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Matrix Metalloproteinases in Myocardial Infarction and Heart Failure

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Abstract

Cardiovascular disease (CVD) is the leading cause of death, accounting for 600,000 deaths each year in the U.S. In addition, heart failure accounts for 37% of healthcare spending. Matrix metalloproteinases (MMPs) increase after myocardial infarction (MI) and correlate with left ventricular dysfunction in heart failure patients. MMPs regulate the remodeling process by facilitating extracellular matrix (ECM) turnover and inflammatory signaling. Due to the critical role MMPs play during cardiac remodeling, there is a need to better understand the pathophysiological mechanism of MMPs, including the biological function of the downstream products of MMP proteolysis. Future studies developing new therapeutic targets that inhibit specific MMP actions to limit the development of heart failure post-MI are warranted. This book chapter focuses on the role of MMPs post-MI, the efficiency of MMPs as biomarkers for MI or heart failure, and the future of MMPs and their cleavage products as targets for prevention of post-MI heart failure.

Keywords

myocardial infarction; matrix metalloproteinases; heart failure; inflammation; fibrosis; omics

Introduction

Despite significant advancements in risk prediction, cardiovascular disease (CVD) remains a leading cause of death.¹ Adverse cardiac remodeling that involves excessive extracellular matrix (ECM) turnover contributes to high morbidity and mortality in patients with myocardial infarction (MI).² Elevated matrix metalloproteinase (MMP) levels strongly correlate with left ventricular dysfunction in CVD patients.

MMPs are a family of 25 proteolytic enzymes that regulate ECM turnover and inflammatory signaling. Only about half of the known MMPs have been measured in the post-MI left ventricle (LV), which leaves a significant knowledge gap in the post-MI MMP literature.³ Following MI, MMPs facilitate ECM degradation and recruit inflammatory cells for removal

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of necrotic cardiomyocytes. The upregulation of pro-inflammatory cytokines initially results in robust MMP activation, however, long-term stimulation increases tissue inhibitor of metalloproteinase (TIMP) levels. This ultimately leads to a decrease in the MMP/TIMP ratio and results in ongoing long-term remodeling.^{4, 5}

The fate of the myocardium post-MI depends on the balance between several competing events that occur during the wound healing response to form the ECM scar (Figure 1). Development of heart failure post-MI can be induced by exaggerated cardiac remodeling leading to impaired cardiac physiology. In response to myocyte injury induced by ischemia and infarction, a series of events occur in three distinct, but temporally overlapping, phases of wound healing: inflammation, proliferation, and maturation.⁶ Each phase contributes to the temporal changes in MMP levels in the post-MI infarct. Multiple cell types in the post-MI myocardium express MMPs, including neutrophils, macrophages, endothelial cells, myocytes, and fibroblasts, making MMPs key regulators in the cardiac remodeling progression.^{7–10} This book chapter focuses on the role of MMPs during the post-MI development of heart failure and discusses the future of MMP inhibitors to prevent the development of heart failure.

MMPs as biomarkers for heart failure

MMPs have been widely studied as possible markers to predict the development of CVD, particularly in post-MI remodeling and heart failure. The use of proteomic techniques over the last 10 years has amplified the discover of candidate biomarkers, due to enhanced sample preparation protocols, improvements in database searching, capabilities of mass spectroscopy, and bioinformatics analytic tools. Combined, these improvements have made identification of biomarkers for heart failure post-MI more attainable. This is especially true when it comes to biomarkers associated with cardiac ECM.^{11, 12}

Discovering novel substrates and the biological functions of peptide fragments generated by MMPs is vital to fully comprehend MMP function post-MI. MMPs have a broad number of substrates that contribute to scar formation and wound healing post-MI. Table 1 lists known MMP substrates and their biological function. MMPs also release ECM fragments called matricryptins or matrikines that are key during the development of heart failure post-MI.^{13–17} Multiple studies have suggested matricryptins could be potential therapeutic targets for heart failure patients.^{14, 18, 19} Below, we summarize our currently knowledge on the involvement of MMPs in post-MI remodeling.

MMP-1

Understanding the role of MMP-1 in the post-MI LV has been hindered due to humans only having one isoform of MMP-1 and mice having two: MMP-1a (59% homology with human MMP-1) and MMP-1b (57% homology with human MMP-1).²⁰ MMP-1 is mainly expressed by leukocytes, fibroblasts, and endothelial cells.²¹ In serum of post-MI patients who undergo reperfusion, MMP-1 increases 4 days after admission reaching a peak concentration around day 14. By day 28 MMP-1 levels decrease by 50% compared to day 14.²² In addition, serum MMP-1 levels negatively correlate with the LV end systolic volume index and positively correlate with LV ejection fraction.²²

MMP-1 preferentially degrades collagens I and III; compared to the 25 known MMPs, MMP-1 has the highest affinity for fibrillar collagen. MMP-1 initiates the degradation of collagen fibers within the LV by cleaving collagen into 3/4 and 1/4 fragments. These fragments then become unfolded and degraded by MMP-2, -9, and -3.²³

MMP-2

MMP-2 is expressed by cardiomyocytes, endothelial cells, vascular smooth muscle cells, macrophages, and fibroblasts.^{24–26} Due to its high constitutive activity, MMP-2 is considered a MMP housekeeping gene that helps regulate normal tissue turnover.²⁷ Post-MI, MMP-2 levels increase both in plasma and within the infarct due to stimulation of the cardiomyocyte and cardiac fibroblast.^{28–30} In patients diagnosed with heart failure there is a 4-fold increase in MMP-2 expression compared to controls.³¹ In rats, MMP-2 mRNA and protein levels elevate within 24 hours post-MI and peak around day 14 post-MI.³² Similar to rats, MMP-2 activity in mice rapidly increases within 4 days post-MI, peaks at day 7, and remains elevated until day 14.³³

Matsumura *et al.* demonstrated the MMP-2 generated fragments of laminin inhibited migration of macrophages into the inflammatory region and resulted in delayed wound healing after MI.³⁴ MMP-2, in addition to MMP-3, -7, and -9, processes vitronectin into multiple fragments, however, the biological function of these fragments in the post-MI environment has not been evaluated.³⁵ Recently, Sheng Zhao *et al.* showed periostin increases collagen fibrogenesis in the human failing heart and was associated with elevated MMP-2 levels.³¹ MMP-2 also generates the matricryptin C-1158/59 from collagen.¹⁴ *In vitro* stimulation with the downstream peptide from C-1158/59 increases fibroblast migration rate and angiogenesis to improve wound healing.

There are multiple MMP-2 polymorphisms, of which only 5 have been associated with MI. Elevations in MMP-2 levels due to the -1575 A/G gene polymorphism increase risk for MI by 4-fold in Hispanic males indicating MMP-2 may act as a strong biomarker for MI incidence in this population.³⁶ Similar to the -1575 A/G polymorphism, a MMP-2 single nucleotide polymorphism, -1306 T/C, displayed a 2-fold increase in promoter activity resulting in increased MMP-2 expression and enzymatic activity. In Hispanics, this polymorphism also associates with increased risk for MI and coronary triple-vessel disease.³⁷ In France, the -1306 T/C showed no association with heart failure related deaths.³⁸

A study in African- and Caucasian-Brazilian patients diagnosed with heart failure of any etiology and reduced ejection fraction (<45%) implicates the -1575 A/G, -1059 A/G, and -790 T/G MMP-2 polymorphisms with a 2.5-fold increase in heart failure risk compared to non-diseased controls.³⁹ Interestingly, all three MMP-2 polymorphisms associate with heart failure related deaths only in Caucasians.³⁹ Similarly, the -790 T/G MMP-2 polymorphism, in addition to the -735 C/T polymorphism, also associates with chronic heart failure in patients from the Czech Republic.⁴⁰ How these polymorphisms effect heart failure related deaths is still unclear.

MMP-3

MMP-3 is secreted by cardiac fibroblasts and macrophages.²⁸ In post-MI patients, circulating MMP-3 concentrations increase steadily between admission and discharge and are higher at 3 months compared to 48 hours after MI.⁴¹ MMP-3 levels at 72–96 hours post-MI associate with left ventricular dysfunction, adverse left ventricular remodeling, and prognosis of heart failure.⁴¹ Although MMP-3 correlates with MI severity, MMP-3 mechanisms of action are not clear.

MMP-3 breaks down multiple ECM components, including collagen, fibronectin, laminins, proteoglycans, and vitronectin.⁴² MMP-3 also activates a number of MMPs including MMP-1, -7, and -9. As such, MMP-3 is considered an upstream MMP activator. MMP-3 proteolytic action on proMMP-1 is critical for the generation of fully active MMP-1.⁴³ Secreted protein acidic and rich in cysteine (SPARC) can also be cleaved by MMP-3 generating three biologically active peptides (Z-1, Z-2, and Z-3).⁴⁴ Fragment Z-1 increases angiogenesis and vascular growth, whereas fragments Z-2 and Z-3 inhibit cell proliferation. MMP-3 also generates tenascin-C fragments.⁴⁵ The significance of these fragments in cardiac pathology is not yet clear.

