal end bud grows extensively branching to form the epithelial ducts. The epithelial ducts expands greatly during puberty in response to both local and systemic signals which involves MMP 2 and MMP 3 causing degradation of the basement membrane and ECM. Morphogenesis of the mammary gland occurs by two distinct mechanisms: terminal end bud (TEB) elongation and secondary branching. Inhibition of MMP function results in deficient primary invasion and has a minor effect on secondary branching [23].

MMP on apoptosis

MMPs exhibit both pro-apoptotic and anti-apoptotic activity. The pro-apoptotic activity of MMPs is due to changes in ECM composition. Their anti-apoptotic action include: cleaving the Fas ligand, proteolytic shedding of tumor associated MHC complex class I related protein and activation of serine/threonine kinase AKT/ Protein kinase B. MMPs lead to apoptosis by cleaving adhesion molecules. MMP-3 induces apoptosis in case of its over-expression in epithelial cells, probably by digestion of laminin. MMPs may also contribute to apoptosis of cells [24].

MMP in cell migration

MMP modulate signal transduction pathways such as proteolysis of extracellular mediators of cell-ECM or cell-cell adhesion, ectodomain shedding, receptor cleavage or exposure of cryptic sites leading to cell motility and invasion. The transmembrane protein E-cadherin is the primary target for the MMP-dependent disruption of cell-cell contacts. Triggering of signal transduction by release of β-catenin can exacerbate additional proteolysis upon induction of the expression of MMPs-2, -9 and -14.

Integrins are also pivotal elements for cell adhesion, migration and invasion. These cell-surface proteins mediate cell-cell and cell matrix adhesion and are involved in molecular signalling and crosstalk processes [25].

MMPs in the immune response and innate immunity

Innate immunity comprises various mechanisms that defend against invading microorganisms, contribute to tissue repair, and regulate the activity and influx of cells that are involved in acquired immunity. Epithelium is the first line of defence by maintaining a tight barrier against the external environment, secreting antimicrobial peptides, and producing chemokines and homing receptors. Injury disrupts the barrier function of the epithelium, creating an entry point for microorganisms and toxins. However, injured epithelial cells respond rapidly to close wounds, a process that involves cell proliferation, spreading and migration. Injury also induces the expression of several MMPs like MMP-1, MMP-7 which are crucial for wound closure [26]. MMP-7 is essential for the chemotatic recruitment of neutrophils. MMP-2 and -9 participate in immune cell recruitment by providing a chemokine gradient of both the CC and the CXC-motif ligands thereby having both pro and anti-inflammatory effect.

During bone resorption osteoclasts are unable to attach to the bone surface if the mineralized bone matrix is covered by an osteoid layer. Osteoid is composed by type I collagen, native types IV and IX collagens, proteoglycans and glycoproteins. Osteoblast-derived collagenase (MMP-13) is as efficient as MMP-1 and MMP-8 in the digestion of type I collagen. Cleavage of collagen I by MMP-13 seems to be the initial step of the entire bone resorption process and exposes the mineralized matrix to osteoclasts. Subsequent, denatured collagen fragments are degraded by gelatinases MMP-2 and MMP-9.

Volume 4, Issue 3; May-June 2021; Page No 330-337

Osteoclasts also express high levels of MMP-9 which plays a distinct role to cathepsin K in the process of bone resorption. MMP-9 cleaves acid insoluble type I collagen at 37°C and presents strong proteolytic activity against denatured type I collagen and type IV collagen. MMP-3, MMP-9 and MMP-13 mRNA levels are increased when osteoblast cultures are stimulated by resorptive factors such as cytokines IL-1b and TNF-a, parathyroid hormone, and prostaglandin E2 [27].

MMP in healing

MMPs play a crucial role in all stages of wound healing by modifying the wound matrix, allowing for cell migration and tissue remodelling. MMP expression and activity are tightly controlled during wound healing; specific MMPs are confined to particular locations in the wound and to specific stages of wound repair. MMP-1, MMP-3, and MMP-9 are the major chemokine regulators during wound healing.

Role of MMP in angiogenesis

Angiogenesis is a process by which new blood vessels are formed from existing vessels. MMPs, may stimulate or inhibit this process and MMP2, MMP9, and MMP14 plays the most important role in angiogenesis. Other MMPs may play a supporting role by complementing the main activity of MMPs

1. Proteolysis of type I collagen
2. Modification of platelet-derived growth factor (PDGF) signalling
3. Regulation of perivascular cells and processing of VEGF.

