# Studies on Matrix Metalloproteinase: A Review of their Structure, Types and Role in Myocardial Infarction

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**Abstract-** Myocardial Infarction. These Matrix Metalloproteinases (MMPs) are a group of enzymes that are responsible for the degradation of extracellular matrix (ECM) and the proteins in ECM during organogenesis, growth and normal tissue turnover. These enzymes are endopeptidases that are depended on calcium and zinc ions for their activity and are thus, known as metalloproteinases. Matrix metalloproteinases are involved in wound healing, angiogenesis, and tumor cell metastasis. They are also significant regulators of the extracellular tissue signaling networks. MMPs are secreted as inactive zymogens which are then activated by a "cysteine switch". The three domain structure of these enzymes has been discussed in this review. The activity of MMPs is regulated at the level of transcription, pro-peptide activation and inhibition by tissue inhibitors of MMPs. Dysregulation in their activity can lead to many pathological conditions. Matrix Metalloproteinases are of various types and are subdivided into groups based on specific characteristics which have been elaborated. A final segment of the review details the current knowledge of the involvement of MMP in specific developmental or pathological conditions, including myocardial infarction. MI affects the left ventricle and thus, the left ventricle undergoes remodeling following MI. Furthermore, the different phases of post-MI left ventricular remodeling have been discussed. Lastly, the review focuses on the postulates of cardiac metalloproteinases actions (CarMA) in myocardial infarction.

**Keywords:** Matrix metalloproteinases, Myocardial Infarction, Post MI Left Ventricular Remodeling

## 1 Introduction

Matrix metalloproteinases (MMPs), also known as matrixins, are calcium-dependent zinc-containing endopeptidases and other the family members include adamalysins, serralysins, and astacins. The MMPs belong to a larger family of proteases known as the metzincin superfamily. Collectively, these enzymes are capable of degrading all kinds of extracellular matrix proteins, but also can process a number of bioactive molecules. They are known to be involved in the cleavage of cell surface receptors, the release of apoptotic ligands (such as the FAS ligand), and chemokine/cytokine inactivation. MMPs are also thought to play a major role in cell behaviors such as cell proliferation, migration (adhesion/depression), differentiation, angiogenesis, apoptosis and host defense. MMPs are involved in both physiological processes, such embryogenesis and organogenesis during development, and in pathological processes such as wound healing, metastasis, and tissue remodeling.[1-3] Humans have 24 matrixin genes including duplicated MMP-23 genes; thus there are 23 MMPs in humans.[4] The activities of most matrixins are very low or negligible in the normal steady-state tissues, but expression is transcriptionally controlled by inflammatory cytokines, growth factors, hormones, cell –cell and cell – matrix interaction[5]. Matrixin activities are also regulated by activation of the precursor zymogens and inhibition by endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs). Thus, the balance between MMPs and TIMPs are critical for the eventual ECM remodeling in the tissue.[4] dysregulation of the MMP/TIMP ratio may lead to unchecked MMP activity leading to adverse events in tissue homeostasis.[6]

## 2 Structure of MMPs

The MMPs have a common domain structure. The three common domains are 1)pro-peptide on the amino-terminus, 2)zinc-containing catalytic domain, and 3)haemopexin-like C-terminal domain, which is linked to the catalytic domain by a flexible hinge region.
The catalytic domain has two zinc ions and at least one calcium ion and of the zinc ions, only one ion (Z1) is catalytic.[6] MMP-23 does not have a catalytic domain.[6]The hemopexin-like domain is called as such because of its sequence homology to hemopexin, a plasma protein involved in heme binding and transport.[6] The propeptide domain consists of about 80 amino acids, the catalytic metalloproteinase domain of about