Due to their ability to regulate MMP-3 activity, MMP-3 polymorphisms have been implicated as regulators of MI prevalence and heart failure outcomes.^{46, 47} For example, the -1171 6A allele has lower promoter activity compared to the 5A allele and is found significantly less frequent in MI patients than in control subjects.^{46, 48} This polymorphism impacts on cardiac survival in heart failure patients with ischemic and non-ischemic cardiomyopathy differ. MMP-3 6A allele is an independent predictor of cardiac mortality in patients with non-ischemic heart failure. In contrast, there is no evidence for any effect of the MMP-3 genotype on cardiac events in patients with ischemic cardiomyopathy.⁴⁹

MMP-7

MMP-7 is expressed in endothelial cells, cardiomyocytes, and macrophages.^{9, 50, 51} In animal models of MI, MMP-7 increases three-fold in both remote and infarct regions at 7 days post-MI.⁹ MMP-7 activity is linked to increased risk for major adverse cardiac events, including decreased post-MI survival and increased hospitalization for congestive heart failure.^{9, 52–54} Elevated serum MMP-7 levels is associated with LV structural remodeling in 144 patients with LV hypertrophy.⁵³

MMP-7 has an extensive portfolio of substrates, including collagen IV, connexin-43, fibronectin, laminin, peroxiredoxins, tenascin-C, and tumor necrosis factor- α .^{9, 54–56} MMP-7 can also cleave other MMPs, including MMP-1, MMP-2, and MMP-9, leading to their activation and implicating MMP-7 as both a direct and indirect regulator for LV remodeling.⁵⁷ Of these substrates, MMP-7 has major effects on connexin-43 and serves as a predominant mechanism for post-MI arrhythmias.⁹

MMP-8

MMP-8 is expressed by neutrophils and macrophages.^{58, 59} MMP-8 is a major player during the inflammatory response. Serum levels of MMP-8 is a significant predictor of LV

remodeling, cardiac rupture, and development of heart failure after MI.^{58, 60} MMP-8 increases six-fold within 6 hours post-MI and peaks at 12 hours due to infiltration of neutrophils.^{59, 61} At day 3 post-MI, MMP-8 spikes again most likely due to macrophage expression during the later stages of remodeling.⁶²

MMP-8 coordinates leukocyte trafficking through cleavage of collagen and chemokine binding proteins.^{63–65} MMP-8 processes bioactive molecules, such as LPS-induced CXC chemokine (LIX).⁶⁶ Cleavage of the N-terminus of LIX by MMP-8 enhances neutrophil chemotaxis in response to lipopolysaccharide stimulation. MMP-8 cleavage of interleukin (IL)-8 and CXCL5, the human orthologues of LIX, also increases neutrophil chemotaxis.⁶⁶ How MMP-8 substrates effect the wound healing response post-MI has not been studied.

MMP-9

MMP-9 is secreted by a wide number of cell types, including cardiomyocytes, endothelial cells, neutrophils, macrophages, and fibroblasts.⁶⁷ Circulating MMP-9 increases at day 1 and remains elevated until day 7 post-MI in mice.⁶⁸ Blankenberg and colleagues were the first to implicate MMP-9 as a novel prognostic biomarker for the development of LV dysfunction and late survival in patients with CVD.^{69, 70} MMP-9 correlates with IL-6, C-reactive protein, and fibrinogen concentrations in the plasma indicating MMP-9 can predict cardiovascular outcome independent of an association with inflammatory markers.⁶⁹ Squire et al. demonstrated that increased MMP-9 correlates with larger LV volumes and greater LV dysfunction following MI.⁷¹

MMP-9 regulates tissue remodeling by directly degrading ECM and activating cytokines and chemokines.⁶⁷ Using an ECM-targeted proteomic approach, Zamilpa *et al.* identified multiple *in vivo* MMP-9 substrates in the post-MI setting including fibronectin, a known *in vitro* MMP-9 substrate.⁷² Cleavage of MMP-9 substrates is both detrimental and beneficial for wound healing post-MI. For example, MMP-9 mediated degradation of CD36 post-MI decreases macrophage phagocytosis and prolongs neutrophil inflammation leading to an enlarged LV post-MI.⁷³ In contrast, MMP-9 cleavage of osteopontin generates two biologically active peptides that increased the migration rate of cardiac fibroblasts resulting in enhanced infarct wound healing.⁷⁴ For this reason, targeting substrates downstream of MMP-9 may serve as a feasible alternative for predicting and preventing LV dysfunction post-MI.

There is clinical evidence that MMP genetic polymorphisms can contribute to MMP protein levels and thus influence cardiovascular outcomes.⁷⁵ The MMP-9 –1562 C/T polymorphism associates with increased MI incidence.⁷⁶ Associations vary across ethnic populations. For example, in healthy white subjects MMP-9 genetic polymorphisms did not associate with plasma MMP-9 levels whereas a positive association was discovered in healthy African American subjects.^{77–79}

In respect to heart failure, the MMP-9 –1562 C/T polymorphisms has had conflicting results.^{49, 76} In a study performed in patients in Brazil, this MMP-9 polymorphism did not associate with heart failure susceptibility or heart failure-related survival.⁴⁹ In a separate study completed in France, increases in the T allele of the MMP-9 polymorphism did not

associate with lower ejection fraction or higher end diastolic diameter, but is an independent predictor of cardiac mortality.³⁸ Both studies had similar patient characteristics excluding patients who had an ejection fraction higher than 45%. This suggests the differences observed were most likely due to the differences in genetic ancestry and that the -1562 C/T polymorphism may not be a strong biomarker across multiple populations. Before this conclusion can be made, the alternative explanation that the two studies measured different end points needs to be ruled out.

MMP-12

Historically macrophages have been regarded as the main cell type to express MMP-12 and hence the earlier term macrophage metalloelastase.^{80–82} In recent literature, neutrophils have been identified as an early source of MMP-12 post-MI.⁸¹ MMP-12 is also expressed by endothelial cells, fibroblasts, and vascular smooth muscle cells.^{83, 84} Post-MI, MMP-12 protein levels increase in the infarct at day 1 and remain elevated through day 7 in mice.⁸¹ MMP-12 inhibition in mice led to impaired cardiac function post-MI compared to saline controls, revealing a protective role for MMP-12 in the post-MI setting.⁸¹

MMP-12 has broad substrate specificity, including type IV collagen fibronectin, heparan sulfate, laminin, and vitronectin.^{85–87} Cleavage of these ECM proteins play a vital role during cardiac remodeling. For example, MMP-12 cleavage of type IV collagen disrupts the basement membrane and enables fibroblast and macrophages to access to the injured site.⁸⁷ MMP-12 can process pro-TNF α into mature TNF α indicating that MMP-12 has the potential to amplify to TNF α -driven inflammation.⁸⁵ MMP-12 also cleaves CD36 into one major fragment, but whether this peptide has biological activity is not known.⁷³

While little is known about MMP-12 mechanisms in the post-MI LV remodeling process, recent evidence indicates the MMP-12 -82 A/G polymorphism increases MI risk, as the MMP-12 -82 AG and GG genotypes were associated with a 3.7 fold increase in risk of having two or three occluded vessels.³⁶ This polymorphism is located at the activator protein-1 transcription factor binding site for MMP-12. *In vitro* studies have indicated the G allele of this polymorphism results in lower MMP-12 promoter activity and thus lower transcriptional activity.³⁶

MMP-14

MMP-14 is expressed in cardiomyocytes, macrophages, and fibroblasts.²⁷ MMP-14 increases 20-fold at 3 days post-MI and peaks at 16 weeks post-MI in non-infarcted LV regions, indicating critical roles in both early and late remodeling events and in both infarct and remote regions.^{8, 24, 32, 88} Elevated MMP-14 in both plasma and the LV infarct post-MI correlate with extensive LV remodeling including significant cardiac fibrosis, reduced LV function, and lower survival.^{62, 88}

Post-MI, MMP-14 degrades collagen, fibronectin, and gelatin leading to a loss of ECM structure and support.⁸⁹ In addition to ECM structural proteins, MMP-14 can process pro-fibrotic signaling molecules, such as transforming growth factor- β and periostin, leading to increased fibrillar collagen synthesis and accumulation.⁹⁰ MMP-14 can also activate MMP-2 and -13.⁹¹ Subsequent activation of these MMPs would result in continued ECM

degradation and instability thereby contributing to adverse LV remodeling, dilation, and possibly heart failure.⁸⁹

MMP-28

MMP-28 is the newest identified member of the MMP family. MMP-28 is expressed by cardiomyocytes, neutrophils, and macrophages.⁹² In contrast to what is generally observed for MMPs post-MI, total MMP-28 actually decreases post-MI due to the loss of myocytes.⁹³ While myocyte-derived MMP-28 decreases, macrophage derived MMP-28 increases in the post-MI LV.⁹³ *In vitro*, MMP-28 has been shown to proteolytically process casein, Nogo-A (a myelin component), and neural cell adhesion molecule-1, however, little is known about the role of MMP-28 post-MI.⁹⁴ Deletion of MMP-28 exaggerates LV dysfunction and cardiac rupture post-MI by reducing the inflammatory and fibrotic response and tilting the balance away from adequate wound healing and high-quality scar formation.⁹³ Inhibition of MMP-28, therefore, would most likely not be a successful target for improving patient outcomes post-MI.

