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Matrix Metalloproteinases in Health and Diseases

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Abstract

Matrix metalloproteinases (MMPs) are a family of extracellular proteases associated with extracellular matrix remodeling. MMP not only can degrade a variety of components of extracellular matrix, but also can cleave and activate various non-matrix proteins, including cytokines, chemokines and growth factors, contributing to both physiological and pathological processes. The activities of MMPs that are involved in various cellular processes such as cellular proliferation, growth and development, angiogenesis, apoptosis, invasion and metastasis. In normal conditions, MMP expression and activity are tightly regulated via interactions between their activators and inhibitors, leading to the development of diverse diseases, such as cardiovascular disease, arthritis, neurodegenerative disease, as well as cancer. This article focuses on the accumulated evidence supporting a wide range of roles of MMPs in various diseases.

Keywords: Matrix Metalloproteinase, ECM, Atherosclerosis, Arthritis.

Introduction

Matrix metalloproteinases (MMPs) are Zn2+ dependent endopeptidases. A catalytic domain of metalloproteinase has several binding sites like special peptide, variable length of hinge-shaped regions and stationary domain of hemopexin which involves near about 200 amino acids.[1] These Matrix MMPs also denominated as matrixins as they hydrolyze proteins of the extracellular matrix (ECM). The ECM is a complex protein network, which functions as a structural support to various cells and acts as reservoir of a variety of proteins like cytokines, chemokines, growth factors and signalling molecule. Each MMP influences on ECM differently by generating distinct chemical, biomechanical, and morphological features of ECM.[2]

Classification of MMPs

MMPs are classified based on their substrate specificity, structural organization, and cellular location. MMPs family contain 28 members of which 23 are expressed in human tissues. As 23 MMPs have been identified in humans, functional redundancy is not

been observed despite their high structural homology and overlap in substrate specificity. From a chemical point of view, the MMPs classified as a collagenases (MMP-1 is designated as collagenase-1, MMP-8 and MMP-13 as a collagenase-2, and /collagenase-3 respectively). Collagenases have the ability to cleave interstitial collagens I, II and III at a specific site three-fourths of the distance from the N-terminus.[3] Collagenases differ in their substrate specificities and functions. Gelatinases i.e. MMP-2 (gelatinase A) and MMP-9 (gelatinase B) belong to gelatinase subgroup. They readily digest the denatured collagens and gelatins. MMP-2 is constitutively expressed by a wide range of cell types, including endothelial cells, macrophages and many malignant cells While MMP-9 is restricted to neutrophils.[4] MMP-2 also cleaves several ECM components, growth factors, and activates proMMP-1, -2 and -13.[5] MMP-2 breaks down collagen type I, II and III while MMP-9 participates in the angiogenic switch necessary for tumor development.[6] The stromelysins have a similar domain structure to those of collagenases but they cannot cleave native fibrillar collagens. MMP-3/ stromelysin-1can activate various MMPs including proMMP-1, -3, -7, -8, -9 and -13. MMP -3 can be activated by plasmin, kallikrein, chymase and tryptase.[7] MMP-10/ Stromelysin-2 are expressed at lower levels than stromelysin-1 generally at normal or malignant cells of epithelial origin, and no expression of stromelysin 2 has been observed in skin fibroblasts.[8,9] MMP-10 activates proMMPs-1, -2, -7, -8 and -9 and itself is activated by plasmin, elastase and cathepsin G.[10]

There are six membrane-type MMPs (MT-MMPs). Among six MT-MMPs, four (MMP-14, -15, -16 and -24) have transmembrane and intracellular domains, whereas two (MMP-17 and -25) have glycosylphosphatidylinositol anchored proteins, which target them to the cell surface. With the exception of MT4-MMP almost all are capable of activating proMMP-2. These enzymes can also digest a number of ECM molecules and MT1-MMP specifically has collagenolytic activity on type I, II and III collagens. [11] They are also more active in ECM degradation and promoting cell invasiveness than the secretory MMPs. These MT-MMPs have important role in the cell surface localization and cellular regulation of other proteases enzymes.[11] Enamelysin (MMP-20), MMP-21 and -22 are derived in a tissue-specific manner by alternative splicing and are expressed in testis, ovary and prostate.[12]

The other group, Matrilysin which lacks a carboxy domain and members of this subgroup are MMP-7, -23, -26. MMP-18 is also widely expressed like other MMPs in normal human tissues and has closest identity with MMP-1, -3, -10 and -11. [13]

The selective ECM degradation by a specific MMP influenced by cell behaviour which includes cell migration & morphology, gene expression profile and activation of intracellular cascades. In addition to degrading ECM proteins, MMPs process many prominent biological factors and non-ECM molecules which directly influencing tissue homeostasis. [5] As proteolytic enzymes, MMPs are tightly regulated at multiple levels, from gene expression to zymogen activation and endogenous inhibition. Post-translation MMP activity in vivo is regulated by activation of the pro-enzyme and endogenous tissue inhibitors of MMPs (TIMP).[14]

