Matrix Metalloproteinase Inhibition After Myocardial Infarction: A New Approach to Prevent Heart Failure?

Esther E.J.M. Creemers, Jack P.M. Cleutjens, Jos F.M. Smits, Mat J.A.P. Daemen

Abstract—Increased activity of matrix metalloproteinases (MMPs) has been implicated in numerous disease processes, including tumor growth and metastasis, arthritis, and periodontal disease. It is now becoming increasingly clear that extracellular matrix degradation by MMPs is also involved in the pathogenesis of cardiovascular disease, including atherosclerosis, restenosis, dilated cardiomyopathy, and myocardial infarction. Administration of synthetic MMP inhibitors in experimental animal models of these cardiovascular diseases significantly inhibits the progression of, respectively, atherosclerotic lesion formation, neointima formation, left ventricular remodeling, pump dysfunction, and infarct healing. This review focuses on the role of MMPs in cardiovascular disease, in particular myocardial infarction and the subsequent progression to heart failure. MMPs, which are present in the myocardium and capable of degrading all the matrix components of the heart, are the driving force behind myocardial matrix remodeling. The recent finding that acute pharmacological inhibition of MMPs or deficiency in MMP-9 attenuates left ventricular dilatation in the infarcted mouse heart led to the proposal that MMP inhibitors could be used as a potential therapy for patients at risk for the development of heart failure after myocardial infarction. Although these promising results encourage the design of clinical trials with MMP inhibitors, there are still several unresolved issues. This review describes the biology of MMPs and discusses new insights into the role of MMPs in several cardiovascular diseases. Attention will be paid to the central role of the plasminogen system as an important activator of MMPs in the remodeling process after myocardial infarction. Finally, we speculate on the use of MMP inhibitors as potential therapy for heart failure. (Circ Res. 2001; 89:201-210.)

Key Words: myocardial infarction ■ therapy ■ matrix metalloproteinase inhibition
damage (infarct size), to the extent of the inflammatory response (infarct healing), and to ventricular wall stress. Thinning of the infarct zone starts early, against a histopathological background of evolving necrosis, edema, and acute inflammation, a period during which the affected myocardium is especially prone to mechanical deformation. One of the determinants of left ventricular remodeling is damage to and loss of the myocardial extracellular matrix (ECM) during the healing process after MI. Matrix metalloproteinases (MMPs), which are present in the myocardium and capable of degrading all the matrix components of the heart, are the driving force behind myocardial matrix remodeling. The finding that acute pharmacological inhibition of MMPs attenuates LV dilatation in the infarcted mouse heart led to the proposal that MMP inhibitors could be used as a potential therapy for patients at risk for the development of heart failure after MI. In the present review, we describe the biology of MMPs and discuss new insights into the role of MMPs in the course of several cardiovascular diseases.

### Family Members of MMPs

MMPs are a family of zinc-containing endoproteinases that share structural domains but differ in substrate specificity, cellular sources, and inducibility. The list of MMPs has grown rapidly in the past several years, and by now >20 mammalian members have been cloned and identified (Table 1). All MMPs share the following functional features: (1) they degrade ECM components; (2) they are secreted in a latent proform and require activation for proteolytic activity; (3) they contain Zn$^{2+}$ at their active site; (4) they need calcium for stability; (5) they function at neutral pH; and (6) they are inhibited by specific tissue inhibitors of metalloproteinases (TIMPs).