VEGF is stored extracellularly: after secretion, VEGF binds to the ECM, from where it must be released to initiate angiogenesis. MMP 9 mobilizes VEGF and initiates angiogenesis.

MMPs can also cleave VEGF, separating the matrix-binding domain from the receptor-binding domain. MMPs contribute to angiogenesis not only by degrading basement membrane and other ECM components, allowing endothelial cells to detach and migrate into new tissue, but also by releasing ECM- bound proangiogenic factors (basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and transforming growth factor (TGF)). In addition, MMP degradation of ECM components generates fragments with now- accessible integrin binding sites, triggering integrin intracellular signalling [28].

VII. MMP IN PATHOLOGY

MMP has various role in pathology

i. PERIODONTAL DISEASES
ii. CARIES, PULP AND PERIAPICAL PATHOGENESIS
iii. ORAL CANCER

Role of MMP in periodontal diseases

Periodontal diseases are defined as chronic inflammatory diseases of the tooth attachment structures. They are considered as the most common cause of tooth loss and one of the most prevalent forms of bone pathologies in humans. The bacterial biofilms attached to the tooth surfaces trigger an intense inflammatory reaction that results in irreversible loss of periodontal tissue attachment and alveolar bone resorption. Matrix metallo proteinases are believed to play an important role in tissue destruction associated with chronic inflammmatory conditions such as periodontal diseases. In oral cavity proteolytic enzymes are released by host cells such as fibroblasts, polymorphonuclear neutrophils, osteoblasts, endothelial cells, macrophages and epithelial cells. MMP are responsible for degrading most extracellular matrix components and thus implicated in tissue destruction and loss of supporting connective tissue. MMP 1, 2, 3, 8, 9 and 13 are most important mediators in periodontal tissue destruction [29,30].

Destruction of periodontal attachment apparatus is the hallmark of periodontal disease, and degradation of type I collagen seen in periodontal tissues is a key step in periodontal attachment loss. Degradation action on collagen fibers is performed by MMPs released by the resident cells of PDL that responds to the inflammatory stimuli. The most common type of MMPs related to tissue destruction belongs to collagenases family and includes mainly MMP-8 and MMP-13, with significant contribution from MMP-9 and MMP-14. Other MMPs are found to play a minor role in periodontal tissue destruction.

Four distinct pathways may be involved with this destruction:

Volume 4, Issue 3; May-June 2021; Page No 330-337

1. Plasminogen-dependent
2. Phagocytic
3. Osteoclastic
4. Matrix metalloproteinase pathway

A wide range of evidences has indicated that the most important pathway is the one which involves matrix metalloproteinases (MMPs).

Each of the major cell types of human periodontal tissues is capable of expressing a unique complement of MMP. MMP stored in specific granules of neutrophils are rapidly released within seconds when the cells are triggered and the response lasts for minutes. Fibroblasts, keratinocyte, macrophages and endothelial cells express MMPs by transcriptional activation where it is releases in 6-12 hours and the response duration lasts for days [31].

Birkedal-hansen (1993) have provided the following evidence that matrix metalloproteinases are involved in tissue destruction in human periodontal disease

1) Cells isolated from normal and inflamed gingiva are capable of expressing a wide variety of matrix metalloproteinase in culture
2) Several matrix metalloproteinases can be detected from the gingiva in vivo;
3) Matrix metalloproteinase-8 and matrix metalloproteinase-3 are readily detected in gingival crevicular fluid from gingivitis and periodontitis patients [4].

MMP -1 has been identified in inflammed gingival tissues and in granulation tissue of chronic periodontitis patients. Higher levels of MMP-1 and MMP-3 are noticed in gingival fibroblasts after stimulation with interleukin-1 and tumor necrosis factor – α. MMP-1 and MMP-3 in periodontal tissues are locally produced by host fibroblasts and then activated participating in periodontal tissue destruction [32].

Periodontal tissue breakdown was associated with the conversion of pro MMP-9 to its activated form in GCF. MMP-9 was detected in junctional and pocket epithelium of inflamed gingival tissues and contribute to gingival responses to periodontal infection in addition to neutrophils [33]. MMP-13 and MMP-14 help in osteoclast attachment to the bone surface as well as osteoclast –matrix interactions that control the bone remodelling process and detected on bony resorption lacunae and ruffled borders of osteoclasts. MMP-13a also degrades fibrinogen and factor XII of the plasma clotting system and it is directly linked to bleeding which is considered as a significant clinical feature of periodontal disease [34].

