Matrix metalloproteinases and myocardial infarction

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Acute myocardial infarction (AMI) is currently one of the most important health problems in many countries around the world. Following AMI, many cytokines and proteolytic enzymes are released. Among these, matrix metalloproteinases (MMPs) are important proteolytic enzymes that lead to degradation of the extracellular matrix and to changes in cardiomyocytes in both infarcted and noninfarcted myocardium. This process is known as cardiac remodelling. It has been demonstrated that more than one type of MMP is present in the circulation after cardiomyocyte injury. A number of studies have demonstrated the correlations between these MMP levels and the severity of a coronary lesion, the progression of left ventricular dimension and the survival rate following AMI in both animal and human studies. MMPs have also been proposed as a possible novel prognostic indicator for myocardial infarction patients. Although the use of MMP inhibitors to improve cardiac outcome in AMI patients has been investigated, discrepancies in the results from those studies indicate that further research is still needed to warrant their beneficial effects. In the present review article, the roles of MMPs as prognostic indicators, as well as the factors influencing MMP expression, are discussed. Current findings on the role of MMP inhibitors in cardiac remodelling and the prognosis after AMI in both animal models and clinical studies are also examined.

Key Words: *Metalloproteinases; Myocardial infarction; Remodelling*

Les métalloprotéinases matricielles et l'infarctus du myocarde

L'infarctus aigu du myocarde (IAM) est l'un des principaux problèmes de santé dans le monde, aujourd'hui. Après un IAM, il y a libération de nombreuses cytokines et enzymes protéolytiques. Les métalloprotéinases matricielles (MPM), enzymes protéolytiques importantes, entraînent la dégradation de la matrice extracellulaire et une modification des cardiomyocytes, et ce, tant dans le myocarde infarci que dans le myocarde non infarci. Le processus s'appelle « remodelage cardiaque ». Il a été démontré que plus d'un type de MPM se trouve dans la circulation après une lésion des cardiomyocytes. Des corrélations ont été établies entre le taux de MPM et la gravité des lésions coronariennes, l'évolution de la grosseur du ventricule gauche et le taux de survie après un IAM dans des études expérimentales sur animal et dans des recherches chez les humains. Des chercheurs ont aussi suggéré de faire des MPM un nouvel indicateur de pronostic chez les patients ayant subi un infarctus aigu du myocarde. Même si des études ont été menées sur l'utilisation des inhibiteurs des MPM dans le but d'améliorer l'état du cœur après un IAM, des résultats divergents indiquent la nécessité de poursuivre les recherches sur le sujet afin de confirmer leurs bienfaits. Il sera question, dans le présent exposé de synthèse, du rôle des MPM comme indicateur de pronostic et des facteurs qui influent sur l'expression des MPM. Nous examinerons également les résultats actuels sur le rôle des inhibiteurs des MPM dans le remodelage cardiaque et sur le pronostic après un IAM dans des modèles animaux et dans des études cliniques.

Acute myocardial infarction (AMI) is one of the most important health problems in many nations around the world. It may be found in many age groups, but is predominant among elderly people (1). The incidence of AMI has been increasing, possibly due to the changes in lifestyle and dietary intake that lead to an increase in coronary risk factors for cardiovascular disease.

AMI has devastating consequences in the early phase, such as cardiac rupture, and in the chronic phase, such as chronic heart failure, for which the risk is mainly determined by infarct size (2). Larger infarct size induces gross morphological, histological and molecular changes of the infarcted and noninfarcted regions. These changes are known as the cardiac remodelling process. The degree of cardiac remodelling is closely related to the incidence of cardiac arrhythmias, heart failure and mortality (3). Cardiac remodelling involves changes in cardiac myocytes and in the extracellular matrix (ECM). The ECM contains a wide array of structural proteins, such as fibrillar collagen, proteoglycans and glycosaminoglycans, and serves as a reservoir for biologically active molecules. Because myocardial collagens maintain the structural integrity of adjoining myocytes and provide the means by which myocyte shortening is translated into cardiac pump function, changes in the ECM result in a loss of normal structural and functional myocardium.