MMPs are secreted by endothelial cells, vascular smooth muscle, fibroblasts, osteoblasts, macrophages, neutrophils, and lymphocytes.[10] The MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9 expression was found in

endothelial cells and vascular smooth muscle cells (VSMCs), while MMP-12 showed expression in VSMCs and fibroblasts.[15] MMP-1, MMP-3, MMP-7, MMP-9, MMP-13, a membrane-type (MT) MMPs, MT-MMP1, and MT-MMP3 were found in the vascular wall. Indeed, leukocytes and dermal fibroblasts are key sources of MMP-2, whereas platelets are source of MMP-1, MMP-2, MMP-3, and MMP-14. [16] MMPs may be inhibited by tissue by biological and synthetic inhibitors and these endogenous tissue inhibitors of metalloproteinases (TIMPs) are widely distributed in many tissues and organs. (refer table no.1)

The MMPs are considered as the predominant proteases in ECM pathophysiological regulation. In this paper, we will review the impact that MMPs on tissue homeostasis and pathology, this will address the need for highly specific matrix metalloproteinase inhibitors (MMPIs), and introduce latest advances in production of selective MMP inhibitors with novel properties.

Physiological Function

As MMPs, a family of highly homologous zinc-dependent endopeptidases, are known for their ability to cleave several extracellular matrix (ECM) constituents as well as nonmatrix proteins. MMPs are secreted or anchored to the cell surface thereby confining their catalytic activities to membrane proteins or proteins within the secretory pathway or extracellular space. They are important regulators of various biologically active and functional molecules such as proinflammatory cytokines, chemokines, growth factors and serine proteinase inhibitors.[1]

MMPs are involved in many physiological processes including embryonic development, inflammation, immunity, Cellular growth and differentiation, cell proliferation and angiogenesis and overexpression of members of MMPs in pathological conditions characterized by connective tissue destruction, as evidenced by chronic arthritis, periodontitis, cardiovascular disease and cancer and, atherosclerosis.

Wound healing

In wound healing, remodeling of collagen which involves the degradation of existing collagen fibrils and the synthesis of new ones remains as a key major resolution.[17] MMPs have been observed to play an important in collagen remodeling during wound resolution. MMPs have been involved in inflammation and this is mediated by number of processes like regulation of chemokine activity, establishment of chemotactic gradients, and extravasation of leukocytes out of the blood into the injured tissue. Inflammatory cells are known to excrete MMPs; however, MMPs including MMP-1, -2, -7, -9, -10 and -28 are expressed in epithelial and stromal cells in wounded tissue. MMP-2 and- 9, and to a less extent MMP-3 basically which are present on epithelial- stromal interface behind the migrating epithelial cells was observed in anterior keratectomy corneal wounds.[18] Overall, these observations suggest that MMPs may be involved in remodelling of the stroma and reformation of the basement membrane.

Embryogenesis

Embryo implantation is a highly controlled process and is regulated by a series of events. Successful embryo implantation depends upon the synchronized development of the invasiveness of embryo and the receptivity of uterine endometrium. [19] During implantation, the endometrium undergoes decidualization and manifests the maximal uterine receptivity which provides a suitable environment for the embryo to implant on uterine mucosa. [20] This event is accompanied by extensive degradation and remodeling of ECM. Three enzyme families, including

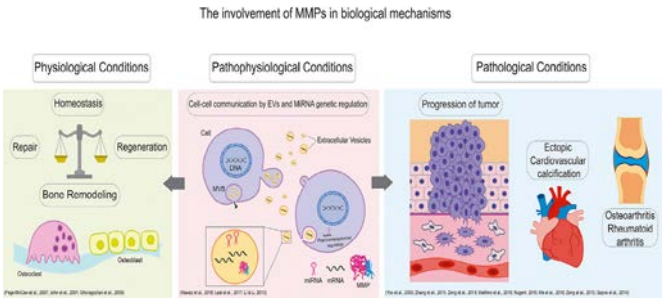
plasminogen activators, cathepsin, and MMPs are responsible for the degradation of ECM.[21]Trophoblastic cells during invasion and penetration of uterine walls majorly rely on ECM remodelling. The ECM components including collagen, fibronectin, and laminin may themselves affect many events which undergo changes in trophoblast. Direct evidence of a crosstalk between ECM components and MMPs was observed when cultured trophoblasts under stimulation by fibronectin, lamin or vitronectin demonstrated induction of MMP-9 expression. [22]Another key phenomenon that regulates the development of trophoblasts is the involvement of a plethora of paracrine and autocrine factors. Thus, MMPs may also be tightly regulated in such hormonal surroundings. Although endometrial expression of these MMP genes is normally tightly regulated during the menstrual cycle while altered patterns of MMPs and TIMP expression have been reported in eutopic and ectopic endometrial tissues obtained from patients with endometriosis.[23,24]MMP-2 and MT1-MMP proteins were found to be high Particularly, MMP-2 as it plays a role in bone embryonic development, tissue repair, and tumorigenesis