### Table 1. MMPs and Their Substrates

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>MMP Classification</th>
<th>Substrate</th>
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<tbody>
<tr>
<td><strong>Collagenases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial collagenase</td>
<td>MMP-1</td>
<td>Collagens I, II, III, VII, and X, gelatin, entactin, aggrecan</td>
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<tr>
<td>Neutrophil collagenase</td>
<td>MMP-8</td>
<td>Collagens I, II, and III, aggrecan</td>
</tr>
<tr>
<td>Collagenase-3</td>
<td>MMP-13</td>
<td>Collagens I, II, and III, gelatin, fibronectin, laminins, tenascin</td>
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<td>Collagenase-4&lt;sup&gt;79&lt;/sup&gt;</td>
<td>MMP-18</td>
<td>Not known</td>
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<td><strong>Gelatinases</strong></td>
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<td></td>
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<td>Gelatinase A</td>
<td>MMP-2</td>
<td>Gelatin, collagens I, IV, V, VII, and X, fibronectin, laminins, aggrecan, tenascin-C, vitronectin</td>
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<tr>
<td>Gelatinase B</td>
<td>MMP-9</td>
<td>Gelatin, collagens IV, V, and XIV, aggrecan, elastin, entactin, vitronectin</td>
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<td><strong>Stromelysins</strong></td>
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<td></td>
</tr>
<tr>
<td>Stromelysin 1</td>
<td>MMP-3</td>
<td>Gelatin, fibronectin, laminins, collagens III, IV, IX, and X, tenascin-C, vitronectin</td>
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<td>Stromelysin 2</td>
<td>MMP-10</td>
<td>Collagen IV, fibronectin, aggrecan</td>
</tr>
<tr>
<td>Stromelysin 3</td>
<td>MMP-11</td>
<td>Fibronectin, gelatin, laminins, collagen IV, aggrecan</td>
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<td><strong>Membrane-type MMPs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MT1-MMP</td>
<td>MMP-14</td>
<td>Collagens I, II, and III, fibronectin, laminins, vitronectin, proteoglycans; activates proMMP-2 and proMMP-13</td>
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<tr>
<td>MT2-MMP</td>
<td>MMP-15</td>
<td>Activates proMMP-2</td>
</tr>
<tr>
<td>MT3-MMP</td>
<td>MMP-16</td>
<td>Activates proMMP-2</td>
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<td>MT4-MMP</td>
<td>MMP-17</td>
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</tr>
<tr>
<td>MT5-MMP&lt;sup&gt;80&lt;/sup&gt;</td>
<td>MMP-24</td>
<td>Activates proMMP-2</td>
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<tr>
<td>MT6-MMP</td>
<td>MMP-25</td>
<td>...</td>
</tr>
<tr>
<td><strong>Others</strong></td>
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<td></td>
</tr>
<tr>
<td>Matrilysin</td>
<td>MMP-7</td>
<td>Gelatin, fibronectin, laminins, collagen IV, vitronectin, tenascin-C, elastin, aggrecan</td>
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<tr>
<td>Metalloelastase</td>
<td>MMP-12</td>
<td>Elastin</td>
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<td>Aggrecan</td>
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<tr>
<td>Endometase</td>
<td>MMP-26</td>
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mMps are also able to activate other MMPs. Gelatinases, the catalytic domain contains the gelatin-binding domain, which has homology to the collagen-binding domain of fibronectin. The hemopexin domain has been shown to play a functional role in substrate binding and interactions with TIMPs. Finally, membrane-type MMPs contain a transmembrane domain in the C-terminal end.

As demonstrated that gelatinases, formerly thought of as having substrate specificity for denatured collagens (gelatins) only, are able to cleave interstitial collagens as well. Gelatinases play a more important role in the remodeling of collagenous ECM than has previously been thought.

Regulation of MMP Activity
Because MMPs, once activated, are collectively capable of degrading the complete ECM, it is important that the activity of these enzymes is kept under tight control. The activity of MMPs is controlled at the following three levels: transcription, activation of the latent proenzymes, and inhibition by their endogenous inhibitors, the TIMPs.

Regulation of MMP Expression
The expression of most MMPs is generally found at low levels in normal adult tissue but is upregulated during certain physiological and pathological remodeling processes. Induction or stimulation at the transcriptional level is mediated by a variety of inflammatory cytokines, hormones, and growth factors (Table 2), such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and CD40. In addition, a cell-surface protein that induces MMP expression, termed extracellular matrix metalloproteinase inducer (EMMPRIN) has been identified in both normal and diseased human tissue.

Other factors such as corticosteroids, retinoic acid, heparin, and IL-4 have been demonstrated to inhibit MMP gene expression. Not all MMPs react similarly to the same
stimulus. For example, transforming growth factor-β (TGF-β) stimulates MMP-2 and MMP-9 but inhibits MMP-1 and MMP-3 synthesis. In the case of interferon-γ (IFN-γ), the impact on MMP expression is cell-type specific. Whereas IFN-γ increases MMP-1 expression in keratinocytes, it decreases MMP-1 expression in macrophages and fibroblasts.