Matrix metalloproteinase (MMP) is a proteolytic enzyme that has been identified in the myocardium, and is likely to contribute to ECM changes and myocardial remodelling. In the past few decades, growing evidence from basic and clinical studies have demonstrated the important role of MMPs in the progression of left ventricular dimension, remodelling and mortality following AMI. In the present article, MMP expression after AMI and its role as a possible prognostic marker are reviewed. Currently available data regarding the role of MMP inhibitors as a possible novel therapeutic intervention are also discussed.

The MMP family

MMPs are a family of protease enzymes composed of more than 25 individual members. All MMPs share the following

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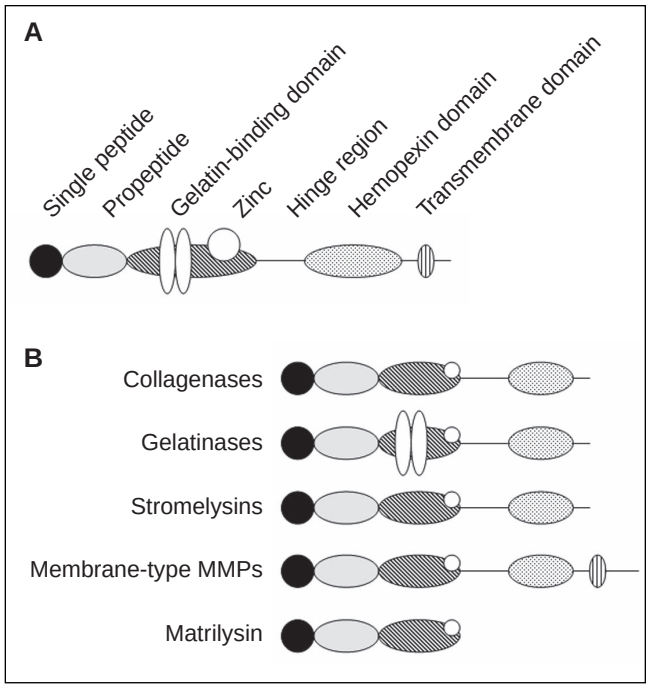

Figure 1) A *Basic domain structure of a matrix metalloproteinase (MMP). MMPs contain at least three homologous protein domains: the signal peptide, which is a domain that targets the enzyme for secretion; the propeptide domain, which is removed when the enzyme becomes activated; and the catalytic domain, which contains the zinc-binding region and is responsible for the proteolytic activity of the enzyme.* **B** *Structural differences between various classes of MMPs. In gelatinases, the catalytic domain contains the gelatin-binding domain, which is homologous with the collagen-binding domain of fibronectin. The hemopexin domain has been shown to play a functional role in substrate binding and interactions with tissue inhibitors of metalloproteinases. Membrane-type MMPs contain a transmembrane domain at the C-terminal end. Modified from reference 4 with permission*