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170 amino acids, a linker 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.[4] Among all the MMPs described so far, 25 MMPs have been discovered where MMP-4,-5, and -6 are encoded by MMPs can be either membrane-bound or secreted[6,7,8]. Membrane-type MMP is often referred to as simply MT-MMPs[6].
All MMPs are secreted and cleavage of the signal sequence yields a zymogen inactivated by a highly conserved prodomain displaying the consensus sequence PRCGVPDV. This prodomain is often called a switch loop as it contains Cys92 whose thiol coordinates with Z1 in the proenzyme[6,9]. The polypeptide linker connecting the catalytic domain to the prodomain can undergo furin cleavage, proconvertase action, sheddase action, or auto-activation to yield the active enzyme.[6]

## 3 Types of MMPs

On the basis of substrate specificity, sequence similarity, and domain organization, vertebrate MMPs can be divided into six groups: [10]

Collagenases: MMP-1, MMP-8, MMP-13, and MMP-18 (Xenopus) are in this group. The key feature of these enzymes is their ability to cleave interstitial collagens I, II, and III at a specific site three-fourths from the N-terminus and they can also digest a number of other ECM and non-ECM molecules. [10] In addition, these collagenases exhibit specificity for other substrates such as gelatin, casein, aggrecan, laminin, versican, perlecan, fibronectin, and tenascin.[11,12]

Gelatinases: Gelatinase A (MMP-2) and gelatinase B (MMP-9) belong to this group. They readily digest the denatured collagens, gelatins.[10] These enzymes have three repeats of a type II fibronectin domain inserted in the catalytic domain, which bind to gelatin, collagens, and laminin.[13] MMP-2, but not MMP-9, digests type I, II, and III collagens.[14,15]

Stromelysins: Stromelysin 1 (MMP-3) and stromelysin 2 (MMP-10) both have similar substrate specificities, but MMP-3 has proteolytic efficiency higher than that of MMP-10 in general.[10] Besides digesting ECM components, MMP-3 activates a number of proMMPs, and its action on a partially processed proMMP-1 is critical for the generation of fully active MMP-1.[16] MMP-11 is called stromelysin 3, but it is usually grouped with "other MMPs" because the sequence and substrate specificity diverge from those of MMP-3.[10] MMP-3 and -10 are intestinal proteases, and are established key players in the development of ulcers in inflammatory bowel disease[17]. In addition, although in chronic human hypertension elevated activity of MMP-3 has been reported [18], MMP-10 experimentally has been shown to regulate tumor cell migration, invasion and EC tube formation[19].

Matrilysins: The matrilysins are characterized by the lack of a hemopexin domain. Matrilysin 1 (MMP-7) and matrilysin 2 (MMP-26),[20] also called endometase,[21] are in this group. Besides ECM components, MMP-7 processes cell surface molecules such as pro–_-defensin, Fas-ligand, pro–tumor necrosis factor (TNF)-_, and E-cadherin. Matrilysin 2 (MMP-26) also digests a number of ECM components.

Membrane-Type MMPs: There are six membrane-type MMPs (MT-MMPs): four are type I transmembrane proteins (MMP-14, MMP-15, MMP-16, and MMP-24), and two are glycosylphosphatidylinositol (GPI) anchored proteins (MMP-17 and MMP-25).[10] MMP-14 was the first MMP discovered possessing a transmembrane domain cloned from lung tumor cells conferring their invasiveness and metastasis.[22] With the exception of MT4-MMP, they are all capable of activating proMMP-2. These enzymes can also digest a number of ECM molecules, and MT1-MMP has collagenolytic activity on type I, II, and III collagens.[23] MT1-MMP null mice exhibit skeletal abnormalities during postnatal development that are most likely due to lack of collagenolytic activity.[24] MT1-MMP also plays an important role in angiogenesis.[25] MT5-MMP is brain specific and is mainly expressed in the cerebellum.[26] MT6-MMP (MMP-25) is expressed almost exclusively in peripheral blood leukocytes and in anaplastic astrocytomas and glioblastomas but not in meningiomas.[27,28]

Other MMPs: Seven MMPs are not classified in the above categories.