Growth, Development, and Involution Growth and development are associated with rapid cell movement and with restructuring and reshaping of the extracellular matrix. Studies have provided evidence for involvement of MMPs and their inhibitors in developmentally regulated processes in review by Werb et al.[25] These include ovulation, embryonic growth and differentiation, trophoblast invasion, parturition, skeletal growth and remodeling, development of organs including salivary glands, tooth germs and ovaries and tadpole tail and uterine post-partum involution. It is been also observed that evidence for involvement of MMPs in these processes is based on identification of MMPs and inhibitors, during particular stages of development. It is also been observed that MMP transcripts and their effect deviation or covariation in modulation of expressed MMPs may affect the either the process or the gene product affects.[26]

Dysregulation of MMP Activity: Physiology To Pathology

(Refer Fig 1)

Figure 1: Involvement of MMPs in biological conditions



MMPs and Cell Death

MMPs are localized to various intracellular sites apart from the proteolysis of extracellular protein and they have intracellular actions which consist rapidly acting on intracellular substrates in response to brain injury during hypoxia, traumatic injury, and prolonged seizure activity. The nucleus has a matrix that resembles the ECM and provides structural

and organizational support for various nuclear processes as well as apoptosis, which involves proteolytic processing of nuclear proteins. The intranuclear gelatinase activity in

ischemic neurons suggest a possible role for gelatinases in nuclear matrix proteolysis. Increased activity of MMPs including MMP-2, MMP-9, and MMP-13 was demonstrated to facilitate oxidative injury in neuronal nuclei of brains following the induction of DNA damage. [27,28]

MMPs in Endothelial Dysfunction

The endothelium dysfunction is characterized by proinflammatory and prothrombic state. Dysfunctional endothelium is represented by reduced vasodilation and changes in phenotype from antiadhesive to proadhesive. Damage of endothelial junctions results in enhanced endothelial permeability, which may facilitate in infiltration of various inflammatory mediators. Activation of endothelial MMP-2 can induce endothelial dysfunction and disintegrity. MMPs have been found to be involved in vascular wall remodeling and atherosclerosis development through inflammatory activation and endothelium dysfunction.[29]

MMPs and oxidative stress

Oxidative stress modifies the function of proteins by multiple mechanisms, including regulation of protein expression, post-translational modifications, and alterations in protein stability. Proteins exist in an oxygen-rich environment reaction so it generates many Reactive oxygen species ROS.[30] Increase in the level of ROS may result in transient cellular alterations, whereas an excessive rise in ROS in cells leads to irreversible oxidative damage ultimately to cell death. ROS regulate many signal transduction pathways by like modifying the structure of proteins, transcription factors, and genes to modulate their functions. In addition to oxidizing proteins, ROS are responsible for deaminating, racemizing, and isomerizing amino acid residues of proteins. These chemical modifications result in protein cleavage, aggregation and loss of catalytic and structural function by distorting the proteins secondary and tertiary structure. [31]

AP-1 and NFjB are a transcription factor in promoter region of MMPs the factors contain redox-sensitive cysteine residues at their DNA-binding site. Oxidation of these Cys residues (SOx) may obstruct the transactivation activity and inhibit the expression of MMPs. Newly synthesized MMP can be directly modified by oxidation of their Cys, Tyr and Met amino acids, resulting in alterations of their functions.[32] Oxidants can both activate and inactivate MMPs by altering critical amino acids via oxidation. [Post-translational modifications such as phosphorylation can either activate or inhibit the function of MMPs. H_2O_2, peroxynitrite and oxidants produced by the xanthine/xanthine oxidase system can activate both MMP-2 and MMP-9 .[33] Augmentation of glutathione levels with N-acetylcysteine treatment has been shown to inhibit MMP activation. The cysteine switch of MMP-9 can also be activated by Nitric Oxide.[34] Overall, oxidative and proteolytic processes can amplify each other and affect the protease/anti-protease balance in the tissues.

Pathological Processes

MMPs are important regulators of the cellular and physiological processes affecting

various biological processes, such as angiogenesis, morphogenesis, tissue repair, and are decisive tools for the occurrence of some diseases, such as cancer, cardiovascular disorders, arthritis, periodontitis and many others

Cancer

Tumor Growth and Metastasis

Invasive growth of primary tumors and metastases are characterised by destruction and remodeling of stromal architecture and many evidences suggests that it is common that one or more MMPs have been expressed among malignant tumor. The complement of MMPs varies from tumor to tumor, and not all tumors express the same type of MMP. Signals coming from the outside at the surrounding micro-environment such as growth factors, extracellular matrix (ECM), adjacent