Clinical use of MMP inhibitors post-MI

MMPs can process a variety of substrates, and the same substrate may be processed by a variety of MMPs; combined, this complexity yields a post-MI *in vivo* environment that is still not fully understood. For this reason, the clinical use of MMP inhibitors (MMPi) in post-MI patients is still under investigation (Figure 2).⁹⁵

Direct non-selective inhibition

Broad-spectrum MMPi have been used in clinical trials as an attempt to prevent heart failure post-MI. To date, more than 25 MMP inhibitors have been investigated in post-MI clinical trials. However, the majority of MMP inhibitors developed to date have not proved efficacious. Side effects due to MMPi treatment includes joint pain, stiffness, edema, skin discoloration, and reduced patient mobility.⁹⁶ However, this musculoskeletal syndrome is reversible on cessation of the drug intake.⁹⁷ Insufficient knowledge about complex biological role of MMPs and lack of specificity are main reasons for clinical failure.^{98, 99}

Animals treated with CP-471,474 (a broad-spectrum MMPi) had attenuated end-diastolic and end-systolic dimensions and increased the number of vessels post-MI.¹⁰⁰ Similarly, pigs, mice, and rabbits treated with PD166793 (another broad-spectrum MMPi) at a concentration that can inhibit MMP-2, -3, -9, and -13, but not MMP-1, had lower LV end-diastolic dimension and increased TIMP-1 concentration in infarct region post-MI.¹⁰⁰⁻¹⁰²

Pigs treated 3 days pre- or post-MI with an orally available broad-spectrum MMPi (PGE-530742) at a concentration that inhibited MMP-2, -3, -8, -9, and -13, but not MMP-1, and -7 increased post-MI end-systolic volume, and attenuated fibrillar collagen content in the infarct zone.¹⁰³ Pre-MI treatment, however, increased collagen content in the border zone and decreased collagen content in the remote zone in comparison to post-MI treatment, demonstrating that timing plays an important role on MMPi effects on ECM remodeling. In a similar study, post-MI mice were given 2*R*-2-[5-[4-[ethyl-methylamino]phenyl] thiophene-2-sulfonylamino]-3-methylbutyric acid (TISAM) orally, at

a dose that inhibited MMP-2, and -9, but not MMP-1, -3, or -7. The treatment improved survival rate, decreased cardiac rupture rate, and decreased macrophage infiltration, but increased necrotic area at day 7 post-MI.³⁴

PG-116800 is an oral MMPi of the hydroxamic acid class with high affinity for MMP-2, -3, -8, -9, -13, and -14 and low affinity for MMP-1 and -7. In a phase II double-blind, multicenter RCT PREMIER (Prevention of Myocardial Infarction Early Remodeling) trial, post-MI patients did not improve in echocardiography parameters or in clinical outcomes after 90 days treatment with PG-116800.⁹⁷ This may be due in part by the clinical dose used, which was four-fold lower than what was shown effective for achieving a LV anti-remodeling effect in pre-clinical studies.¹⁰³

Doxycycline is an antibiotic used at sub-antimicrobial doses as a broad-spectrum MMPi. Its use is approved by FDA for periodontal disease treatment.¹⁰⁴ Rats treated with doxycycline showed attenuated mRNA transcription and protein expressions of MMP-8, MMP-13, TIMP-1, TIMP-2, and type I collagen content in the remote zone post-MI.¹⁰⁵ In another study, rats treated with doxycycline showed attenuated MMP-2 activity, increased TIMP-1 expression, and improved endothelial dysfunction post-MI.¹⁰⁶ In the phase II TIPTOP (Early Short-term Doxycycline Therapy In Patients with Acute Myocardial Infarction and Left Ventricular Dysfunction to Prevent The Ominous Progression to Adverse Remodeling) trial, treatment with doxycycline (100 mg twice daily) reduced end-diastolic volumes index, infarct size, and infarct severity in comparison to patients who received only the standard treatment.¹⁰⁷

Direct selective inhibition

First generation MMPi targeted a broad range of MMPs and therefore lacked specificity and selectivity, leading to less effective use and inconclusive results.¹⁰⁸ The Fields laboratory developed a potent and highly selective MMP-9 inhibitor (MMP-9i).^{109, 110} A recent study in mice showed that early inhibition of MMP-9 had no effect on infarct size or survival. By day 7 post-MI, MMP-9i enhanced infarct wall thinning and worsened cardiac dysfunction opposing studies utilizing MMP-9 deleted mice.^{73, 108} This was due in part by MMP-9i treatment increasing expression of *Mmp8*, *Mmp12*, and *Mmp14*, and decreasing collagen deposition. MMP-9i treatment also increased neutrophil numbers at day 1 post-MI and macrophage infiltration at day 7 post-MI.

A selective MMP-12 inhibitor (RXP 470.1; MMP-12i) was also found to promote adverse cardiac function post-MI.⁸¹ This is in contrast to an atherosclerotic model, where MMP-12 inhibition was found to reduce atherosclerosis progression in apo-E null mice by inhibiting MMP-12 activity in macrophages.⁹⁸ Post-MI, MMP-12i repressed neutrophil functions leading to impaired cardiac wound healing. This suggests MMP-12i in an acute inflammation model may be harmful while MMP-12i in a chronic inflammation model may be favorable.

These studies reveal that using a selective MMP inhibitor will require complete assessment and complex data interpretation. Studies utilizing MMPi diverge greatly from those seen with global or cell-specific MMP deletion.^{108, 111} In addition, the overall effect of MMPi

differs among CVD pathologies and timing of intervention. This is due in part by the fact that MMPs have both detrimental and beneficial mechanisms that are dependent on injury stimuli and on substrate availability.⁸¹

Indirect MMP inhibition

While the use of direct MMP inhibitors is still under examination, MMP inhibition is being achieved through indirect mechanisms. The majority of current medications used for MI and heart failure (e.g., angiotensin converter enzyme (ACE) inhibitors, angiotensin receptor antagonists, beta-blockers, and statins) act as indirect inhibitors for MMPs.

ACE inhibitors are well documented to improve post-MI outcomes.¹¹² The catalytic domain of ACE is similar to that of MMPs, thus ACE inhibitors simultaneously have an inhibitory effect on MMPs.¹¹³ For example, captopril and lisinopril inhibit MMP-2 activity at concentrations greater than 4 and 1 mmol/L, whereas MMP-9 was inhibited by 87 nmol/L of captopril.^{114, 115} ACE inhibitors bind to S1 and S1' subsite of MMP-9, which forms a deep hydrophobic pocket similar to the hydrophobic moieties in the ACE active site.¹¹³ Lisinopril is stabilized to the MMP-9 active site by specific hydrogen bonds and hydrophobic interactions, and its hydrophobic group showed greater affinity with the S1 site in comparison to the S1' site.¹¹³ In addition, imidapril is stabilized to the MMP-9 active site with less molecular distortion, which may explain the greater MMP-9 inhibitory activity of imidapril compared to lisinopril.¹¹⁶ In fact, in vivo experiments showed that hamsters treated with lisinopril or imidapril had decreased MMP-9 activity in the post-MI LV, with MMP-9 activity being lower in the group that received imidapril compared to lisinopril.¹¹⁶ In a separate study, post-MI patients treated with perindopril showed decreased levels of MMP-1 in plasma and attenuated LV dysfunction.¹¹⁷

Similarly to ACE inhibitors, angiotensin II receptor antagonists inhibit MMPs levels and improve ECM remodeling post-MI.¹¹⁸ Rats treated with losartan showed attenuated mRNA transcription and protein expression of MMP-8, MMP-13, TIMP-1, TIMP-2, and type I collagen content in the remote zone post-MI.¹¹⁸ Treatment with valsartan (a selective angiotensin II type 1 receptor antagonist, AT₁) but not PD123319 (a selective angiotensin II type 2 receptor antagonist) decreased levels of MMP-2, -3, and -9 post-MI in rats, indicating that angiotensin II receptor blockade effects on ECM remodeling is due to inhibition of the AT₁ receptor.¹¹⁹ Deletion of the AT₁ receptor in mice increased survival rate and decreased LV remodeling post-MI.¹²⁰ Moreover, patients treated with trandolapril and valsartan showed attenuated MMP-9 levels in plasma and suppressed LV remodeling post-MI.¹²¹ While further investigation is needed to assess the mechanism whereby ACE inhibitors and angiotensin II receptor antagonists decrease MMPs and ameliorate LV dysfunction post-MI, the therapeutic inhibition of MMPs by inhibition of the angiotensin pathway is encouraging.