**Activation Mechanisms of Latent MMPs**

Although transcriptional regulation is essential for MMP production, matrix degradation requires the latent enzymes to be activated by proteolytic cleavage. Three different activation mechanisms have been described: (1) stepwise activation, (2) activation at the cell surface by MT-MMPs, and (3) intracellular activation.

The first step during stepwise activation of MMPs often involves proteinases such as plasmin, trypsin, chymase, elastase, or kallikrein. Of these proteinases, plasmin is thought to be the most potent physiological activator in vivo. Plasmin attacks the proteinase-susceptible region in the propeptide domain of the MMP, which induces conformational changes in the propeptide and renders the activation site to be readily cleaved by a second proteinase, usually another MMP. The generation of plasmin from plasminogen by the action of plasminogen activators occurs largely at the cell surface, where both plasminogen and urokinase activators are bound to plasminogen binding sites and urokinase plasminogen activator receptors (uPARs), respectively.

Cell surface activation of MMPs is considered to be important for pericellular degradation of the ECM during cell migration. In addition to the plasminogen system, other enzymes are capable of activating MMPs at the plasma membrane. In 1994, Sato et al. cloned a membrane-type MMP (MT1-MMP) and identified it as an activator of latent MMP-2 on the plasma membrane. Currently, five MT-MMPs have been cloned, and it has been demonstrated that MT-MMPs also activate other MMPs.

The first evidence that members of the MMP family are activated intracellularly came from Pei and Weiss in 1995. They demonstrated that stromelysin 3 (MMP-11) could be activated by the Golgi-associated subtilisin-like proteinase furin and could be secreted as an active enzyme. Subsequently, Sato et al. reported that MT1-MMP, expressed in Escherichia coli was also activated by furin, indicating that MT-MMPs are also likely to be activated intracellularly. The precise mechanism of intracellular activation and the contribution to extracellular MMP activity has, however, not been clarified.

**Endogenous MMP Inhibitors**

Fully activated MMPs can be inhibited by interaction with naturally occurring, specific inhibitors, the TIMPs. TIMPs are expressed by a variety of cell types and are present in most tissues and body fluids. At present, the TIMP family consists of four structurally related members, TIMP-1, -2, -3 and -4. TIMPs bind noncovalently to active MMPs in a 1:1 molar ratio. Inhibition is accomplished by their ability to interact with the zinc-binding site within the catalytic domain of active MMPs. There is a certain degree of specificity in the activity of different TIMPs toward distinct members of the MMP family. Whereas 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.

**MMPs in Physiology and Disease**

The turnover of ECM is an integral part of development, morphogenesis, and tissue remodeling. In this regard, MMPs are involved in many physiological processes, such as embryonic development, ovulation, bone remodeling, and wound healing. Their enhanced activity has also been implicated in numerous disease processes, including arthritis, tumor cell metastasis, periodontal disease, atherosclerosis, and cardiac diseases.

Studies using synthetic MMP inhibitors have provided more insights into the role of MMPs in the pathogenesis of several diseases. Most MMP inhibitors used at the present time are representatives of one chemical class, the hydroxamates. Inhibition is accomplished by binding of the hydroxamic group to the zinc atom present in MMPs. MMP inhibitors have been successfully applied in several animal models of inflammation and cellular invasion. Administration of broad-range MMP inhibitors (BB-94, AG3340) prevented tumor cell invasion, metastasis, and tumor angiogenesis in rodents. Several MMP inhibitors are currently being evaluated as treatment for patients with advanced cancer. Preliminary clinical reports have described a decrease in tumor marker levels in patient serum as evidence of an antitumor effect. In arthritis, it was recently shown that the
MMP inhibitor Ro32-3555 prevented cartilage breakdown in both rheumatoid arthritis and osteoarthritis in rats. During dermal wound healing in rats, broad-range inhibition of MMP activity by ilomastat (GM6001) resulted in an enhanced wound strength that was associated with a decreased inflammatory response. In thioglycollate-induced peritonitis in the mouse, ilomastat reduced the cellular infiltrate into the peritoneum. MMP inhibitors have also been suggested for therapy of vascular diseases. In the case of abdominal aortic aneurysms, the broad-range MMP inhibitor batimastat limited the expansion of experimental abdominal aortic aneurysms in rats and interfered with the inflammatory response seen in these aneurysms. Other investigators have focused on the role of MMPs and the effect of MMP inhibition during neointima formation. In balloon catheter–injured rat carotid arteries, administration of ilomastat resulted in a 97% decrease in the number of smooth muscle cells that migrated into the neointima, which retarded intima formation. In pigs, it was recently demonstrated that the oral MMP inhibitor marinastat inhibited constrictive arterial remodeling, which is the major determinant of restenosis after balloon angioplasty. Because of the positive outcome of the first clinical trials using synthetic MMP inhibitors in the treatment of corneal ulcers and lung cancer, it is feasible that MMP inhibitors will be used in the future for other clinical indications as well.