TABLE 1
Matrix metalloproteinases (MMPs) and their substrates

Enzyme	MMP classification	Substrate
Gelatinases		
Gelatinase A	MMP-2	Gelatin, collagens I, IV, V, VII and X, fibronectin, laminins, aggrecan, tenescin-C, vitronectin
Gelatinase B	MMP-9	Gelatin, collagens IV, V and XIV, aggrecan, elastin, entactin, vitronectin
Collagenases		
Interstitial collagenase	MMP-1	Collagens I, II, III, VII and X, gelatin, entactin, aggrecan
Neutrophil collagenase	MMP-8	Collagens I, II and III, aggrecan
Collagenase III	MMP-13	Collagens I, II, III, gelatin, fibronectin, laminins, tenascin
Collagenase IV	MMP-18	Not known
Stromelysins		
Stromelysin 1	MMP-3	Gelatin, fibronectin, laminins, collagens III, IV, IX and X, tenascin-C, vitronectin
Stromelysin 2	MMP-10	Collagen IV, fibronectin, aggrecan
Stromelysin 3	MMP-11	Fibronectin, gelatin, laminins, collagen IV, aggrecan
MT-MMPs		
MT1-MMP	MMP-14	Collagens I, II and III, fibronectin, laminins, vitronectin, proteoglycans, activated pro-MMP-2 and pro-MMP-13
MT2-MMP	MMP-15	Activated pro-MMP-2
MT3-MMP	MMP-16	Not known
MT4-MMP	MMP-17	Activated pro-MMP-2
MT5-MMP	MMP-24	–
MT6-MMP	MMP-25	–
Other		
Matrilysin	MMP-7	Gelatin, fibronectin, laminins, collagen IV, tenascin-C, elastin, vitronectin, aggrecan
Metalloelastase	MMP-12	Elastin
Enamelysin	MMP-20	Aggrecan
	MMP-23	–
Endometase	MMP-26	–
Unnamed	MMP-19	Not known

MT Membrane-type. Modified from reference 4 with permission

functional features (4): they degrade the ECM component; almost all of them are secreted in a latent proform and need to be activated for their proteolytic activity, except MMP-11, which is released to the ECM as an active enzyme; they contain zinc at their active site; they require calcium for their stability; they function at neutral pH; and they are inhibited by specific tissue inhibitors of metalloproteinases (TIMPs).

The MMP family shares a similar basic domain structure (Figure 1) and can be divided into four groups based on structure and in vitro substrate specificity for various ECM components (Table 1). The first group is known as the collagenases. These include MMP-1 (interstitial collagenase), MMP-8 (neutrophil collagenase) and MMP-13 (collagenase III), and all of them can cleave fibrillar collagens types I, II and III. The second group contains the gelatinases, including MMP-2 and MMP-9, which are known for their ability to degrade gelatins. Gelatinases are also capable of degrading collagen type IV in basement membranes. The third group constitutes the stromelysins (MMP-3, -10 and -11). They are active against a broad spectrum of ECM components, including proteoglycans, laminins, fibronectin, vitronectin and some types of collagens. The last group contains the membrane-type (MT) MMPs, which degrade several ECM components and are also able to activate other MMPs. MT-MMPs are tethered to the cell membrane by one of two ways: either they have transmembrane domains with small cytoplasmic tails or they are anchored to the membrane by glycosylphosphatidylinositol. MT-MMPs are proteolytically diverse and serve several biological functions, including degradation of the local ECM, activation of other MMPs and processing of other biologically active signalling molecules (5).

Recently, more evidence has demonstrated that substrate specificity is not absolute, but gradual. For example, gelatinase, which was formerly assumed to specifically degrade gelatin (denatured collagen), has been found to be able to degrade fibrillar collagen. This finding suggests that gelatinase is an important enzyme in AMI, because it can initiate and continue the degradation of the fibrillar collagen (6). All cell types in the

myocardium, either in a basal condition (myocytes, fibroblasts and endothelial cells) or in response to inflammation (macrophages and neutrophils), can normally express one or more types of MMPs (7).

In addition to the action of MMPs on the ECM, MMPs also have various effects on cardiac myocytes and endothelial cells. It has been shown that MMP-2 plays a proapoptotic role in beta-adrenergic receptor-stimulated apoptosis in adult rat ventricular myocytes (8,9). In a chronic heart failure model (10), MMP-9 has been shown to play a role in endothelial cell apoptosis and endothelial-myocyte uncoupling. In the present review, the roles of MMPs on the ECM are mainly discussed.