The National Institutes for Health and Clinical Excellence (NICE) recommends aldosterone antagonist therapy should be given within 3 to 14 days post-MI (preferably after treatment with ACE inhibitor has been initiated) to treat and prevent LV systolic dysfunction and heart failure in post-MI patients.¹²² Aldosterone increases MMP-2 and -9 activity in cultured adult rat ventricular myocytes through modulating mitogen/extracellular signal-regulated

kinase and extracellular signal-regulated kinase 1/2 phosphorylation, and increasing ROS production.¹²³ Pretreatment with spironolactone (aldosterone receptor antagonist) abolished the aldosterone-induced increase in MMP activity and decreased collagen deposition post-MI.^{123, 124} Long-term treatment (24 weeks) with spironolactone in heart failure patients improved LV dysfunction, and attenuated plasma MMP-9, TIMP-1, and type I collagen carboxyterminal telopeptide concentrations.¹²⁵

Others vasoactive peptides, such as endothelin-1, can alter MMP expression and ECM remodeling post-MI. The endothelin receptor subtype A (ET_A) is predominate on myocytes and its activation induces myocyte hypertrophy.^{126, 127} Thus, endothelin increases collagen expression and collagenase activity in cardiac fibroblasts.¹²⁸ Rats treated with sitaxsentan (ET_A receptor antagonist) attenuated MMP-1, -2, and -9, increased TIMP-1, and improved post-MI cardiac dilation.¹²⁹

The American Heart Association and American College of Cardiology recommend initiating beta-adrenergic antagonists in all post-MI patients and continuing therapy indefinitely.¹³⁰ Dogs treated with atenolol, at supra-therapeutic doses, showed decreased MMP activity and improved LV stiffness in an experimental pacing-induced heart failure model.¹³¹ Rats treated with metoprolol showed decreased MMP-2 mRNA levels and decreased oxidative stress markers post-MI.¹³² Similar results were observed in post-MI pigs treated with carvedilol or metoprolol, both of which decreased MMP-2 activity, MCP-1 expression, and macrophage infiltration.¹³³ Patients with heart failure treated with standard therapy plus carvedilol showed reduced MMP-9 activity in plasma.¹³⁴

Antiplatelet, anticoagulant, and thrombolytic therapies are administered after cardiovascular events to improve patient outcome.¹³⁵ Post-MI patients treated with tissue plasminogen activator (tPA) showed increased plasma MMP-9 levels.¹³⁶ Direct thrombin inhibitors and heparin are commonly used in post-MI therapy.^{137, 138} Heparin treatment increases MMP-1 and -2 in cultured fibroblasts, and MMP-1, -2, -3, and -9 in mesangial cells.^{139, 140} The effect of heparin therapy on MMPs *in vivo* has not been determined.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) are highly associated with risk of MI, however, selective cyclooxygenase-2 inhibitors reduce C-reactive protein levels and improve endothelial function.¹⁴¹ Aspirin is an NSAID administered as an antiplatelet and is highly recommended for patients after first MI or with heart failure.¹⁴² MMP-2 gene expression was attenuated with NSAID treatment by inhibiting specific protein (SP)-1 transcription factor from binding to the MMP-2 promoter site.¹⁴³ Up to date, no studies have examined the effects of NSAIDs on MMPs post-MI. *In vitro* experiments in human endothelial cells indicate that aspirin attenuates MMP-1 but not MMP-2 or -9.^{144, 145}

Statins (hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) exert a variety of pleiotropic effects, such as inhibiting isoprenoid intermediates production, which decrease the activation of Rho-family small GTP-binding proteins.¹⁴⁶ The inhibitory effect of statins on MMP-9 expression is dependent on nitrite-mediated mechanisms.¹⁴⁷ Interestingly, macrophages treated with statins showed increased MMP-12 expression, which is consistent with the concept that MMP-12 may be beneficial post-MI.⁸⁰ Human

cardiac myofibroblasts treated with simvastatin showed reduced TNF α -induced invasion by MMP-9-dependent mechanisms.¹⁴⁸ Patients treated with pravastatin showed decreased MMP-2, MMP-9, c-reactive protein, and CD40L levels post-MI.^{149–151} Combined there is ample evidence to support MMPs as off targets of a variety of CVD drugs.

General considerations

Multiple clinical studies have demonstrated the role of direct and indirect MMPi during the development of end-stage heart failure and LV remodeling. However, clinic trials using nonspecific MMPi have been inconclusive.⁹⁷ In addition, animal studies with direct MMPi have given mixed results. To develop a successful therapeutic treatment, additional studies are needed to understand the entire composite of MMP roles. Identifying the downstream effects of MMPs may provide answers and serve as novel and more selective treatment strategies for post-MI patients.⁷³

Future Directions

While the cardiac MMP literature field has exploded over the last 15 years, future research is needed. There is a need to better understand the biological function of MMPs in cardiac maintenance and tissue repair after injury. Out of the 25 MMPs identified to date, about half of the known MMPs have been characterized post-MI with MMP-2 and –9 being the main focus. In addition, the role of the MMPs that have been studied is complicated by to interactions between MMP family members. For example, inhibition of a specific MMP can result in an increase of other MMPs due to compensatory effects. MMPs also compete with each other for the same substrate. Competition assays evaluating the interaction with other MMPs is necessary in order to fully characterize the role of MMPs in the post-MI environment.

Furthermore, each MMP has a broad range of substrates that include chemokines, cytokines, adhesion molecules and growth factors as well as ECM components such as collagen and fibronectin.⁷² Post-MI, small fragments or peptides generated by MMP proteolysis are increased both in plasma and in the infarct area. Evaluating the efficacy of using MMP cleavage products for diagnostic and therapeutic purposes in heart failure is warranted.

Temporal and spatial MMP patterns during LV remodeling need to be determined to gain a more extensive understanding of MMPs. For example, MMP-9 gene deletion has proven beneficial post-MI in mice, yet, macrophage-specific transgenic overexpression of MMP-9 has also shown to be beneficial by attenuating the post-MI inflammatory response.¹¹¹ This suggests that timing and concentration of MMPs may dictate divergent mechanisms of response.^{108, 111} Combined, the elucidation of these MMP mechanisms will help us to more completely understand how MMPs coordinate the post-MI response.

Conclusion

In conclusion, understanding the role of MMPs during post-MI remodeling remains an important issue.¹⁵² A better understanding of pathophysiological processes, including the

biological function of the downstream products of MMPs, may lead to new strategies for the post-MI patient, particularly therapies limiting heart failure progression.

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References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics–2012 update: A report from the American Heart Association. *Circulation*. 2012; 125:e2–e220. [PubMed: 22179539]
2. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. Behalf of an international forum on cardiac remodeling. *J Am Coll Cardiol*. 2000; 35:569–582. [PubMed: 10716457]
3. Lindsey ML, Iyer RP, Jung M, DeLeon-Pennell KY, Ma Y. Matrix metalloproteinases as input and output signals for post-myocardial infarction remodeling. *J Mol Cell Cardiol*. 2016; 91:134–140. [PubMed: 26721597]
4. Wilson EM, Gunasinghe HR, Coker ML, Sprunger P, Lee-Jackson D, Bozkurt B, et al. Plasma matrix metalloproteinase and inhibitor profiles in patients with heart failure. *J Card Fail*. 2002; 8:390–398. [PubMed: 12528092]
5. Spinale FG, Coker ML, Krombach SR, Mukherjee R, Hallak H, Houck WV, et al. Matrix metalloproteinase inhibition during the development of congestive heart failure: Effects on left ventricular dimensions and function. *Circ Res*. 1999; 85:364–376. [PubMed: 10455065]
6. Ertl G, Frantz S. Healing after myocardial infarction. *Cardiovasc Res*. 2005; 66:22–32. [PubMed: 15769445]
7. Lindsey M, Wedin K, Brown MD, Keller C, Evans AJ, Smolen J, et al. Matrix-dependent mechanism of neutrophil-mediated release and activation of matrix metalloproteinase 9 in myocardial ischemia/reperfusion. *Circulation*. 2001; 103:2181–2187. [PubMed: 11331260]
8. Coker ML, Jolly JR, Joffs C, Etoh T, Holder JR, Bond BR, et al. Matrix metalloproteinase expression and activity in isolated myocytes after neurohormonal stimulation. *Am J Physiol Heart Circ Physiol*. 2001; 281:H543–551. [PubMed: 11454555]
9. Lindsey ML, Escobar GP, Mukherjee R, Goshorn DK, Sheats NJ, Bruce JA, et al. Matrix metalloproteinase-7 affects connexin-43 levels, electrical conduction, and survival after myocardial infarction. *Circulation*. 2006; 113:2919–2928. [PubMed: 16769909]
10. Heymans S, Luttun A, Nuyens D, Theilmeier G, Creemers E, Moons L, et al. Inhibition of plasminogen activators or matrix metalloproteinases prevents cardiac rupture but impairs therapeutic angiogenesis and causes cardiac failure. *Nat Med*. 1999; 5:1135–1142. [PubMed: 10502816]
11. Lindsey ML, Hall ME, Harmancey R, Ma Y. Adapting extracellular matrix proteomics for clinical studies on cardiac remodeling post-myocardial infarction. *Clinical proteomics*. 2016; 13:19. [PubMed: 27651752]
12. Barallobre-Barreiro J, Didangelos A, Schoendube FA, Drozdov I, Yin X, Fernandez-Caggiano M, et al. Proteomics analysis of cardiac extracellular matrix remodeling in a porcine model of ischemia/reperfusion injury. *Circulation*. 2012; 125:789–802. [PubMed: 22261194]
13. Davis GE, Bayless KJ, Davis MJ, Meininger GA. Regulation of tissue injury responses by the exposure of matricryptic sites within extracellular matrix molecules. *Am J Pathol*. 2000; 156:1489–1498. [PubMed: 10793060]
14. Lindsey ML, Iyer RP, Zamilpa R, Yabluchanskiy A, DeLeon-Pennell KY, Hall ME, et al. A novel collagen matricryptin reduces left ventricular dilation post-myocardial infarction by promoting scar formation and angiogenesis. *J Am Coll Cardiol*. 2015; 66:1364–1374. [PubMed: 26383724]