MMPs in Cardiac Diseases

In 1975, Montfort and Perez-Tamayo demonstrated that collagenase is present in the normal myocardium. It is located in the interstitium, in the neighborhood of its substrate, fibrillar collagen. It is now known that myocardial MMPs are produced by fibroblast-like cells, inflammatory cells, as well as by cardiomyocytes, that they are predominantly present in their latent form, and that they are increasingly expressed and activated in several pathological conditions of the heart. A number of studies have demonstrated increased expression and activity of MMP-1, -2, -3, and -9 in human, rat, and porcine hearts during the remodeling process after MI. Although the data on the exact time course of postinfarction myocardial MMP activity is diverse, it becomes more and more clear that MMP activation starts early (<1 day after MI). Early upregulation of MMP activity after infarction strongly suggests an involvement of MMPs in the repair process of the heart. In this regard, MMPs might be involved in several aspects of infarct healing, including early ECM degradation, cell migration (inflammatory cells, fibroblasts), angiogenesis, remodeling of newly synthesized connective tissue, and the regulation of growth factor activities.

The function of MMPs during the healing and remodeling process of the left ventricle after MI is being clarified in studies using broad-range MMP inhibitors and genetically modified mice. Rohde et al first demonstrated that in vivo MMP inhibition attenuates early left ventricular (LV) dilatation 4 days after experimental MI in mice. We have also studied the effects of a broad-range MMP inhibitor on LV remodeling and infarct healing 1 and 2 weeks after MI in mice. In that study, infarcted mice allocated ilomastat treatment showed a significant decrease in LV dilatation after MI as measured by echocardiography. MMP inhibitor treatment resulted in a delay in infarct healing, clearly evidenced by larger necrotic areas (56%), thicker infarcted walls (32%), lower cell densities (37%), and a reduction in the deposition of collagen (68%) in the infarct. These effects of MMP inhibition on LV remodeling and healing were most prominent 7 days after MI. Attenuated LV dilatation after MMP inhibitor treatment might depend on preservation of the ECM in the infarct zone, early after MI. Delayed wound healing by MMP inhibition has also been demonstrated in vascular and dermal wounds, where MMP activity facilitated the migration of inflammatory cells and smooth muscle cells into the wound. The negative effects of MMP inhibition on collagen deposition may seem paradoxical, because it may be expected that MMP inhibition prevents collagen degradation and thus promotes collagen accumulation. An inhibitory effect of MMP inhibition on collagen deposition is however not new, because ilomastat treatment has comparable effects during neo-intima formation. There are several possible explanations for these effects of MMP inhibition. First, the delay in healing reduced the migration of myofibroblast-like cells into the infarct. Because myofibroblasts are the main cell type responsible for collagen synthesis, a lower number of myofibroblasts may result in a reduction of collagen deposition. Second, MMPs may interfere in other pathways than ECM degradation, which are active during the repair process of the heart. In this view, MMPs regulate the activity of certain growth factors, such as TNF-α, TGF-β, and IL-1β. Decreased activity of TGF-β might reduce the synthesis of new collagen fibers.