Regulation of MMP activity

MMP activity can be regulated at three levels, including transcription, activation of the proenzyme and endogenous inhibition. The expression of MMPs varies among different physiological and pathological states. The level of expression for most MMPs is generally low in normal adults. Proinflammatory cytokines such as interleukin (IL)-1 and -6, transforming growth factor-beta (TGF-β) and tumour necrosis factor-alpha, as well as growth factors such as epidermal growth factor and platelet-derived growth factor, can stimulate MMP synthesis (4). Corticosteroids, heparin and IL-4 can inhibit MMP gene expression (4). The response to these factors depends on the MMP and the cell type. For example, TGF-β stimulates MMP-2 and MMP-9, but inhibits MMP-1 and MMP-3 synthesis (11). In addition, the synthesis of MMPs can be stimulated by a cell surface protein termed the ECM metalloproteinase inducer (12).

Almost all MMPs are secreted as proenzymes, and their enzyme activities are inhibited at active sites by bonding between the propeptide and the active site (zinc). Proteolytic cleavage at the propeptide domain dissociates this bond and exposes the active site (7). Several proteinases are involved in proteolytic cleavage activation, including plasmin, trypsin, chymase, elastase and kallikrein. Among these proteinases, plasmin is thought to be the most potent physiological activator (4). MMP-11 and MT-MMP are different from the other MMPs in activation. MMP-11 is cleaved intracellularly and secreted as an active enzyme. MT-MMPs are also activated intracellularly, and their active forms can subsequently activate other MMPs (13).

MMP activity is inhibited specifically in the tissue by TIMPs. TIMPs are a family of enzymes that inhibit the activity of MMPs, and they consist of four structurally related members: TIMP-1, -2, -3 and -4 (4). All TIMPs inhibit all MMPs with different specificities. TIMPs interact with the zinc binding site of the catalytic domain of active MMPs and prevent substrate access. They can also bind the latent MMPs at the amino terminus to prevent autoactivation (14) and have some degree of specificity for MMP inhibition. TIMP-1 potently inhibits the activity of most MMPs, with the exception of MMP-2 and MT1-MMP. TIMP-2 is a potent inhibitor of most MMPs except MMP-9. In addition, TIMP-2 can form a complex with MT1-MMP at the cell membrane, which possibly plays a regulatory role in the proteolytic activation of MMP-2. An insoluble ECM-bound TIMP-3 has been shown to bind MMP-1, -2, -3, -9 and -13. TIMP-4 inhibits MMP-1, -3, -7 and -9, and shows a high level of expression in adult human cardiac tissue. Despite the existence of some TIMPs in plasma, the majority of MMPs in plasma are nonspecifically inhibited by $alpha_2$ macroglobulin (15).

Myocardial infarction and MMPs

Following AMI, myocytes and the interstitium are changed immediately. With a light microscope, it can be seen that severe prolonged ischemia can cause myocyte vacuolization, often termed myocytolysis (16). Myocytolysis is characterized by cell swelling, lysis of myofibrils and nuclei, absence of neutrophilic response, and healing by lysis and phagocytosis of necrotic myocytes, ultimately leading to scar formation (16). With an electron microscope, it can be seen that infarcted cardiac myocytes are reduced in size and the number of glycogen granules. They also have intracellular edema, cell swelling, and distortion of the transverse tubular system, sarcoplasmic reticulum and mitochondria (17). The swollen mitochondria obtained from ischemic myocardium contain deposits of calcium phosphate and amorphous matrix densities, which represents the irreversible phase of myocardial infarction (MI) (16). Regarding the interstitial tissue, ventricular interstitial connective tissue is normally rich in type I and type III fibrillar collagen (16). The nature of collagen in the ECM is determined by the balance between MMPs and TIMPs. The imbalance between MMPs and TIMPs is the major factor responsible for cardiomyocyte and interstitial changes following AMI in the infarcted and remote areas (18-20).