15. Ma Y, de Castro Bras LE, Toba H, Iyer RP, Hall ME, Winniford MD, et al. Myofibroblasts and the extracellular matrix network in post-myocardial infarction cardiac remodeling. *Pflugers Arch*. 2014; 466:1113–1127. [PubMed: 24519465]
16. Yabluchanskiy A, Chilton RJ, Lindsey ML. Left ventricular remodeling: One small step for the extracellular matrix will translate to a giant leap for the myocardium. *Congestive heart failure*. 2013; 19:E5–8. [PubMed: 23350683]
17. Ma Y, Halade GV, Lindsey ML. Extracellular matrix and fibroblast communication following myocardial infarction. *J Cardiovasc Transl Res*. 2012; 5:848–857. [PubMed: 22926488]
18. Diez J, Panizo A, Gil MJ, Monreal I, Hernandez M, Pardo Mindan J. Serum markers of collagen type i metabolism in spontaneously hypertensive rats: Relation to myocardial fibrosis. *Circulation*. 1996; 93:1026–1032. [PubMed: 8598066]
19. McGavigan AD, Maxwell PR, Dunn FG. Serological evidence of altered collagen homeostasis reflects early ventricular remodeling following acute myocardial infarction. *Int J Cardiol*. 2006; 111:267–274. [PubMed: 16297470]
20. Balbin M, Fueyo A, Knauper V, Lopez JM, Alvarez J, Sanchez LM, et al. Identification and enzymatic characterization of two diverging murine counterparts of human interstitial collagenase (mmp-1) expressed at sites of embryo implantation. *J Biol Chem*. 2001; 276:10253–10262. [PubMed: 11113146]
21. Spinale FG, Coker ML, Bond BR, Zellner JL. Myocardial matrix degradation and metalloproteinase activation in the failing heart: A potential therapeutic target. *Cardiovasc Res*. 2000; 46:225–238. [PubMed: 10773226]
22. Hirohata S, Kusachi S, Murakami M, Murakami T, Sano I, Watanabe T, et al. Time dependent alterations of serum matrix metalloproteinase-1 and metalloproteinase-1 tissue inhibitor after successful reperfusion of acute myocardial infarction. *Heart*. 1997; 78:278–284. [PubMed: 9391291]
23. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: Structure, function, and biochemistry. *Circ Res*. 2003; 92:827–839. [PubMed: 12730128]
24. Lindsey ML, Goshorn DK, Squires CE, Escobar GP, Hendrick JW, Mingoia JT, et al. Age-dependent changes in myocardial matrix metalloproteinase/tissue inhibitor of metalloproteinase profiles and fibroblast function. *Cardiovasc Res*. 2005; 66:410–419. [PubMed: 15820210]
25. Porter KE, Turner NA. Cardiac fibroblasts: At the heart of myocardial remodeling. *Pharmacology & therapeutics*. 2009; 123:255–278. [PubMed: 19460403]
26. Chow AK, Cena J, Schulz R. Acute actions and novel targets of matrix metalloproteinases in the heart and vasculature. *Br J Pharmacol*. 2007; 152:189–205. [PubMed: 17592511]
27. Vanhoutte D, Schellings M, Pinto Y, Heymans S. Relevance of matrix metalloproteinases and their inhibitors after myocardial infarction: A temporal and spatial window. *Cardiovasc Res*. 2006; 69:604–613. [PubMed: 16360129]
28. Lindner D, Zietsch C, Becher PM, Schulze K, Schultheiss HP, Tschöpe C, et al. Differential expression of matrix metalloproteinases in human fibroblasts with different origins. *Biochem Res Int*. 2012; 2012:875742. [PubMed: 22500233]
29. Baghirova S, Hughes BG, Poirier M, Kondo MY, Schulz R. Nuclear matrix metalloproteinase-2 in the cardiomyocyte and the ischemic-reperfused heart. *J Mol Cell Cardiol*. 2016; 94:153–161. [PubMed: 27079252]
30. Lovett DH, Mahimkar R, Raffai RL, Cape L, Maklashina E, Cecchini G, et al. A novel intracellular isoform of matrix metalloproteinase-2 induced by oxidative stress activates innate immunity. *PLoS One*. 2012; 7:e34177. [PubMed: 22509276]
31. Zhao S, Wu H, Xia W, Chen X, Zhu S, Zhang S, et al. Periostin expression is upregulated and associated with myocardial fibrosis in human failing hearts. *J Cardiol*. 2014; 63:373–378. [PubMed: 24219836]
32. Peterson JT, Li H, Dillon L, Bryant JW. Evolution of matrix metalloproteinase and tissue inhibitor expression during heart failure progression in the infarcted rat. *Cardiovasc Res*. 2000; 46:307–315. [PubMed: 10773235]

33. Tao ZY, Cavasin MA, Yang F, Liu YH, Yang XP. Temporal changes in matrix metalloproteinase expression and inflammatory response associated with cardiac rupture after myocardial infarction in mice. *Life Sci.* 2004; 74:1561–1572. [PubMed: 14729404]
34. Matsumura, S-i, Iwanaga, S., Mochizuki, S., Okamoto, H., Ogawa, S., Okada, Y. Targeted deletion or pharmacological inhibition of mmp-2 prevents cardiac rupture after myocardial infarction in mice. *J Clin Invest.* 2005; 115:599–609. [PubMed: 15711638]
35. Imai K, Shikata H, Okada Y. Degradation of vitronectin by matrix metalloproteinases-1, -2, -3, -7 and -9. *FEBS Lett.* 1995; 369:249–251. [PubMed: 7544295]
36. Perez-Hernandez N, Vargas-Alarcon G, Martinez-Rodriguez N, Martinez-Rios MA, Pena-Duque MA, Pena-Diaz Ade L, et al. The matrix metalloproteinase 2-1575 gene polymorphism is associated with the risk of developing myocardial infarction in mexican patients. *J Atheroscler Thromb.* 2012; 19:718–727. [PubMed: 22785600]
37. Delgado-Enciso I, Gonzalez-Hernandez NA, Baltazar-Rodriguez LM, Millan-Guerrero RO, Newton-Sanchez O, Bayardo-Noriega A, et al. Association of matrix metalloproteinase-2 gene promoter polymorphism with myocardial infarction susceptibility in a mexican population. *J Genet.* 2009; 88:249–252. [PubMed: 19700865]
38. Mizon-Gerard F, de Groote P, Lamblin N, Hermant X, Dallongeville J, Amouyel P, et al. Prognostic impact of matrix metalloproteinase gene polymorphisms in patients with heart failure according to the aetiology of left ventricular systolic dysfunction. *European heart journal.* 2004; 25:688–693. [PubMed: 15084374]
39. Beber AR, Polina ER, Biolo A, Santos BL, Gomes DC, La Porta VL, et al. Matrix metalloproteinase-2 polymorphisms in chronic heart failure: Relationship with susceptibility and long-term survival. *PLoS One.* 2016; 11:e0161666. [PubMed: 27551966]
40. Vasku A, Goldbergova M, Holla LI, Spinarova L, Spinar J, Vitovec J, et al. Two mmp-2 promoter polymorphisms (-790t/g and -735c/t) in chronic heart failure. *Clin Chem Lab Med.* 2003; 41:1299–1303. [PubMed: 14580155]
41. Kelly D, Khan S, Cockerill G, Ng LL, Thompson M, Samani NJ, et al. Circulating stromelysin-1 (mmp-3): A novel predictor of lv dysfunction, remodelling and all-cause mortality after acute myocardial infarction. *European journal of heart failure.* 2008; 10:133–139. [PubMed: 18234553]
42. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: Structure, function, and biochemistry. *Circ Res.* 2003; 92:827–839. [PubMed: 12730128]
43. Suzuki K, Enghild JJ, Morodomi T, Salvesen G, Nagase H. Mechanisms of activation of tissue procollagenase by matrix metalloproteinase 3 (stromelysin). *Biochemistry.* 1990; 29:10261–10270. [PubMed: 2176865]
44. Sage EH, Reed M, Funk SE, Truong T, Steadele M, Puolakkainen P, et al. Cleavage of the matricellular protein sparc by matrix metalloproteinase 3 produces polypeptides that influence angiogenesis. *J Biol Chem.* 2003; 278:37849–37857. [PubMed: 12867428]
45. Midwood KS, Hussenet T, Langlois B, Orend G. Advances in tenascin-c biology. *Cell Mol Life Sci.* 2011; 68:3175–3199. [PubMed: 21818551]
46. Terashima M, Akita H, Kanazawa K, Inoue N, Yamada S, Ito K, et al. Stromelysin promoter 5a/6a polymorphism is associated with acute myocardial infarction. *Circulation.* 1999; 99:2717–2719. [PubMed: 10351963]
47. Wang J, Xu D, Wu X, Zhou C, Wang H, Guo Y, et al. Polymorphisms of matrix metalloproteinases in myocardial infarction: A meta-analysis. *Heart.* 2011; 97:1542–1546. [PubMed: 21900582]
48. Ye S, Eriksson P, Hamsten A, Kurkinen M, Humphries SE, Henney AM. Progression of coronary atherosclerosis is associated with a common genetic variant of the human stromelysin-1 promoter which results in reduced gene expression. *J Biol Chem.* 1996; 271:13055–13060. [PubMed: 8662692]
49. Velho FM, Cohen CR, Santos KG, Silvello D, Martinelli N, Biolo A, et al. Polymorphisms of matrix metalloproteinases in systolic heart failure: Role on disease susceptibility, phenotypic characteristics, and prognosis. *J Card Fail.* 2011; 17:115–121. [PubMed: 21300300]
50. Furman C, Copin C, Kandoussi M, Davidson R, Moreau M, McTaggart F, et al. Rosuvastatin reduces mmp-7 secretion by human monocyte-derived macrophages: Potential relevance to atherosclerotic plaque stability. *Atherosclerosis.* 2004; 174:93–98. [PubMed: 15135256]