Metalloelastase (MMP-12) is mainly expressed in macrophages[29] and is essential for macrophage

migration.[30] Besides elastin, it digests a number of other proteins.

MMP-19 was identified by cDNA cloning from liver[31] and as a T-cell–derived autoantigen from patients with rheumatoid arthritis (RASI).[32]

Enamelysin (MMP-20), which digests amelogenin, is primarily located within newly formed tooth enamel. Amelogenin imperfecta, a genetic disorder caused by defective enamel formation, is due to mutations at MMP-20 cleavage sites.[33]

MMP-22 was first cloned from chicken fibroblasts,[34] and ahuman homologue has been identified on the basis of EST sequences. The function of this enzyme is not known.

MMP-23, also called cysteine array MMP, is mainly expressed in reproductive tissues.[35] The enzyme lacks the cysteine switch motif in the prodomain. It also lacks the hemopexin domain; instead, it has a cysteine-rich domain followed by an immunoglobulin-like domain. It is proposed to be a type II membrane protein harboring the transmembrane domain in the N-terminal part of the propeptide. Because it has a furin recognition motif in the propeptide, it is cleaved in the Golgi and released as an active enzyme into the extracellular space.[36]

The latest addition to the MMP family is epilysin, or MMP-28, mainly expressed in keratinocytes.[37,38] Expression patterns in intact and damaged skin suggest that MMP-28 might function in tissue hemostasis and wound repair.[37-39]

## 4 Role of MMPs in Myocardial Infarction

Myocardial infarction (MI) occurs when prolonged reduction in blood flow to a region of the heart results in permanent death of myocytes. Over the following days and weeks, the dead myocytes are gradually replaced by a collagenous scar. This progression of myocardial wound healing following infarction is a dynamic process generally divided into three stages: inflammation/necrosis, fibrosis/proliferation, and long-term remodeling/maturation. [40-42]
Following a myocardial infarction (MI), the left ventricle (LV) undergoes a series of events
that substantially alters LV structure and function.[43]

## 5 Phases of Left Ventricular Remodeling following MI

The first phase starts immediately after MI and lasts for approximately three days. During this time, the infarct tissue expands resulting in LV chamber dilation, and the inflammatory response is initiated.[44] In the absence of reperfusion, neutrophils are the first inflammatory cells to infiltrate the necrotic myocardium and release reactive oxygen species and proteases. With reperfusion, all leukocyte types enter simultaneously.[45] Structural remodeling of the ischemic area is initiated as inflammatory cells and necrotic myocytes secrete and activate matrix metalloproteinases (MMPs) including MMP1, 2, 3, 7, 8, 9, 12, 13, and 14.[46-48] These proteinases degrade cell and matrix material aiding phagocytic macrophages in the resorption of necrotic tissue.

During the second phase that occurs at 3–7 days post-MI, the LV continues to dilate and becomes spherical, and there is a reduction in ejection fraction and an increase in myocardial strain. Necrotic cardiomyocytes in the infarct region are removed while viable myocytes in the peri-infarct region undergo compensatory hypertrophy. Macrophage infiltration peaks to remove necrotic myocytes and apoptotic neutrophils, as well as activate cardiac fibroblasts that secrete extracellular matrix (ECM) for infarct scar formation.[49] The formation of the infarct scar results from a balance between ECM degradation and synthesis. Excessive ECM degradation by matrix metalloproteinases (MMPs) can lead to excessive thinning of the LV free wall with resultant aneurysm or rupture.[50] As a result, the LV is most vulnerable to rupture during this time period in both animal models of permanent artery occlusion and humans who are not successfully re-perfused. Excessive ECM degradation can also disrupt cardiomyocyte alignment and impair contraction or electrical signaling.[51] Conversely, excessive ECM synthesis by fibroblasts can lead to a stiff and non-compliant LV, the development of diastolic dysfunction, and ultimately progression to heart failure. Therefore, successful wound healing post-MI relies on a balance between sufficient ECM degradation and synthesis.[43]