The activities of MMPs and TIMPs have been comprehensively evaluated in clinical and experimental studies. Several species of animals were studied at different times and in various enzymes. Herzog et al (21) were the first to demonstrate the early increasing activity of MMP-1 and MMP-2 1 h after coronary ligation in both the infarcted and noninfarcted zones. MMP-9 was increased in the infarcted zone 2 h after MI. Cleutjens et al (22) demonstrated a rise in MMP-1 that began on day 2 after AMI was induced in a rat heart and peaked on day 7, before declining thereafter at the infarcted zone. The changes in MMP-2 and MMP-9 were seen in a similar way. The investigators also demonstrated an increase in TIMP mRNA in the infarcted zone 6 h after AMI, which reached a maximum on day 2 before slowly declining. No changes in MMP activity in the remote area were seen. MMP activity was measured by zymography in that study (22). Using near-infrared fluorescent imaging, Chen et al (23) demonstrated that MMP-1 and MMP-9 levels in mice were increased in the infarcted zone two to four days after AMI was induced and increased afterward. MMP-9 was also increased in the remote area on day 4 after AMI, with a lower level than in the infarcted zone. MMP-2 was increased at one week after MI, and reached a maximum at two and three weeks in the infarcted zone; it also presented in the remote area at a low but detectable level (23). The study also demonstrated that MMP-9, which increased in the myocardium, was leukocyte-derived. From a large animal study (24), AMI was induced in sheep, and the tissue levels of MMPs and TIMPs were studied at eight weeks. Wilson et al (24) found that the region- and type-specific changes in MMPs occurred after MI. For example, levels of MMP-1 and MMP-9 were unchanged in the remote area, significantly decreased in the transitional zone and were undetectable in the infarcted region, while MMP-13, MMP-8 and MT1-MMP significantly increased in the transitional and infarcted regions compared with the control region. TIMP abundance decreased significantly in the transition region after

MI and fell to undetectable levels within the MI region (24). The study also demonstrated that increased MT1-MMP levels and decreased TIMP-4 levels correlated to the extent of regional left ventricular remodelling (24).

In clinical studies of AMI patients, there were differences in patient characteristics, interventions, as well as timing and methods of MMP measurement, which could be the reason for the discrepancies in findings. In AMI patients on medical therapy (25), using a sandwich enzyme immunoassay, which could not distinguish between the active and inactive MMP proenzymes, patient serum MMP-2 levels on day 0 were increased twofold and sustained until day 7. MMP-9 had two different serial changes. In one-half of AMI patients, significant MMP-9 elevations (twofold increase versus the control group) were seen on day 0, and the levels remained higher than in control subjects until day 3 before gradually decreasing. In the other one-half of patients, MMP-9 levels were similar to those in the control group on day 0 and were then transiently increased, with a peak on day 3 before gradually decreasing (25). There are no provided data of any clinical characteristic differences between the two groups of temporal change patterns. In another study (26) of acute ST-segment elevation MI (STEMI) patients in which the majority received thrombolytic therapy, when using the same technique (sandwich enzyme immunoassay), plasma MMP-9 levels peaked on days 1 and 4, and decreased on day 2 (26).

In patients with AMI who underwent successful reperfusion therapy with angioplasty, MMP-1 was below the control level for the initial four days, increased thereafter to reach peak concentration around day 14 and then returned to the control range (27). Serum TIMP-1 was below the control level on admission, gradually increased and reached a peak around day 14 (27). In patients with suspected acute coronary syndrome who underwent cardiac catheterization, MMP levels were measured and compared between patients with and without confirmed AMI. MMP-1 levels increased during the hospital stay in patients with confirmed MI (28). MMP-2 levels in AMI patients were found to be higher at baseline and throughout the monitoring period than in patients confirmed to not have had MI. MMP-9 levels in AMI patients were lower in those who were confirmed to not have MI throughout the period. Recently, using zymography to measure MMP activity, Wagner et al (29) demonstrated that in acute STEMI patients within 24 h, plasma MMP-9 levels at the time of percutaneous coronary intervention were higher than in the control group, while MMP-2 levels were not different (29).