51. Boixel C, Fontaine V, Rucker-Martin C, Milliez P, Louedec L, Michel JB, et al. Fibrosis of the left atria during progression of heart failure is associated with increased matrix metalloproteinases in the rat. *J Am Coll Cardiol*. 2003; 42:336–344. [PubMed: 12875773]
52. Sato A, Aonuma K, Imanaka-Yoshida K, Yoshida T, Isobe M, Kawase D, et al. Serum tenascin-c might be a novel predictor of left ventricular remodeling and prognosis after acute myocardial infarction. *J Am Coll Cardiol*. 2006; 47:2319–2325. [PubMed: 16750702]
53. Zile MR, Desantis SM, Baicu CF, Stroud RE, Thompson SB, McClure CD, et al. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. *Circ Heart Fail*. 2011; 4:246–256. [PubMed: 21350055]
54. Chiao YA, Zamilpa R, Lopez EF, Dai Q, Escobar GP, Hakala K, et al. In vivo matrix metalloproteinase-7 substrates identified in the left ventricle post-myocardial infarction using proteomics. *J Proteome Res*. 2010; 9:2649–2657. [PubMed: 20232908]
55. Agnihotri R, Crawford HC, Haro H, Matrisian LM, Havrda MC, Liaw L. Osteopontin, a novel substrate for matrix metalloproteinase-3 (stromelysin-1) and matrix metalloproteinase-7 (matrilysin). *J Biol Chem*. 2001; 276:28261–28267. [PubMed: 11375993]
56. von Bredow DC, Nagle RB, Bowden GT, Cress AE. Degradation of fibronectin fibrils by matrilysin and characterization of the degradation products. *Exp Cell Res*. 1995; 221:83–91. [PubMed: 7589259]
57. von Bredow DC, Cress AE, Howard EW, Bowden GT, Nagle RB. Activation of gelatinase-tissue-inhibitors-of-metalloproteinase complexes by matrilysin. *Biochem J*. 1998; 331(Pt 3):965–972. [PubMed: 9560329]
58. Fertin M, Lemesle G, Turkieh A, Beseme O, Chwastyniak M, Amouyel P, et al. Serum mmp-8: A novel indicator of left ventricular remodeling and cardiac outcome in patients after acute myocardial infarction. *PLoS One*. 2013; 8:e71280. [PubMed: 23967183]
59. Webb CS, Bonnema DD, Ahmed SH, Leonardi AH, McClure CD, Clark LL, et al. Specific temporal profile of matrix metalloproteinase release occurs in patients after myocardial infarction: Relation to left ventricular remodeling. *Circulation*. 2006; 114:1020–1027. [PubMed: 16923753]
60. Iyer RP, de Castro Bras LE, Jin YF, Lindsey ML. Translating Koch's postulates to identify matrix metalloproteinase roles in postmyocardial infarction remodeling: Cardiac metalloproteinase actions (carma) postulates. *Circ Res*. 2014; 114:860–871. [PubMed: 24577966]
61. Deten A, Volz HC, Holz A, Briest W, Zimmer HG. Effect of propranolol on cardiac cytokine expression after myocardial infarction in rats. *Mol Cell Biochem*. 2003; 251:127–137. [PubMed: 14575314]
62. Wilson EM, Moainie SL, Baskin JM, Lowry AS, Deschamps AM, Mukherjee R, et al. Region- and type-specific induction of matrix metalloproteinases in post-myocardial infarction remodeling. *Circulation*. 2003; 107:2857–2863. [PubMed: 12771000]
63. Marini S, Fasciglione GF, de Sanctis G, D'Alessio S, Politi V, Coletta M. Cleavage of bovine collagen I by neutrophil collagenase mmp-8. Effect of pH on the catalytic properties as compared to synthetic substrates. *J Biol Chem*. 2000; 275:18657–18663. [PubMed: 10749856]
64. Van Lint P, Wielockx B, Puimege L, Noel A, Lopez-Otin C, Libert C. Resistance of collagenase-2 (matrix metalloproteinase-8)-deficient mice to TNF-induced lethal hepatitis. *J Immunol*. 2005; 175:7642–7649. [PubMed: 16301674]
65. Van Lint P, Libert C. Chemokine and cytokine processing by matrix metalloproteinases and its effect on leukocyte migration and inflammation. *J Leukoc Biol*. 2007; 82:1375–1381. [PubMed: 17709402]
66. Tester AM, Cox JH, Connor AR, Starr AE, Dean RA, Puente XS, et al. LPS responsiveness and neutrophil chemotaxis in vivo require PMN MMP-8 activity. *PLoS One*. 2007; 2:e312. [PubMed: 17375198]
67. Yabluchanskiy A, Ma Y, Iyer RP, Hall ME, Lindsey ML. Matrix metalloproteinase-9: Many shades of function in cardiovascular disease. *Physiology*. 2013; 28:391–403. [PubMed: 24186934]
68. DeLeon-Pennell KY, de Castro Bras LE, Iyer RP, Bratton DR, Jin YF, Ripplinger CM, et al. P. Gingivalis lipopolysaccharide intensifies inflammation post-myocardial infarction through matrix metalloproteinase-9. *J Mol Cell Cardiol*. 2014; 76C:218–226.

69. Blankenberg S, Rupprecht HJ, Poirier O, Bickel C, Smieja M, Hafner G, et al. Plasma concentrations and genetic variation of matrix metalloproteinase 9 and prognosis of patients with cardiovascular disease. *Circulation*. 2003; 107:1579–1585. [PubMed: 12668489]
70. Kelly D, Cockerill G, Ng LL, Thompson M, Khan S, Samani NJ, et al. Plasma matrix metalloproteinase-9 and left ventricular remodelling after acute myocardial infarction in man: A prospective cohort study. *European heart journal*. 2007; 28:711–718. [PubMed: 17339265]
71. Squire IB, Evans J, Ng LL, Loftus IM, Thompson MM. Plasma mmp-9 and mmp-2 following acute myocardial infarction in man: Correlation with echocardiographic and neurohumoral parameters of left ventricular dysfunction. *Journal of cardiac failure*. 2004; 10:328–333. [PubMed: 15309700]
72. Zamilpa R, Lopez EF, Chiao YA, Dai Q, Escobar GP, Hakala K, et al. Proteomic analysis identifies in vivo candidate matrix metalloproteinase-9 substrates in the left ventricle post-myocardial infarction. *Proteomics*. 2010; 10:2214–2223. [PubMed: 20354994]
73. DeLeon-Pennell KY, Tian Y, Zhang B, Cates CA, Iyer RP, Cannon P, et al. Cd36 is a matrix metalloproteinase-9 substrate that stimulates neutrophil apoptosis and removal during cardiac remodeling. *Circ Cardiovasc Genet*. 2016; 9:14–25. [PubMed: 26578544]
74. Lindsey ML, Zouein FA, Tian Y, Padmanabhan Iyer R, de Castro Bras LE. Osteopontin is proteolytically processed by matrix metalloproteinase 9. *Can J Physiol Pharmacol*. 2015; 93:879–886. [PubMed: 26176332]
75. Spinale FG. Matrix metalloproteinase gene polymorphisms in heart failure: New pieces to the myocardial matrix puzzle. *European heart journal*. 2004; 25:631–633. [PubMed: 15084366]
76. Wang X, Shi LZ. Association of matrix metalloproteinase-9 c1562t polymorphism and coronary artery disease: A meta-analysis. *J Zhejiang Univ Sci B*. 2014; 15:256–263. [PubMed: 24599689]
77. Lacchini R, Metzger IF, Luizon M, Ishizawa M, Tanus-Santos JE. Interethnic differences in the distribution of matrix metalloproteinases genetic polymorphisms are consistent with interethnic differences in disease prevalence. *DNA Cell Biol*. 2010; 29:649–655. [PubMed: 20590473]
78. Metzger IF, Luizon MR, Lacchini R, Tanus-Santos JE. Genetic variants in matrix metalloproteinase-9 gene modify metalloproteinase-9 levels in black subjects. *DNA Cell Biol*. 2012; 31:504–510. [PubMed: 21936677]
79. Demacq C, Vasconcellos VB, Marcaccini AM, Gerlach RF, Silva WA Jr, Tanus-Santos JE. Functional polymorphisms in the promoter of the matrix metalloproteinase-9 (mmp-9) gene are not linked with significant plasma mmp-9 variations in healthy subjects. *Clin Chem Lab Med*. 2008; 46:57–63. [PubMed: 18194081]
80. Arian MC, Shapiro SD, Mariani TJ. Induction of macrophage elastase (mmp-12) gene expression by statins. *Journal of cellular physiology*. 2005; 204:139–145. [PubMed: 15605420]
81. Iyer RP, Patterson NL, Zouein FA, Ma Y, Dive V, de Castro Bras LE, et al. Early matrix metalloproteinase-12 inhibition worsens post-myocardial infarction cardiac dysfunction by delaying inflammation resolution. *Int J Cardiol*. 2015; 185:198–208. [PubMed: 25797678]
82. Molet S, Belleguic C, Lena H, Germain N, Bertrand CP, Shapiro SD, et al. Increase in macrophage elastase (mmp-12) in lungs from patients with chronic obstructive pulmonary disease. *Inflamm Res*. 2005; 54:31–36. [PubMed: 15723202]
83. Serrati S, Cinelli M, Margheri F, Guiducci S, Del Rosso A, Pucci M, et al. Systemic sclerosis fibroblasts inhibit in vitro angiogenesis by mmp-12-dependent cleavage of the endothelial cell urokinase receptor. *J Pathol*. 2006; 210:240–248. [PubMed: 16917801]
84. Wu L, Tanimoto A, Murata Y, Sasaguri T, Fan J, Sasaguri Y, et al. Matrix metalloproteinase-12 gene expression in human vascular smooth muscle cells. *Genes Cells*. 2003; 8:225–234. [PubMed: 12622720]
85. Chandler S, Cossins J, Lury J, Wells G. Macrophage metalloelastase degrades matrix and myelin proteins and processes a tumour necrosis factor-alpha fusion protein. *Biochem Biophys Res Commun*. 1996; 228:421–429. [PubMed: 8920930]
86. Gronski TJ Jr, Martin RL, Kobayashi DK, Walsh BC, Holman MC, Huber M, et al. Hydrolysis of a broad spectrum of extracellular matrix proteins by human macrophage elastase. *J Biol Chem*. 1997; 272:12189–12194. [PubMed: 9115292]