MMP-8 also increases the expression of mRNA in inflamed gingival tissues. Clinical improvement obtained by periodontal treatment was directly correlated to significant reductions in MMP-8 levels. The mean MMP-8 concentration in the saliva and GCF of the healthy individuals was 10 fold less than that of periodontally compromised patients [35].

MMP in caries, pulp and periapical pathogenesis

Dental caries is an infectious microbiologic disease of the teeth that results in localized dissolution and destruction of calcified tissues.

Demineralization in caries lesions is caused by microbial acids and lesion progression in dentin is accompanied with degradation of dentin organic matrix caused by microbial enzymes. The pH changes taking place in caries lesion are extremely powerful activators for MMPs. There are two possible sources for the MMPs in caries lesions. Salivary and GCF MMPs are reserved in plaque which is also the potential site for acid activation. MMPs are also produced by odontoblasts and they are present in mineralized human dentin. The presence of both pro- and active forms of MMP-8, -2 and -9 in human dentinal caries lesions. Since the active forms are short-lived, the presence of active MMPs indicates activation in site, suggesting their active role in the dentin matrix degradation [36].

MMP and cancer

In almost every type of human cancer the expression and activity of MMPs are increased. Early expression of MMPs, either by the tumor cells themselves or by surrounding stromal cells, helps to remodel the ECM and release ECM and/or membrane- bound growth factors, which provides a favorable microenvironment for the establishment of the primary tumor. MMPs regulate tumor growth by favoring the release of cell proliferating factors such as insulin- like growth factor (IGF) which binds to specific- binding protein. MMPs degrade

Volume 4, Issue 3; May-June 2021; Page No 330-337

components of ECM, facilitating angiogenesis, tumor cell invasion, and metastasis [37].

VIII. CONCLUSION

MMP are important components in many biological and pathological process because of their ability to degrade extracellular matrix components. They act as biomarkers for active periodontal disease. Although matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases are involved in the pathogenic process of active periodontitis, the relative balance of matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases could be useful periodontal diagnostic tests.

REFERENCES

1. Nisha KJ .Role of MMP in periodontitis and its management – a review. Biomed J Sci & Tech Res. 2018;2 (1).
2. Cauwe B, Van den Steen PE and Opdenakker G .The biochemical, biological, and pathological kaleidoscope of cell surface substrates processed by matrix metalloproteinases. Crit. Rev. Biochem. Mol. Biol.2007;42:113–185.
3. Lepilahti JM, Ahonen MM, Hernandez M. Oral rinse MMP-8 point of care immuno test identifies patents with strong periodontal inflammatory burden. Oral Dis.2011;17:115–122.
4. Birkedal-Hansen H. Role of matrix metalloproteinases in human periodontal diseases. J. Periodontol. 1993;64:474–484.
5. Gursoy UK, Kononen E, Huumonen S. Salivary type I collagen degradation end-products and related matrix metalloproteinases in periodontitis. J Clin Periodontol. 2003;40:18–25.
6. Verma RP, Hansch C. Matrix metalloproteinase (MMPs): chemical-biological functions and (Q) SARS. Bioorg Med Chem. 2007;15:2223–2268.
7. Woessner JF, Jr. Catabolism of collagen and non-collagen protein in the rat uterus during post-partum involution. The Biochemical journal.1962;83:304-314.
8. Gross J and Lapiere CM. Collagenolytic activity in amphibian tissues: a tissue culture assay. Proc. Natl. Acad. Sci. USA.1962;48:1014–1022.
9. Klein T, Bischoff R. Physiology and pathophysiology of matrix metalloproteases: Amino Acids. 2011;41:271–290.
10. Maciejczyk M. The Significance of MMPs in Oral Diseases. Adv Clin Exp Med. 2016;25(2): 383–390.
11. Irit Sagi, Jean Gaffney. Matrix metallo proteinase biology. First edition. John Wiley and Sons, Inc;2015.1.
12. Butler GS, Tam EM & Oveall CM. The canonical methionine 392 of matrix metalloproteinase 2 is not required for catalytic efficiency or structural integrity. The Journal of Biological Chemistry.2004;279(15):15615-20.
13. Loffek. Biological role of matrix metalloproteinases: A critical balance. Eur respir J. 2011;38:191–208.
14. Yan C, Boyd DD. Regulation of matrix metalloproteinase gene expression. J Cell Physiol. 2007;211:19–26.
15. Page-McCaw. Matrix metalloproteinases and the regulation of tissue Remodelling. Nat Rev Mol Cell Biol. 2007 March;8(3):221–233.
16. Springman EB, Angleton EL, Birkedal-Hansen H, Van Wart HE. Multiple modes of activation of latent human fibroblast collagenase: Evidence for the role of a Cys 73 active-site zinc complex in latency and a “cysteine switch” mechanism for activation. Proc Natl Acad Sci. USA. 1990;87:364–368.
17. Hyun-Jeong R and William C. Parks: Control of Matrix Metalloproteinase Catalytic Activity. Matrix Biol. 2007;26(8):587–596.
18. Murphy G, Willenbrock F. Tissue inhibitors of matrix metalloendopeptidases, Methods Enzymol. 1995;248:496-510.
19. Amour A, Slocombe PM, Webster A, Butler M, Knight CG, Smith BJ et al. TNF-alpha