MMP levels may be increased by cardiac interventions such as stent implantation or balloon angiography (30). The increase in MMP level is greater after stent implantation than after other cardiac interventions (30). MMP-9 and MMP-2 levels were found to rise after stent implantation and balloon angiography (30). Subjects undergoing percutaneous revascularization had higher MMP-9 levels following revascularization than those who underwent angiography without angioplasty (28). MMP-1 levels were increased 24 h after coronary angioplasty (28). After cardiac intervention, transient increases in TIMP-1 and -2 were also observed. However, the levels were no different between balloon angiography and stent implantation (30).

Factors influencing MMP expression

It has been proposed that there may be other factors controlling the expression of MMPs and TIMPs. Creemers et al (31) demonstrated that the plasminogen system plays an important role in cardiac wound healing after MI in mice. Plasminogen-deficient mice were shown to have depressed MMP-2 and MMP-9 activity. Furthermore, necrotic cardiomyocytes were not removed, and the formation of granulation and fibrous tissue did not occur in these mice (31,32). Elevated plasma brain natriuretic peptide levels have been shown to cause an increase in MMP-9 activity (33). At this time, few data are available regarding the factors that control MMPs.

Recently, several investigators have identified MMP genes that may relate to the development of coronary artery disease and MI. A report (34) demonstrated that the MMP-3 5A allele is a marker for determining susceptibility to MI in Chinese people. However, a recent study (35) did not find a correlation between 5A/6A polymorphisms in the MMP-3 gene and the risk of coronary heart disease and AMI. In that study, serum MMP-3 levels were not different between genotypes. Pollanen et al (36) reported that there was a significant interaction between MMP-3 and MMP-9 genotypes in an area of complicated lesions (ie, a plaque area with ulceration or thrombosis). They found that men with high promoter activity genotypes of both loci had, on average, an area of complicated lesions more than two times larger than men who had low promoter activity genotypes. Further investigations are needed to identify the definite factor(s) influencing MMP expression.

MMPs as a prognostic indicator

MMPs play a role in coronary artery disease in the aspects of both atherosclerotic plaque and myocardium after MI. Therefore, the role of MMPs as a prognostic indicator can be through the factor that provokes acute coronary events from vulnerable plaque and that which is involved in cardiac remodelling.

Regarding the role in atherosclerotic plaque, previous studies (37,38) have demonstrated that the plasma MMP-9 level in patients with coronary artery disease correlated to the severity of coronary atherosclerotic plaques and the presence of plaque rupture in the culprit lesion. The prognostic role of MMP-9 was also demonstrated by Blankenberg et al (39), who demonstrated that the MMP-9 level could be used as a predictor for cardiovascular mortality in patients with coronary artery disease (24). Additionally, MMP-9 levels correlated with the survival rate in patients after successful cardiopulmonary resuscitation (40). In a cross-sectional study, Renko et al (41) reported similar findings, in that the MMP-9 level was an independent predictor of recurrent MI in patients with a history of AMI.

The expression of MMP-1 has been observed at a higher level in ruptured plaques than in the unruptured plaques of patients with AMI or unstable angina (42). MMP-3 level has been proposed as a possible marker of plaque instability in patients with acute coronary syndrome (43). Concerning the role of MMPs as a prognostic indicator for cardiac remodelling, a number of studies (26,40,41) found a relationship between the levels of MMPs and the prognosis of injured myocardium.

MMP-9 and MMP-2 have been studied for their roles in left ventricular remodelling. Squire et al (26) demonstrated that in patients with acute STEMI, the peak serum MMP-9 level correlated with echocardiographic and neurohormonal measurements of left ventricular dysfunction six weeks after AMI. This role was confirmed by two recent studies (29,44). Matsunaga et al (44) showed a positive correlation between gelatinous activity (MMP-9 and MMP-2) after two weeks in AMI