87. Shipley JM, Wesselschmidt RL, Kobayashi DK, Ley TJ, Shapiro SD. Metalloelastase is required for macrophage-mediated proteolysis and matrix invasion in mice. *Proc Natl Acad Sci U S A*. 1996; 93:3942–3946. [PubMed: 8632994]
88. Lindsey ML, Zamilpa R. Temporal and spatial expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases following myocardial infarction. *Cardiovasc Ther*. 2012; 30:31–41. [PubMed: 20645986]
89. Spinale FG, Janicki JS, Zile MR. Membrane-associated matrix proteolysis and heart failure. *Circ Res*. 2013; 112:195–208. [PubMed: 23287455]
90. Mu D, Cambier S, Fjellbirkeland L, Baron JL, Munger JS, Kawakatsu H, et al. The integrin $\alpha(v)\beta 8$ mediates epithelial homeostasis through mt1-mmp-dependent activation of $\text{tgf-}\beta 1$. *J Cell Biol*. 2002; 157:493–507. [PubMed: 11970960]
91. Knauper V, Will H, Lopez-Otin C, Smith B, Atkinson SJ, Stanton H, et al. Cellular mechanisms for human procollagenase-3 (mmp-13) activation. Evidence that mt1-mmp (mmp-14) and gelatinase a (mmp-2) are able to generate active enzyme. *J Biol Chem*. 1996; 271:17124–17131. [PubMed: 8663255]
92. Ma Y, Chiao YA, Zhang J, Manicone AM, Jin YF, Lindsey ML. Matrix metalloproteinase-28 deletion amplifies inflammatory and extracellular matrix responses to cardiac aging. *Microsc Microanal*. 2012; 18:81–90. [PubMed: 22153350]
93. Ma Y, Halade GV, Zhang J, Ramirez TA, Levin D, Voorhees A, et al. Matrix metalloproteinase-28 deletion exacerbates cardiac dysfunction and rupture after myocardial infarction in mice by inhibiting m2 macrophage activation. *Circ Res*. 2013; 112:675–688. [PubMed: 23261783]
94. Werner SR, Mescher AL, Neff AW, King MW, Chaturvedi S, Duffin KL, et al. Neural mmp-28 expression precedes myelination during development and peripheral nerve repair. *Dev Dyn*. 2007; 236:2852–2864. [PubMed: 17823957]
95. Iyer RP, Jung M, Lindsey ML. Using the laws of thermodynamics to understand how matrix metalloproteinases coordinate the myocardial response to injury. *Metalloproteinases in medicine*. 2015; 2:75–82. [PubMed: 27376092]
96. Kaludercic N. Inhibiting metalloproteinases with pd 166793 in heart failure: Impact on cardiac remodeling and beyond. *Cardiovasc Ther*. 2008; 26:24–37. [PubMed: 18466418]
97. Hudson MP, Armstrong PW, Ruzyllo W, Brum J, Cusmano L, Krzeski P, et al. Effects of selective matrix metalloproteinase inhibitor (pg-116800) to prevent ventricular remodeling after myocardial infarction: Results of the premier (prevention of myocardial infarction early remodeling) trial. *Journal of the American College of Cardiology*. 2006; 48:15–20. [PubMed: 16814643]
98. Johnson JL, Devel L, Czarny B, George SJ, Jackson CL, Rogakos V, et al. A selective matrix metalloproteinase-12 inhibitor retards atherosclerotic plaque development in apolipoprotein e-knockout mice. *Arterioscler Thromb Vasc Biol*. 2011; 31:528–535. [PubMed: 21212406]
99. Robichaud TK, Steffensen B, Fields GB. Exosite interactions impact matrix metalloproteinase collagen specificities. *J Biol Chem*. 2011; 286:37535–37542. [PubMed: 21896477]
100. Lindsey ML, Gannon J, Aikawa M, Schoen FJ, Rabkin E, Lopresti-Morrow L, et al. Selective matrix metalloproteinase inhibition reduces left ventricular remodeling but does not inhibit angiogenesis after myocardial infarction. *Circulation*. 2002; 105:753–758. [PubMed: 11839633]
101. Mukherjee R, Brinsa TA, Dowdy KB, Scott AA, Baskin JM, Deschamps AM, et al. Myocardial infarct expansion and matrix metalloproteinase inhibition. *Circulation*. 2003; 107:618–625. [PubMed: 12566376]
102. Rohde LE, Ducharme A, Arroyo LH, Aikawa M, Sukhova GH, Lopez-Anaya A, et al. Matrix metalloproteinase inhibition attenuates early left ventricular enlargement after experimental myocardial infarction in mice. *Circulation*. 1999; 99:3063–3070. [PubMed: 10368126]
103. Yarbrough WM, Mukherjee R, Escobar GP, Mingoia JT, Sample JA, Hendrick JW, et al. Selective targeting and timing of matrix metalloproteinase inhibition in post-myocardial infarction remodeling. *Circulation*. 2003; 108:1753–1759. [PubMed: 12975256]
104. Peterson JT. Matrix metalloproteinase inhibitor development and the remodeling of drug discovery. *Heart Fail Rev*. 2004; 9:63–79. [PubMed: 14739769]
105. Zhang P, Yang YJ, Chen X, Ruan YM, Zhou YW, Tian Y, et al. effects of doxycycline on the expression of matrix metalloproteinase and tissue inhibitor of mmp in myocardium after acute

- myocardial infarction: An animal experiment with rats. *Zhonghua yi xue za zhi*. 2004; 84:1288–1293. [PubMed: 15387968]
106. Camp TM, Tyagi SC, Aru GM, Hayden MR, Mehta JL, Tyagi SC. Doxycycline ameliorates ischemic and border-zone remodeling and endothelial dysfunction after myocardial infarction in rats. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2004; 23:729–736.
 107. Cerisano G, Buonamici P, Valenti R, Sciagra R, Raspanti S, Santini A, et al. Early short-term doxycycline therapy in patients with acute myocardial infarction and left ventricular dysfunction to prevent the ominous progression to adverse remodelling: The tiptop trial. *Eur Heart J*. 2014; 35:184–191. [PubMed: 24104875]
 108. Iyer RP, de Castro Bras LE, Patterson NL, Bhowmick M, Flynn ER, Asher M, et al. Early matrix metalloproteinase-9 inhibition post-myocardial infarction worsens cardiac dysfunction by delaying inflammation resolution. *J Mol Cell Cardiol*. 2016; 100:109–117. [PubMed: 27746126]
 109. Lauer-Fields JL, Sritharan T, Stack MS, Nagase H, Fields GB. Selective hydrolysis of triple-helical substrates by matrix metalloproteinase-2 and -9. *J Biol Chem*. 2003; 278:18140–18145. [PubMed: 12642591]
 110. Lauer-Fields JL, Whitehead JK, Li S, Hammer RP, Brew K, Fields GB. Selective modulation of matrix metalloproteinase 9 (mmp-9) functions via exosite inhibition. *J Biol Chem*. 2008; 283:20087–20095. [PubMed: 18499673]
 111. Zamilpa R, Ibarra J, de Castro Bras LE, Ramirez TA, Nguyen N, Halade GV, et al. Transgenic overexpression of matrix metalloproteinase-9 in macrophages attenuates the inflammatory response and improves left ventricular function post-myocardial infarction. *J Mol Cell Cardiol*. 2012; 53:599–608. [PubMed: 22884843]
 112. Pfeffer MA. Ace inhibitors in acute myocardial infarction: Patient selection and timing. *Circulation*. 1998; 97:2192–2194. [PubMed: 9631866]
 113. Yamamoto D, Takai S, Miyazaki M. Prediction of interaction mode between a typical ace inhibitor and mmp-9 active site. *Biochemical and biophysical research communications*. 2007; 354:981–984. [PubMed: 17275782]
 114. Kuntze LB, Antonio RC, Izidoro-Toledo TC, Meschiari CA, Tanus-Santos JE, Gerlach RF. Captopril and lisinopril only inhibit matrix metalloproteinase-2 (mmp-2) activity at millimolar concentrations. *Basic & clinical pharmacology & toxicology*. 2014; 114:233–239. [PubMed: 25767848]
 115. Yamamoto D, Takai S, Miyazaki M. Inhibitory profiles of captopril on matrix metalloproteinase-9 activity. *European journal of pharmacology*. 2008; 588:277–279. [PubMed: 18501888]
 116. Yamamoto D, Takai S, Jin D, Inagaki S, Tanaka K, Miyazaki M. Molecular mechanism of imidapril for cardiovascular protection via inhibition of mmp-9. *Journal of molecular and cellular cardiology*. 2007; 43:670–676. [PubMed: 17884087]
 117. Papadopoulos DP, Economou EV, Makris TK, Kapetanios KJ, Moyssakis I, Votteas VE, et al. Effect of angiotensin-converting enzyme inhibitor on collagenolytic enzyme activity in patients with acute myocardial infarction. *Drugs under experimental and clinical research*. 2004; 30:55–65. [PubMed: 15272643]
 118. Zhang P, Yang YJ, Chen X, Ruan YM, Zhou YW, Tian Y, et al. [comparison of doxycycline, losartan, and their combination on the expression of matrix metalloproteinase, tissue inhibitor of matrix metalloproteinase, and collagen remodeling in the noninfarcted myocardium after acute myocardial infarction in rats. *Zhongguo yi xue ke xue yuan xue bao. Acta Academiae Medicinae Sinicae*. 2005; 27:53–61. [PubMed: 15782494]
 119. Yang D, Ma S, Li D, Tang B, Yang Y. Angiotensin ii receptor blockade improves matrix metalloproteinases/tissue inhibitor of matrix metalloproteinase-1 balance and restores fibronectin expression in rat infarcted myocardium. *Biochemical and biophysical research communications*. 2009; 388:606–611. [PubMed: 19695229]
 120. Harada K, Sugaya T, Murakami K, Yazaki Y, Komuro I. Angiotensin ii type 1a receptor knockout mice display less left ventricular remodeling and improved survival after myocardial infarction. *Circulation*. 1999; 100:2093–2099. [PubMed: 10562266]