stromal cells, cytokines, and chemokines, profoundly affect fates of stem cell.[35] MMPs are discussed as important proteases in the context of delivering signals, guiding cellular phenotypes in extracellular matrix remodeling. An often-fatal characteristic of malignant tumors is their ability for tissue invasion and the generation of metastases. [36] MMPs are also active in the later stages of cancer development in that they promote metastasis, as well as other aspects of tumor growth. In conjunction, MMPs play several key roles in the metastasis mechanism and might contribute to all stages of tumor progression and implantation. MMPs, through their capacity to degrade ECM proteins mare important components of oncologic disease processes. [36] The human genome sequence has revealed more than500 genes that encode proteases or protease-like proteins, with a large number being associated with tumor processes.[37]Among these, the MMPs have been the focus of a large amount of anti-cancer research and clinical trials studies shows that MMP-9 plays role in malignant transformation of various cells and is associated with tumor metastasis.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the vessel wall that is largely driven by an innate immune response.[38] In pathogenesis of atherosclerosis, a pivotal role is played by innate immunity receptors such as toll-like receptors (TLR) and receptors for advanced glycation end products (RAGE). [39] TLR and RAGE mediate in macrophages and leukocyte recruitment and are remarkably involved in the initiation and progression of atherosclerosis [40]. This process is characterized by the accumulation of lipids, smooth muscle cell proliferation, cell apoptosis, necrosis, and fibrosis.MMPs also plays important role in all stages of atherosclerosis through vascular inflammation, endothelial dysfunction, smooth muscle cell migration, vascular calcification, extracellular matrix degradation, and plaque activation and destabilization.[41] MMPs participate in the immune response and play a key role in vascular inflammation that is strongly associated with atherosclerosis. [42] Exposure of vascular cell walls to inflammatory mediators produced under chronic inflammation may lead to excessive MMPs activity in the arterial wall resident and recruited cells. In response to proinflammatory mediators, monocytes enhance MMPs expression and play a key role in inflammatory cell migration and invasion into the arterial wall. The expression of MMPs is controlled by different microRNA molecules. MicroRNA regulation of extracellular matrix components is crucial in the process of atherosclerotic plaque destabilization.[43]

Exosomes may serve as biomarkers for the development of atherosclerosis, providing potential roles for diagnosis and treatment.[44] Quantitative analysis of MMP-rich extracellular vesicles can be used as a parameter to assess calcification and plaque neovascularization in monitoring the clinical course of cardiovascular diseases. MMPs analysis also seems to be helpful in identifying patients at risk of cardiovascular disease. MMPs can also be a therapeutic target for preventing and controlling the development of atherosclerosis, including progression of plaque formation and its instability. [45]

MMP-9 is a strong independent predictor of atherosclerotic plaque instability in stable coronary heart disease (CHD) patients, where MMP-9 levels are positively associated with the size of the necrotic core of coronary atherosclerotic plaques. It was shown that serum MMP-9 and the MMP-9/TIMP-1 molar ratio may be useful in acute coronary syndrome (ACS)

diagnosis and prognosis. MMP-9 activation in serum was associated with poor cardiovascular outcome.[46]

Arthritis

Osteoarthritis (OA), the most common form of arthritis, is characterized by the destruction of articular cartilage. The main constituents of articular or joint cartilage are type II collagen and various proteoglycans, such as aggrecan, chondroitin sulfate, and hyaluronan. Tensile strength of articular cartilage is due to the triple-helical structure of type II collagen.

MMP-7 activates bone differentiation and extracellular matrix degradation and MMP-9 seems to be involved in osteoclast-based bone remodeling. The excessive production of MMP-13 by chondrocytes during onset and in progression of OA resulting the extracellular matrix degradation.[47]

In rheumatoid arthritis (RA), the MMP's activities are directly related to cartilage degradation. Endogenous MMP-2 and MMP-9 collaborate to survival, proliferation, migration, and invasion of RA synovial fibroblast. In addition, MMP-9 stimulates RA synovial fibroblast-mediated inflammation and degradation of cartilage, contributing to joint destruction. [48]

Pulmonary fibrosis occurs following repeated bouts of lung injury which can be observed in cystic fibrosis, usual interstitial pneumonitis (UIP)/ idiopathic pulmonary fibrosis (IPF), and acute respiratory distress syndrome (ARDS). Pulmonary fibrosis is result of excess collagen production as compared with degradation. [49] Fibrosis may be the result of a change in collagen composition, resulting in decreased degradation, or an increase in the production of protease inhibitors. A greater proportion of type I collagen compared with type III collagen is observed in lung fibrotic tissue compared to normal lung tissue. Fibrotic tissue also has increased amounts of collagen binding biomolecules, such as fibronectin and proteoglycans, increased proportion of hydroxylated Lys residues within the collagen, and an increase in collagen crosslinking. An increased tissue inhibitor of metalloproteinase (TIMP) to MMP ratio and decreased collagenolysis in the lung is found in human UIP/IPF patients. Knockout studies have implicated MT1- MMP and cathepsin K as key collagenases in fibrosis. [50]