The particular importance of MMP-9 activity during infarct healing and LV remodeling has recently been demonstrated in two studies. In the first study, Heymans et al reported that MMP-9 deficiency in mice retarded the wound healing process after MI, which was demonstrated by a reduced leukocyte influx into the infarct and by larger residual necrotic areas. In addition, that study demonstrated that lack of proteolytic activity of MMP-9 almost completely protected against infarct rupture, an acute and usually fatal event after MI. The significance of MMP-9 activity in early infarct healing and rupture was emphasized by the observation that MMP-9 was predominantly found in leukocytes and macrophages and that its activity peaked around day 2, the period in which most of the ruptures occur. In the second study, Ducharme et al demonstrated that targeted deletion of MMP-9 also attenuated LV cavity enlargement until at least 15 days after experimental MI in mice. Limited LV dilatation was accompanied with a reduced inflammatory response and a decrease in collagen deposition in the infarct of MMP-9–deficient mice.

The most striking observation in the aforementioned animal studies is the reduction in LV dilatation after MI that can be achieved with MMP inhibitor treatment. In humans, it is known that extensive LV dilatation after infarction increases the risk of complications such as the development of congestive heart failure, aneurysm formation, and cardiac rupture. Together, these positive effects of MMP inhibition on LV dilatation in animal models led to the proposal to use MMP inhibitors as a potential therapy for patients at risk for the development of heart failure after MI.
In addition to MI, dilated cardiomyopathy is associated with an upregulation of MMP activity.53–57 Spinale et al58 reported that MMP inhibition limited LV dilatation and resulted in a reduction in wall stress during the development of congestive heart failure in an experimental model of rapid cardiac pacing in pigs. Finally, the consequence of increased MMP activity on cardiac performance has been studied in transgenic mice expressing myocardial MMP-1, an interstitial collagenase that is normally absent in the mouse genome. At an age of 6 months, these mice exhibited LV hypertrophy and hypercontractility, whereas at an age of 12 months these mice displayed a loss of cardiac interstitial collagen, coincident with a marked deterioration of systolic and diastolic function.3 In conclusion, the studies described above have demonstrated a causal relationship between proteolytic activity, disruption of the myocardial ECM, architectural remodeling of the heart, and cardiac performance.

Interestingly, in the promoters of MMP-1, -3, -9, and -12, polymorphisms have been identified, which appear to influence MMP gene expression.59 Polymorphisms in MMP-3, -9, and -12 have already been associated with susceptibility to cardiovascular diseases such as coronary artery disease and abdominal aortic aneurysms.59,60 These observations also indicate that variations in the levels of MMP transcription in patients suffering from MI might contribute to differences in infarct healing, LV remodeling, and the transition to end-stage heart failure or cardiac rupture. Further research is needed to identify a possible correlation between these events after MI and MMP polymorphisms. The observation that levels of MMPs and TIMPs are altered in the serum of patients after MI has raised the possibility that MMP and TIMP levels could predict the clinical outcome.61,62 Correlations of serum TIMP-1 levels with LV end-systolic volumes and with LV ejection fractions have already been found.61

**TIMPs and Cardiac Diseases**

Studies of cardiac tissue of patients with ischemic cardiomyopathy demonstrated in addition to an increase in MMP activity a decrease in TIMP-1, -3, and -4 expression while TIMP-2 expression was unchanged.55,56,63 The functional role of TIMP-1 in the control of LV geometry and cardiac function was recently studied in TIMP-1–deficient mice. Echocardiography in these mice demonstrated an 18% increase in LV end-diastolic volume and a 38% increase in cardiac mass at 4 months of age. Reduced myocardial collagen content probably accounted for the increased LV dilatation. These results suggest that constitutive TIMP-1 expression contributes to the maintenance of normal LV myocardial structure.64

The function of TIMP-1 has also been studied in the setting of MI. Adenoviral human TIMP-1 overexpression in the mouse after MI resulted in diminished leukocyte influx, less neovascularization of the infarct, larger residual necrotic areas, and decreased collagen content in the infarct. These parameters indicate that infarct healing is delayed after TIMP-1 overexpression.51 In that study, ∼30% of the infarcted control mice suffered fatal cardiac rupture of the LV wall. However, complete prevention of cardiac rupture was achieved after TIMP-1 overexpression. Together, these results indicate that TIMP-1 is an important endogenous inhibitor of myocardial MMP activity.