The third phase begins around day 7 post-MI and continues indefinitely. This phase involves the chronic LV remodeling response that occurs at a highly variable rate in both animal models and patients.[43] The possible outcomes of this phase ranges from formation of minor scar tissue with no further progression of fibrosis and no residual symptoms to extensive adverse remodeling with resultant congestive heart failure.[52]

Cardiac Metalloproteinases actions (CarMA):

1. MMP increases Post-MI- MMP protein expression likewise increases in all cases of MI, either in a linear relationship or over a threshold level of expression for cell types which have low MMP expression in the absence of MI.[53] In particular, MMPs-1, -2, -3, -7, -8, -9, -13, and -14

levels increase; and even in the case of MMP-28, where total levels decrease post-MI, macrophage derived MMP-28 increases.[54-59] The increase in an MMP seen post-MI could be due to one of two reasons: a) there is an influx of cells not present in the normal myocardium that can express the MMP, or b) there is an upregulation of ectopic expression, such that cell types that normally do not express the specific MMP at high levels are now producing it.[53]

2. MMP stimulates cell signaling in vitro- MI-relevant cells stimulated with an MMP will display biological functions similar to what is observed during LV remodeling in vivo, if that MMP has a causal role. Basically, this postulate raises the possibility that MMPs can serve in direct signaling capacities, which separates this role from that of an enzyme.[60]
3. Modulation of an MMP alters LV remodeling- In the case of MI, our postulate decrees that interventions blocking or enhancing MMP functions will significantly affect LV remodeling. [53]Concentrations of a few specific MMPs (e.g., MMP-9) directly correlate to the extent of LV dysfunction post-MI.[60] The assumption has been that an increase in an MMP is always detrimental and that MMPs should be inhibited, but this has not always been the case as we have recently seen for MMP-12 inhibition.[61] Inhibiting MMP-12 beginning at 3 hours post-MI exacerbates LV dilation and dysfunction, suggesting beneficial components of MMP-12 activity.[61] The MMP inducer, EMMPRIN, increases in the LV of acute MI patients and may play a critical role in LV remodeling post-MI.[62] TIMP-1 deletion, as a mechanism to increase MMP activity, aggravated LV remodeling after MI, presumably through stimulating ECM turnover.[63]
4. MMP proteolytic products regulate cardiac remodeling- MMP cleavage products should directly serve as MMP substitutes in regulating particular aspects of the post-MI LV remodeling phenotype, such that adding back substrate in an MMP null background should recapitulate the MMP wild type phenotype or at least a component of the phenotype.[60] MMP-cleavage products as biomarkers in human patients may provide increased diagnostic capabilities for the early detection of disease. [53] Post-MI, ECM undergoes proteolysis directed by MMPs that leads to the generation of ECM peptide fragments called matricryptins or matrikines.[64] Matricryptins are substrate fragments produced from the cleavage of such ECM proteins as collagens (I, IV, XVIII, and XV), connective tissue glycoproteins (fibronectin, thrombospondin-1, laminin, and secreted protein acidic and rich in cysteine (SPARC)), and elastin. [65] Matricryptins serve as bioactive signaling molecules to regulate the post-MI inflammatory and scar formation responses.[64]

## CONCLUSION

Matrix Metalloproteinases are an important group of enzymes which play a role in degrading the extracellular matrix. These enzymes have a three-domain structure which include the pro-domain, the catalytic domain and the haemopexin domain. They are secreted as inactive zymogens that are activated by removing the pro-domain. MMP family can be divided into six groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other non-classified MMPs. Matrixins play a major role in myocardial infarction and function in the post-MI left ventricular remodeling. This remodeling has three main phases and the MMPs are secreted in the inflammatory phase. There are four main cardiac metalloproteinases actions which include: the increase in MMP post MI, stimulation of in vitro cell signaling by MMPs, alteration in LV modeling with modulation of an MMP and the regulation of cardiac remodeling by MMP proteolytic products.

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