Kidney diseases

Acute kidney injury (AKI) produced by renal ischemia-reperfusion injury characterised of increased expressions of MMP-2, -9 and TIMP-2 and decreased expression of TIMP-1.The increased MMP-9 activity during ischemic injury of kidneys can be linked with degradation of junction proteins in both the endothelial cell fraction and glomeruli which leads to increased vascular permeability in AKI .[51] In patients with Chronic Kidney Disease CKD it is found that elevated serum and plasma levels of MMP-2 and MMP-9. These findings are result of reduced ECM degradation which favours the development of renal fibrosis at later time points. And this is pathologically characterized by thickened basement membrane and expansion of the glomerular mesangial matrix and tubulointerstitial space, which is due to excessive deposition of ECM. Multiple studies have demonstrated the upregulated levels of MMP-2, -7, -8 and -9 in serum and urine from patients with type 1 or type 2 diabetes. In addition, the urinary MMP-9 concentration was reported to be correlated with the degree of albuminuria in type 2 diabetic nephropathy.[52] The study by Provenzano M. et al. [53] discovered that the role of MMPs in increasing the risk of peripheral vascular disease (PVD) by the specific factors related to CKD. The study further suggests that the possibility of a strict link between PVD mediated by MMPs. Particularly MMP-2 and

MMP-9 also sustained by an increase in NGAL circulating levels that are also known to be directly related to diabetic status and inversely to estimated glomerular filtration rate (eGFR) levels.

Liver Fibrosis

Liver fibrosis is a result of the wound-healing response to chronic injury including viral hepatitis and alcoholic/non-alcoholic steatohepatitis. MMPs and TIMPs along with a large amount of ECMs, especially fibrillar collagen type I and type III are produced following the injury to hepatic stellate cells (HSCs). These HSCs initially exhibit a matrix-degrading phenotype, later in chronic phases of liver injury shows pro-fibrotic phenotype. This degradation of liver matrix is characterised by decreased degradation of fibrillar collagens which accumulate in liver fibrosis.[54] Based on their proteolytic activity, various MMPs have been reported as anti-fibrotic enzymes in liver fibrosis. For example, overexpression of collagenases (MMP-1, -8 and -13) in a rat model of liver fibrosis was associated with the recovery from fibrosis and induced normal hepatocyte proliferation. [55] Furthermore, MMP-2 has been reported to act as a protective effect against the progression of fibrosis in liver by inhibiting type I collagen synthesis.

CNS Diseases

The ECM in central nervous system (CNS) is composed mainly of proteoglycans and essential for neuronal cell development. ECM proteins expressed to play important role for survival activity of CNS, such as microglial activation, inflammation and blood-brain barrier (BBB) disruption. Various MMPs have found to be widely expressed in the CNS, their expression levels in the normal adult brain are quite low while upregulated in injury and in several neurological disorders, such as multiple sclerosis (MS), Alzheimer's disease (AD) and Parkinson's disease (PD), suggesting that MMPs play critical roles in their pathophysiological mechanisms. [56,57]

Crohn's disease (CD) Rautava J et al. [58]observed that relation between a complex inflammatory disease of the gastrointestinal tract, and the tendency of such patients to develop periodontitis, caries, and oral mucosal lesions. The study postulates that the dysregulation of the immune system in CD may have an effect on MMP-8 levels in the oral cavity. In this context, MMP-8 seems to be the key inflammatory mediator in these conditions; In fact, elevated MMP-8 levels have been detected in CD patients both in the intestine and in the oral cavity and in periodontal disease.

Conclusion

In the current review, we widely discuss the role of MMPs, especially in the context of normal physiological functions and pathological conditions. Despite considerable research efforts over the past few decades, many emerging findings related to MMPs are still being reported from research laboratories around the world every year and that makes the role of MMPs in vivo more and more complex and important. There are fundamental challenges to be overcome in applying the MMPs-targeted therapy in the clinical setting. Nonetheless, it is hoped that the previous, ongoing and future studies will together translate their findings into novel medical strategies for various diseases soon.

References

1. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res 2006; 69:562–573.
2. I. Solomonov, E. Zehorai, D. Talmi-Frank, S.G. Wolf, A. Shainskaya, A. Zhuravlev et al Distinct biological events generated by ECM proteolysis by

two homologous collagenases. Proc. Natl. Acad. Sci. U. S. A. 2016; 113:10884–9.