patients with successful coronary angioplasty, as well as changes in left ventricular volume in the next six months. Wagner et al (29) also found that MMP-9 appears to be a robust and very early marker of left ventricular remodelling in patients with AMI treated with primary angioplasty and stenting. MMP-9 appears to better risk-stratify patients with MI than does pro-brain natriuretic peptide, tumour necrosis factor-alpha, high-sensitivity C-reactive protein or creatine kinase. However, inconsistent findings in the correlation of MMP-2 level and left ventricular remodelling were observed between the two studies. Squire et al (26) found a higher left ventricular volume associated with lower plasma MMP-2 levels. The discrepancies in their findings may be due to different patient characteristics and methods of MMP measurement. The former study included patients who received thrombolytic therapy, which can affect the MMP level, whereas the latter study included patients who underwent primary percutaneous coronary intervention. MMP levels were measured in the former study, whereas MMP activity was determined in the latter study.

MMP-1 levels have also been shown to negatively correlate with left ventricular ejection fraction after AMI with successful reperfusion therapy (27), as well as with the risk of developing cardiac rupture (45). In addition to MMP activity, patients with AMI have been shown to have serum TIMP-1 levels that negatively correlate with left ventricular volume and positively correlate with left ventricular ejection fraction (27).

In an experimental study (46), a gene knockout model has been investigated to identify the role of MMPs in AMI. Hayashidani et al (46) demonstrated that MMP-2 knockout mice had a better survival rate and lower incidence of cardiac rupture after AMI induced by coronary ligation. In the study, the MMP-9 level was not different between wild type and MMP-2 knockout mice.

Clinical use of MMPs in AMI patients

Although the evidence of elevated MMPs in the setting of AMI, particularly MMP-9, which has been consistently reported, the clinical application of MMP measurement is still somewhat far from reach. Chen et al (23) showed that the MMP-9 level in myocardium after AMI was leukocyte-derived; furthermore, any factors that affect inflammation, such as treatment, intervention and total atherosclerotic burden, may interfere with MMP level and activity. In addition, despite the Wagner et al (29) report indicating that MMP-9 was a strong predictor in late heart failure and adverse left ventricular remodelling in acute STEMI patients undergoing primary angioplasty and stent implantation, there are insufficient data to strongly support the prognostic significance of MMPs over current markers in other settings. Studies with adequate power that take into account the effects of different clinical characteristics and interventions influencing the temporal changes in MMPs with appropriate MMP assays are needed to warrant a clinical application of MMPs in the future.

MMP inhibitors and AMI in animal models

Growing evidence in both animal and human studies that show that MMPs play an important role in cardiac remodelling after AMI has led many investigators to look into the possible benefits of the MMP inhibitor (MMPi) in AMI. It has been demonstrated that MMP-9 knockout mice had a lower incidence of cardiac rupture, lower left ventricular dilation and less collagen organization at the infarcted site (47). MMP-2 knockout mice also had greater survival after AMI and less left ventricular adverse remodelling (18,46). Selective inhibition of TIMP-1 in TIMP-1 knockout mice has also been shown to exacerbate left ventricular remodelling after AMI (48). The role of TIMP-1 activity alteration was confirmed by Jayasankar et al (49), who demonstrated that in left coronary artery ligation-induced MI in rats, TIMP-1 gene transfer inhibited MMP activity, and preserved cardiac function and geometry in ischemic cardiomyopathy.

It has been shown that exogenous MMPi administration also has a beneficial effect on cardiac remodelling after AMI. Rohde et al (50) demonstrated that the administration of MMPi attenuated early left ventricular dilation four days after MI. The effect on late-phase healing was demonstrated by administering exogenous MMPi five days after circumflex artery ligation-induced MI in pigs (19). The study showed that exogenous MMPi attenuated the degree of post-MI left ventricular dilation and expansion of the infarct during the late phase of MI healing. The effects of selective MMPi have also been investigated. In a mouse model of MI (18), the administration of MMP-2 selective inhibitor to wild type mice led to a pronounced improvement in their survival rates, as in mice with targeted deletion of the MMP-2 gene, by preventing cardiac rupture, even though no effect on infarct size was observed. Yarbrough et al (51) also demonstrated that the administration of exogenous MMPi to inhibit MMP-2, -3, -9 and -13, but not MMP-1 and -7, may reduce the progression of left ventricular end-diastolic volume after MI. Their findings suggest that the inhibition of MMP-1 and -7 may not be required to favourably influence left ventricular remodelling.