**Plasminogen System as a Regulatory System for MMP Activity in the Heart**

Plasmin, one of the serine proteases, is the active enzyme of the plasminogen system and degrades a variety of ECM components. A relevant feature of plasmin is the proteolytic amplification that can be achieved by activating several MMPs.65 The generation of plasmin is primarily controlled by the balance between the plasminogen activators (tissue-type plasminogen activator [tPA] and urokinase plasminogen activator [uPA]) and their physiological inhibitors, the plasminogen activator inhibitors (PAIs). Two recent studies identified the plasminogen system as an important regulatory system in the onset of cardiac wound healing. In the first study, we demonstrated that infarct healing was virtually abolished in plasminogen-deficient mice. In the absence of plasminogen, inflammatory cells did not migrate into the infarcted myocardium. Necrotic cardiomyocytes were not removed, and the formation of granulation tissue and scar tissue did not occur, until at least 5 weeks after MI. In these scarless infarcted hearts, LV dilatation was not affected compared with wild-type mice. In addition, gelatinolytic activity of MMP-2 and MMP-9 was depressed in the Plg−/− mice. In the absence of plasminogen, MMPs are not activated, and PAIs remain unoccupied.66 In the second study, Heymans et al51 demonstrated that uPA deficiency and adenoviral PAI-1 overexpression, but not tPA or uPAR deficiency, resulted in impaired cardiac healing. In addition, uPA deficiency or adenoviral PAI-1 overexpression protected against cardiac rupture. Three distinct observations strongly suggest that the effects of plasminogen and uPA deficiency are (partly) mediated by reduced activation of MMPs. First, uPA was coexpressed with MMP-9 in infiltrating leukocytes.51 Second, MMP activity was reduced in both uPA−/− and Plg−/− infarcts. And third, MMP inhibition has comparable, although
less pronounced, effects on infarct healing and cardiac rupture as uPA and plasminogen deficiency. Together, these two studies have identified the plasminogen system as a new and important regulatory system in cardiac wound healing (Figure 2). The mechanisms through which components of the plasminogen system mediate infarct healing are based on the proteolytic activity of plasmin. Besides degrading ECM components and activating MMPs, which are essential conditions for cell migration, the plasminogen system may act through other mechanisms. In this regard, plasmin can activate or liberate growth factors from the ECM. For example, TGF-β1, a potent inhibitor of cell proliferation and a mediator of collagen deposition, is activated by plasmin. Reduced activation of latent TGF-β1 was indeed found in 4-day-old infarcts of uPA-deficient mice, indicating that the downstream pathway of the plasminogen system in infarct healing also includes the activation of TGF-β1.

These findings with respect to components of the plasminogen system may indicate that increased expression of plasminogen or uPA may predispose to cardiac rupture, whereas increased levels of PAI-1 may be protective. On the other hand, as the principal inhibitor of fibrinolysis, it has been reported that high PAI-1 levels may accelerate the atherosclerotic process by allowing fibrin deposition and thrombosis within developing lesions. So far, epidemiological studies have related increased levels of PAI-1, due to genetic or metabolic determinants, to atherothrombosis. The influence of increased PAI-1 levels on the risk of MI is still debated. Finally, it has been reported that other serine proteases (i.e., serine elastase, trypsin, and cathepsin G) are able to activate MMPs and destroy the inhibitory activity of TIMPs. The role of serine elastase has been investigated in relation to myocardial ischemia/reperfusion injury, and it was demonstrated that inhibitors of these enzymes are protective against MI. This was accomplished by inhibition of neutrophil accumulation into the ischemic reperfused myocardium and by inactivating cytotoxic metabolites (proteases and superoxide radical) released from neutrophils.