3. Chakrabarti S, Patel KD. Matrix metalloproteinase-2 (MMP-2) and MMP-9 in pulmonary pathology. Exp Lung Res 2005; 31:599–621.
4. Aoudjit F, Masure S, Opdenakker G et al. Gelatinase B (MMP-9), but not its inhibitor (TIMP-1), dictates the growth rate of experimental thymic lymphoma. Int J Cancer 1999; 82:743–747.
5. Mccawley LJ, Matrisian LM. Matrix metalloproteinases: they're not just for matrix anymore! Curr Opin Cell Biol 2001; 13:534–540.
6. Bergers G, Brekken R, Mcmahon G et al. Matrix metalloproteinase- 9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol 2000; 2:737–744.
7. Nagase H, Woessner JF Jr. Matrix metalloproteinases. J Biol Chem 1999; 274:21491-4.
8. Vaalamo M, Karjalainen-Lindsberg ML, Puolakkainen P et al. Distinct expression profiles of stromelysin-2 (MMP-10), collagenase-3 (MMP-13), macrophage metalloelastase (MMP-12), and tissue inhibitor of metalloproteinases-3 (TIMP-3) in intestinal ulcerations. Am J Pathol 1998; 152:1005–1014.
9. Delany AM, Brinckerhoff CE. Post-transcriptional regulation of collagenase and stromelysin gene expression by epidermal growth factor and dexamethasone in cultured humanfibroblasts. J Cell Biochem 1992; 50:400–410.
10. Parks WC, Mecham RP. Matrix Metalloproteinases. Academic Press, New York, 1998.
11. Ohuchi E, Imai K, Fujii Y et al. Membrane type 1 matrix metalloproteinase digests interstitial collagens and other extracellular matrix macromolecules. J Biol Chem 1997;272:2446–2451.
12. Gururajan R, Grenet J, Lahti JM et al. Isolation and characterization of two novel metalloproteinase genes linked to the Cdc2L locus on human chromosome 1p36.3. Genomics 1998; 52:101–106.
13. Cossins J, Dudgeon TJ, Catlin G et al. Identification of MMP-18, a putative novel human matrix metalloproteinase. Biochem Biophys Res Commun 1996; 228:494–498.
14. 14. Gupta, S.P. Matrix metalloproteinase inhibitors: Specificity of binding and structure-activity relationships. Exp. Suppl. 2012;103: v–vi.
15. Overview of MMP Biology and Gene Associations in Human Diseases Role of matrix metalloproteinase in human body pathologies. Tamara Djuric and Maja Zivkovic.2017.DOI: 10.5772/intechopen.70265
16. Snehasikta Swarnakar , Sumit Paul, Laishram Pradeeepkumar Singh, Russel J Reiter. Matrix metalloproteinases in health and disease: regulation by Melatonin. J. Pineal Res. 2011; 50:8–20
17. Singer AJ, Clark RAF. Cutaneous wound healing. N Engl J Med 1999; 341:738–746.
18. Mulholland B, Tuft SJ, Khaw PT. Matrix metalloproteinase distribution during early corneal wound healing. Eye (Lond) 2005; 19:584–588.
19. Krussel JS, Bielfeld P, Polan ML et al. Regulation of embryonic implantation. Eur J Obstet Gynecol Reprod Biol 2003; 110:2–9.
20. Wang H, Dey SK. Roadmap to embryo implantation: clues from mouse models. Nat Rev Genet 2006; 7:185–199.

21. Red-Horse K, Zhou Y, Genbacev O et al. Trophoblast differentiation during embryo implantation and formation of the maternal-fetal interface. J Clin Invest 2004; 114:744–754.
22. Bischof P, Truong K, Campana A. Regulation of trophoblastic gelatinases by proto-oncogenes. Placenta 2003; 24:155–163.
23. Paul S, Sharma AV, Mahapatra PD et al. Role of melatonin in regulating matrix metalloproteinase-9 via tissue inhibitors of metalloproteinase-1 during protection against endometriosis. J Pineal Res 2008; 44:439–449.
24. Collette T, Maheux R, Mailloux J et al. Increased expression of matrix metalloproteinase-9 in the eutopic endometrial tissue of women with endometriosis. Hum Reprod 2006; 21:3059–3067.
25. Werb, Z., C. M. Alexander and R. R. Adler: Expression and Function of Matrix Metalloproteinases in Development. In: Matrix Metalloproteinases and Inhibitors. (H. Birkedal-Hansen, Z. Werb, H. G. Welgus and H. E. Van Wart., Eds.) Matrix. Spec. Suppl. No. ;1992:337-343
26. Delaisse, J.-M., Y. Eeckhout and G. Vaes: Bone-Resorbing Agents Affect the Production and Distribution of Procollagenase as Well as the Activity of Collagenase in Bone Tissue. Endocrinology. 1988; 123:264-276.
27. Rosenberg GA (2009) Matrix metalloproteinases and their multiple roles in neurodegenerative diseases. Lancet Neurol 8:205–216.
28. Rosenberg GA. Neurological diseases in relation to the blood-brain barrier. J Cereb Blood Flow Metab.2012; 32:1139–1151.
29. Sariahmetoglu M, Crawford BD, Leon H et al. Regulation of matrix metalloproteinase-2 (MMP-2) activity by phosphorylation. FASEB J.2007; 21:2486–2495.
30. Trachootham D, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat Rev Drug Discov. 2009; 8:579–591.
31. Hipkiss AR. Accumulation of altered proteins and ageing: causes and effects. Exp Gerontol.2006; 41:464–473.
32. Rees MD, Kennett EC, Whitelock JM et al. Oxidative damage to extracellular matrix and its role in human pathologies. Free Radic Biol Med 2008; 44:1973–2001.
33. Fu X, Kao JLF, Bergt C et al. Oxidative cross-linking of tryptophan to glycine restrains matrix metalloproteinase activity: specific structural motifs control protein oxidation. J Biol Chem 2004; 279:6209–6212.
34. Nelson KK, Melendez JA. Mitochondrial redox control of matrix metalloproteinases. Free Radic Biol Med 2004; 37:768–784.
35. Overall CM, Lopez-Otin C. Strategies for MMP inhibition in cancer: innovations for the post-trial era. Nat Rev Cancer. 2002; 2:657–672.
36. Lopez-Otin C, Overall CM. Protease degradomics: a new challenge for proteomics. NatRevMolCell Biol. 2002; 3:509–519.
37. Coussens LM, Fingleton B, Matrisian LM. Matrix metalloproteinase inhibitors and cancer–trials and tribulations. Science 2002; 295:2387–2392.
38. Wolf, D.; Ley, K. Immunity and inflammation in atherosclerosis. Circ. Res. 2019;124: 315–327.
39. Olejarz,W.; Lacheta, D.; Gluszko, A.; Migacz, E.; Kukwa,W.; Szczepanski, M.J.; Tomaszewski, P.; Nowicka, G. RAGE and TLRs as key targets for