In addition to the direct inhibition of MMPs, MMP activity can also be inhibited by altering upstream activators. Treatment with an endothelin$_1$ receptor blocker (sitaxsentan) three days after MI prevented an increase in MMP-1, -2 and -9, as well as a decrease in TIMP-1, and prevented left ventricular dilation (52). TGF-β may suppress the release of MMPs in ischemic reperfusion-injured myocardium, and may reduce the extension of myocardial necrosis and ventricular dysfunction (53).

Regarding currently approved drugs, Zhang et al (20) and Camp et al (54) demonstrated that the administration of doxycycline may suppress enhanced mRNA; the protein expression of MMP-2, MMP-8, MMP-13, TIMP-1 and TIMP-2, and the deposition of type I collagen in the noninfarcted myocardium of left coronary artery ligation-induced MI in rats. Doxycycline works by ameliorating endothelial dysfunction via the inhibition of MMP activity. However, no reduction in infarct size has been observed after doxycycline administration. A recent study using losartan demonstrated its ability to reduce MMP-8, MMP-13, TIMP-1 and TIMP-2 levels in rats (55).

The timing of MMP inhibition has been proposed as an important issue, because some MMP activities are essential for the healing process after AMI. MMPi treatment has been shown to result in delayed infarct healing, a larger area of necrosis and reduction of collagen deposition (4,47,51). Yarbrough et al (51) found no difference in the effect of MMPi administration three days before and three days after MI on an infarcted area, and no attenuation of increasing left ventricular volume compared with the nontreatment group. However, there was a difference in the collagen deposition between the pre- and post-MI treatment groups, in which collagen content

was increased in the border zone and decreased in the remote zone of the pre-MI treatment group compared with the post-MI treatment group.

MMPi and MI in clinical study

Since the significant correlation of MMPs and the cardiac remodelling process was identified in MI patients, the role of MMPi has been investigated. In a small, sample-sized clinical study, Brown et al (56) demonstrated that inflammatory markers, such as MMP-9 level, C-reactive protein and IL-6, were reduced after doxycycline administration for six months in patients with coronary artery disease. However, clinical benefits of doxycycline such as a composite end point of sudden death, fatal MI, nonfatal MI or troponin-positive unstable angina, could not be identified in their study. Other medications, such as angiotensin-converting enzyme inhibitors, exogenous MMPi and TIMP-1, have been investigated for their benefits on the attenuation of the left ventricular remodelling process. Papadopoulos et al (57) investigated the benefits of angiotensin-converting enzyme inhibitors in the remodelling process and found that it reduced the collagenolytic activity by reducing MMP-1 levels and decreased the progression of LV dimension after MI. Tziakas et al (58) observed a significant reduction in the levels of MMP-9, TIMP-1 and IL-6 after 30 days of atorvastatin administration. This may be due to the pleiotropic effect of atorvastatin in reducing inflammatory mediators.

CONCLUSIONS

Growing evidence strongly indicates that MMP-1, MMP-2, MMP-3, MMP-9 and TIMP-1 activity correlates to adverse pathophysiology and clinical outcomes in AMI patients. Supportive evidence of their significance from basic and clinical studies has increased; however, much knowledge is still needed to gain understanding of the role of MMPs in AMI. Furthermore, their lack of plasma profiles in various clinical settings makes it difficult to use them as a routine marker in AMI. The role of endogenous and/or exogenous MMPi in the improvement of the remodelling process is also not yet strongly supported by currently available data. Further investigations are needed to warrant the benefit of MMPs as a cardiac marker and MMPi in AMI patients.

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