Volume 4, Issue 3; May-June 2021; Page No 330-337

converting enzyme (TACE) is inhibited by TIMP-3, FEBS Lett. 1998;435:39.

20. Murphy G, Knaffuper V. Relating matrix metalloproteinase structure to function: why the `hemopexin' domain?, Matrix Biol. 1997;15:511-518.
21. Nagase H. Activation mechanisms of matrix metalloproteinases. Biol. Chem. 1997;378: 151-160.
22. Rinkenberger JL, Cross JC and Werb Z. Molecular genetics of implantation in the mouse. Develop Genet. 1997;21:6–20.
23. Sternlicht MD, Kouros-Mehr H, Lu P, Werb Z. Hormonal and local control of mammary branching morphogenesis. Differentiation. 2006;74:365–381.
24. Gialeli C, Theocharis AD, Karamanos NK. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. FEBS J. 2011;278:16–27.
25. Hood JD, Cheresh DA. Role of integrins in cell invasion and migration, Nat. Rev. Cancer. 2002;2: 91–100.
26. Parks WC. Matrix metalloproteinases in repair. Wound Repair Regen. 1999;7:423–432.
27. Eeckhout Y, Delaisse JM. The role of collagenase in bone resorption: an overview. Pathol Biol. 1988;36:1139-46.
28. Seiki M. The cell surface: the stage for matrix metalloproteinase regulation of migration. Curr Opin Cell Biol. 2002;14:624–632.
29. Hannas AR, Pereria JC, Granjeiro JM, Tjaderhane L. The role of matrix metalloproteinases in the oral environment. Acta odontol scand.2007;65(1):1-13.
30. Uitto VJ, Overall CM, Mcculloh C. Proteolytic host cell enzymes in gingival crevicular fluid. . Periodontol 2000.2003;31:77-104.
31. Denis FK. Regulators of tissue destruction and homeostasis as diagnostic aids in periodontology. Periodontology 2000. 2000;24: 215–225.
32. Domeij H, Yucel-Lindberg T, Modeer T. Signal pathways involved in the production of MMP-1 and MMP-3 in human gingival fibroblasts. Eur J Oral Sci.2002;110(4):302-6.
33. Smith PC, Munoz VC, Collados L, Oyarzun AD. In situ detection of MMP-9 in gingival epithelium of human periodontal disease. J Periodontal Res.2004;39(2):87-92.
34. Hernandez M, Martinez B,Tejerina JM,Valenzuela MA,Gamaonal J . MMP-13 and TIMP-1 determinants in progressive chronic periodontitis. J Clin Periodontal.2007;34(9):729-35.
35. Pussinen PJ, Paju S, Mantyla P, Sorsa T. Serum microbial and host derived markers of periodontal disease. Curr med chem.2007;14(22):2402-12.
36. Tjaderhane L, Larjava H, Sorsa T. The activation and function of host matrix metalloproteinases in dentin matrix breakdown in caries lesions. J Dent Res.1998;77: 1622–1629.
37. Charu K. Seesaw of matrix metalloproteinases. Journal of Cancer Research and Therapeutics.2016;12(1).

Volume 4, Issue 3; May-June 2021; Page No 330-337