antiatherosclerotic therapy. Biomed. Res. Int.2018; 76:752-86.

40. Olejarz,W.; Gluszko, A.; Cyran, A.; Bednarek-Rajewska, K.; Proczka, R.; Smith, D.F.; Ishman, S.L.; Migacz, E.; Kukwa,W. TLRs and RAGE are elevated in carotid plaques from patients with moderate-to-severe obstructive sleep apnea syndrome. Sleep Breathing Physiology and Disorders. 2020; 1:1–8.
41. Wang, X.; Khalil, R.A. Matrix metalloproteinases, vascular remodeling, and vascular disease. Adv. Pharmacol. 2018;81: 241–330.
42. Nissinen, L.; Kahari, V.M. Matrix metalloproteinases in inflammation. Biochim. Biophys. Acta. 2014; 1840:2571–2580.
43. Kowara, M.; Cudnoch-Jedrzejewska, A.; Opolski, G.; Wlodarski, P. MicroRNA regulation of extracellular matrix components in the process of atherosclerotic plaque destabilization. Clin. Exp. Pharmacol. Physiol. 2017; 44: 711–718.
44. Lu, X. The role of exosomes and exosome-derived micrornas in atherosclerosis. Curr. Pharm. Des. 2017; 23: 6182–6193.
45. Alique, M.; Ramirez-Carracedo, R.; Bodega, G.; Carracedo, J.; Ramirez, R. Senescent microvesicles: A novel advance in molecular mechanisms of atherosclerotic calcification. Int. J. Mol. Sci. 2018; 19:2003.
46. Ezhov, M.; Safarova, M.; Afanasieva, O.; Mitroshkin, M.; Matchin, Y.; Pokrovsky, S. Matrix metalloproteinase 9 as a predictor of coronary atherosclerotic plaque instability in stable coronary heart disease patients with elevated lipoprotein(a) levels. Biomolecules. 2019; 9:129.
47. B. Caterson, C.R. Flannery, C.E. Hughes, C.B. Little, Mechanisms involved in cartilage proteoglycan catabolism, Matrix Biol. 2000;19:333–344.
48. Xue M, McKelvey K, Shen K, Minhas N, March L, Park SY, et al. Endogenous MMP-9 and not MMP-2 promotes rheumatoid synovial fibroblast survival, inflammation and cartilage degradation. Rheumatology (Oxford). 2014; 53:2270-9.
49. W. McKleroy, T.H. Lee, K. Atabai. Always cleave up your mess: targeting collagen degradation to treat tissue fibrosis, Am. J. Physiol. Lung Cell. Mol. Physiol. 2013;304: L709–L721.
50. Matrix metalloproteinase protein inhibitors: highlighting a new beginning for metalloproteinases in medicine Vishnu Mohan1 Dalit Talmi-Frank1 Valeria Arkadash, Niv Papo Irit Sagi. Metalloproteinases In Medicine.2016;3: 31–47.
51. Caron, A.; Desrosiers, R.R.; Beliveau, R. Ischemia injury alters endothelial cell properties of kidney cortex: Stimulation of MMP-9. Exp. Cell Res. 2005; 310: 105–116.
52. Pawlak, K.; Mysliwiec, M.; Pawlak, D. Peripheral blood level alterations of MMP-2 and MMP-9 in patients with chronic kidney disease on conservative treatment and on hemodialysis. Clin. Biochem. 2011;44: 838–843.
53. Provenzano, M.; Andreucci, M.; Garofalo, C.; Faga, T.; Michael, A.; Ielapi, N.; Grande, R.; Sapienza, P.; Franciscis, S.; Mastroroberto, P.; et al. The Association of Matrix Metalloproteinases with Chronic Kidney Disease and Peripheral Vascular Disease: A Light at the End of the Tunnel? Biomolecules.2020;10:154.
54. Benyon, R.C.; Arthur, M.J. Extracellular matrix degradation and the role of hepatic stellate cells. Semin. Liver Dis. 2001; 21:373–384.