MMP Inhibitors as a New Therapy for Heart Failure

The positive effects of MMP inhibition on LV dilatation in animal models led to the proposal to use MMP inhibitors as a potential therapy for patients at risk for the development of heart failure after MI. Although the promising results in animal studies encourage the design of clinical trials with MMP inhibitors, several issues have to be studied more extensively. First, the precise effect of MMP inhibitor treatment on cardiac function is not completely known. Second, the timing of MMP inhibitor administration after infarction has to be resolved, and third, the choice between narrow-versus broad-range MMP inhibitors must be made.

With respect to evaluation of cardiac function after MMP inhibitor treatment, Rohde et al. used short-axis echocardiography to study cardiac function in infarcted mice. That study demonstrated that MMP inhibition resulted in significant improvement in fractional shortening and a somewhat smaller increase in end-systolic and end-diastolic dimensions in the infarcted mouse heart. Because the endpoint of the latter study was only 4 days after MI, further research is needed to determine the long-term effects of MMP inhibitors on cardiac function. Recent advances in conductance technology allow the measurement of LV pressure-volume loops in the mouse heart. This technique, which can be used in closed-thorax preparations, will probably be critical for the assessment of cardiac function in MMP inhibitor–treated or MMP knockout mice. Although the mouse infarct model is an excellent model to initially study the effects of pharmacological agents on cardiac function and LV remodeling, it will be necessary to evaluate the effects in other species before extrapolation to humans.

With respect to the timing of the MMP inhibitor administration, it should be noted that some of the animal studies described above started drug delivery before induction of the infarct. In patients, in whom MMP inhibitors are to be given after infarction by definition, the positive effect on LV dilatation might be smaller, because early infarct expansion might not be prevented.

Selective versus broad-range MMP inhibition is another important, yet unresolved, issue with respect to the possible treatment of heart failure. Broad-range MMP inhibition might be favorable to achieve maximal effects on ECM degradation. However, possible disadvantages of broad-range MMP inhibition include negative side effects such as musculoskeletal toxicity, as seen after treatment with marimastat. With respect to the important role of MMPs in physiological processes, broad-range MMP inhibition might affect normal tissue as well. Selective inhibition of one or a few carefully chosen MMPs might be better in this regard. Inhibition of a single MMP will probably be of little therapeutic value because it is known that heart failure is associated with an elevation of multiple MMPs. The issue of selective versus broad-range MMP inhibition has been addressed in other fields of research as well. In dermal wound healing, selective inhibition of MMPs seems desirable, because nonspecific MMP inhibition would most likely impair reepithelialization, as a result of inhibition of MMP-1. Inhibition of MMP-13 would be more favorable in dermal wound healing, because MMP-13 has been held responsible for the degradation of collagens I and III and may play a role in the pathogenesis of chronic cutaneous wounds. In cancer research, selective inhibition of the gelatinases (MMP-2 and -9) has been demonstrated to prevent tumor growth and invasion. Extrapolated from gene-targeting studies in mice, MMP-9 might be one of the candidates for selective inhibition after MI, because the deficiency in MMP-9 alone reduced LV chamber enlargement after infarction. Furthermore, MMP-9 gene disruption also prevented fatal cardiac rupture to occur. Although the synthesis of selective MMP inhibitors for all individual MMPs is currently a focus for many pharmaceutical companies, there is still a long way to go to meet this goal.

Tetracyclines are frequently as effective as other MMP inhibitors in vivo, and their beneficial influence on ECM degradation can usually be achieved at remarkably low (nanomolar) concentrations. Although the mechanism of MMP inhibition seems to be different using tetracycline compared with broad-range MMP inhibitors, the clinical
effect, ie, decreased ECM degradation might be the same. In combination with their clinical availability, low cost, and well-recognized safety profile, the use of tetracyclines appears to represent an ideal starting point for clinical studies on MMP inhibition after MI. 28

Conclusion
Some of the current therapies after MI retard the development of heart failure. However, none of these therapies is able to prevent the LV expansion process completely. For this reason, additional therapy for these patients is desirable. Animal studies suggest that inhibition of myocardial MMP activity may be a promising therapeutic approach to slow down the time course of the development of heart failure and dysfunction. Further research is needed to evaluate long-term effects of MMP inhibitor treatment after infarction, to resolve the issue of selective versus broad-range MMP inhibition and to evaluate the best time point after infarction to start MMP inhibitor treatment.

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References


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