55. Iimuro, Y.; Nishio, T.; Morimoto, T.; Nitta, T.; Stefanovic, B.; Choi, S.K.; Brenner, D.A.; Yamaoka, Y. Delivery of matrix metalloproteinase-1 attenuates established liver fibrosis in the rat. Gastroenterology 2003; 124:445–458.
56. Lorenzl, S.; Albers, D.S.; Relkin, N.; Ngyuen, T.; Hilgenberg, S.L.; Chirichigno, J.; Cudkowicz, M.E.; Beal, M.F. Increased plasma levels of matrix metalloproteinase-9 in patients with Alzheimer's disease. Neurochem. Int. 2003; 43:191–196.
57. Yong, V.W.; Zabad, R.K.; Agrawal, S.; Goncalves Dasilva, A.; Metz, L.M. Elevation of matrix metalloproteinases (MMPs) in multiple sclerosis and impact of immunomodulators. J. Neurol. Sci. 2007; 259:79–84.
58. Rautava, J.; Gürsoy, U.K.; Kullström, A.; Könönen, E.; Sorsa, T.; Tervahartiala, T.; Gürsoy, M. An Oral Rinse Active Matrix Metalloproteinase-8 Point-of-Care Immunotest May Be Less Accurate in Patients with Crohn's Disease. Biomolecules 2020; 10:395-99.

Legend Table

Table 1: Classification, Functions and related pathology of MMP family

Class	Members of each class	Tissue specific site /Production	Function/substate	Diseases
Collagenases	MMP-1	Endothelial cells, VSMCs, vascular wall, platelets, fibroblasts, macrophages hepatocytes	Ability to cleave interstitial Degrade collagen : I, II, III, VII,IX	Rheumatoid arthritis
	MMP-8	Macrophages, neutrophils Collagens: I, II, III; Aggrecan link protein smooth muscle cells.	Degrade collagen : I, II, III,	Osteosarcoma, Chrons disease, Periodontitis, Colorectal cancer
	MMP-13	Vascular wall, SMCs, macrophages Collagens: I, II, III epithelial and neuronal cells	Degrade collagen : III,IV,X	Osteoarthritic chondrocytes
	MMP-18	mammary glands, placenta, lung, pancreas, ovary	Degrades fibronectin, Laminin	Osteosarcoma
Gelatinases	MMP-2	Endothelial cells, VSMCs, adventitia leukocytes, dermal fibroblasts, platelets	Denature Gelatin type I	Prostate cancer and Breast cancer, Chronic kidney disease, lung cancer
	MMP-9	Macrophages osteoblasts	Denature Gelatin type I & IV	Atherosclerosis Chronic kidney disease,Osteoarthritis
Stromelysins	MMP-3	Endothelial cells, VSMCs, vascular wall, platelets	Degrade fibronectin and laminin	Rheumatoid arthritis synovial fibroblasts
	MMP-10	Uterus Collagens: II, IV, V;	Degrade fibronectin and laminin activate procollagenase	Pelvic lymph node metastasis (LNM)
	MMP-11	Uterus, brain, Placenta	Degrades weak structural proteins of ECM	Osteosarcoma

Matrilysins	MMP-7	vascular wall, uterus, liver, pancreas, prostate and skin	Degrades casein and gelatin fibronectin activates procollagen	Gastric cancer, Ovarian cancer
	MMP-26	Cancer cells of epithelial origin	Degrades fibronectin, fibrinogen,Activates procollagen B	Carcinomas of the lung, prostate and breast, angiogenesis.
Membrane-type MMPs	MMP-14	fibroblasts, uterus, brain	Activates MMP 2 and 13, deragdes Aggrecan	Gastric cancer
	MMP-15	Fibroblasts, leukocytes, Heart	Broad range of substrate	Glioblastoma
	MMP-16	Vascular wall, leukocytes	Degrades collagen type III, Activates MMP 2	Glioblastoma
	MMP-17	Lung, placenta Brain	Activates MMP2 by cleavage, Degrades COMP , alpha 2 macroglobulin	Brain cancer
	MMP-24	Leukocytes, lung, pancreas, kidney,	Degrade by cleavage N-Cadherin	Glioblastoma
	MMP-25	Leukocytes	Cleaves Vimentin and Alpha 1 proteinase inhibitor	Bacterial infection, inflammation
Others	MMP-12	Macrophage	Degrade soluble and insoluble elastin	Melanoma
	MMP-19	RASI 1 : leucocytes Organs: colon, intestine, ovary, testis, prostate, thymus, spleen, pancreas,	Broad range of substrate	Osteoarthritis
	MMP-20	Enamelysin dental tissue (enamel)	Degrades Aggregan and COMP	Bacterial infection, inflammation
	MMP-21	MMP identified on chromosome 1	Specific function in embryogenesis	Multiple sclerosis
	MMP-23	human ovary cDNA testicles, intestine	Regulates the surface expression of potassium channel	Not specific
	MMP-28	Epilysinbasal keratinocytes epidermis	Degrades casein and structural proteins of ECM	Colorectal cancer