121. Miyazaki S, Kasai T, Miyauchi K, Miyazaki T, Akimoto Y, Takagi A, et al. Changes of matrix metalloproteinase-9 level is associated with left ventricular remodeling following acute myocardial infarction among patients treated with trandolapril, valsartan or both. *Circulation Journal*. 2010; 74:1158–1164. [PubMed: 20378999]
122. Jones K, Saxon L, Cunningham W, Adams P, Guideline Development G. Secondary prevention for patients after a myocardial infarction: Summary of updated nice guidance. *Bmj*. 2013; 347:f6544. [PubMed: 24227827]
123. Rude MK, Duhaney T-AS, Kuster GM, Judge S, Heo J, Colucci WS, et al. Aldosterone stimulates matrix metalloproteinases and reactive oxygen species in adult rat ventricular cardiomyocytes. *Hypertension*. 2005; 46:555–561. [PubMed: 16043662]
124. Mill JG, Milanez MdaC, de Resende MM, Gomes MdaG, Leite CM. Spironolactone prevents cardiac collagen proliferation after myocardial infarction in rats. *Clin Exp Pharmacol Physiol*. 2003; 30:739–744. [PubMed: 14516412]
125. Li MJ, Huang CX, Okello E, Yanhong T, Mohamed S. Treatment with spironolactone for 24 weeks decreases the level of matrix metalloproteinases and improves cardiac function in patients with chronic heart failure of ischemic etiology. *The Canadian journal of cardiology*. 2009; 25:523–526. [PubMed: 19746242]
126. Modesti PA, Vanni S, Paniccia R, Bandinelli B, Bertolozzi I, Polidori G, et al. Characterization of endothelin-1 receptor subtypes in isolated human cardiomyocytes. *Journal of cardiovascular pharmacology*. 1999; 34:333–339. [PubMed: 10470989]
127. Shubeita HE, McDonough PM, Harris AN, Knowlton KU, Glembotski CC, Brown JH, et al. Endothelin induction of inositol phospholipid hydrolysis, sarcomere assembly, and cardiac gene expression in ventricular myocytes. A paracrine mechanism for myocardial cell hypertrophy. *The Journal of biological chemistry*. 1990; 265:20555–20562. [PubMed: 2173712]
128. Guarda E, Katwa LC, Myers PR, Tyagi SC, Weber KT. Effects of endothelins on collagen turnover in cardiac fibroblasts. *Cardiovascular research*. 1993; 27:2130–2134. [PubMed: 8313419]
129. Podesser BK, Siwik DA, Eberli FR, Sam F, Ngoy S, Lambert J, et al. Et(a)-receptor blockade prevents matrix metalloproteinase activation late postmyocardial infarction in the rat. *American journal of physiology. Heart and circulatory physiology*. 2001; 280:H984–991. [PubMed: 11179039]
130. Gheorghiade M, Goldstein S. Beta-blockers in the post-myocardial infarction patient. *Circulation*. 2002; 106:394–398. [PubMed: 12135934]
131. Senzaki H, Paolucci N, Gluzband YA, Lindsey ML, Janicki JS, Crow MT, et al. B-blockade prevents sustained metalloproteinase activation and diastolic stiffening induced by angiotensin ii combined with evolving cardiac dysfunction. *Circulation research*. 2000; 86:807–815. [PubMed: 10764416]
132. Bernstein M, Tyagi SC. B-blocker improves cardiac function by reducing oxidative stress and metalloproteinase activity after myocardial infarction. *J Appl Res*. 2001; 1
133. Cimmino G, Ibanez B, Giannarelli C, Prat-Gonzalez S, Hutter R, Garcia M, et al. Carvedilol administration in acute myocardial infarction results in stronger inhibition of early markers of left ventricular remodeling than metoprolol. *Int J Cardiol*. 2011; 153:256–261. [PubMed: 20864196]
134. Song G, Hennessy M, Zhao YL, Li Q, Han WD, Qi Y, et al. Adrenoceptor blockade alters plasma gelatinase activity in patients with heart failure and mmp-9 promoter activity in a human cell line (ecv304). *Pharmacol Res*. 2006; 54:57–64. [PubMed: 16574429]
135. McDaniel MC. Anticoagulation after anterior myocardial infarction: Primum non nocere, or first do no harm. *JACC Cardiovascular interventions*. 2015; 8:163–165. [PubMed: 25616921]
136. Tziakas DN, Chalikias GK, Hatzinikolaou EI, Stakos DA, Tentes IK, Kortsaris A, et al. Alteplase treatment affects circulating matrix metalloproteinase concentrations in patients with st segment elevation acute myocardial infarction. *Thrombosis research*. 2006; 118:221–227. [PubMed: 16126256]
137. Nutescu EA, Shapiro NL, Chevalier A. New anticoagulant agents: Direct thrombin inhibitors. *Cardiol Clin*. 2008; 26:169–187. v–vi. [PubMed: 18406993]

138. Nutescu EA, Shapiro NL, Chevalier A, Amin AN. A pharmacologic overview of current and emerging anticoagulants. *Cleve Clin J Med*. 2005; 72(Suppl 1):S2–6. [PubMed: 15853173]
139. Tyagi SC, Kumar S, Katwa L. Differential regulation of extracellular matrix metalloproteinase and tissue inhibitor by heparin and cholesterol in fibroblast cells. *Journal of molecular and cellular cardiology*. 1997; 29:391–404. [PubMed: 9040053]
140. Zhou Q, Yuichiro Y, Masatoshi T, Terukatsu A. Effect of heparin on high glucose induced proliferation and expression of matrix metalloproteinases in normal human mesangial cells. *South Univ Technol*. 2005; 12:359–364.
141. Bhatt DL. Nsaids and the risk of myocardial infarction: Do they help or harm? *European heart journal*. 2006; 27:1635–1636. [PubMed: 16782714]
142. Awtry EH, Loscalzo J. Aspirin. *Circulation*. 2000; 101:1206–1218. [PubMed: 10715270]
143. Pan M-R, Hung W-C. Nonsteroidal anti-inflammatory drugs inhibit matrix metalloproteinase-2 via suppression of the erk/sp1-mediated transcription. *The Journal of biological chemistry*. 2002; 277:32775–32780. [PubMed: 12087091]
144. Mehta JL, Chen J, Yu F, Li DY. Aspirin inhibits ox-ldl-mediated lox-1 expression and metalloproteinase-1 in human coronary endothelial cells. *Cardiovascular research*. 2004; 64:243–249. [PubMed: 15485683]
145. Kiran MS, Sameer Kumar VB, Viji RI, Sudhakaran PR. Temporal relationship between mmp production and angiogenic process in huvecs. *Cell Biol Int*. 2006; 30:704–713. [PubMed: 16829143]
146. Koh KK. Effects of statins on vascular wall: Vasomotor function, inflammation, and plaque stability. *Cardiovascular research*. 2000; 47:648–657. [PubMed: 10974215]
147. Meschiari CA, Pinheiro LC, Guimaraes DA, Gerlach RF, Tanus-Santos JE. Sodium nitrite attenuates mmp-9 production by endothelial cells and may explain similar effects of atorvastatin. *Naunyn-Schmiedeberg's archives of pharmacology*. 2016; 389:223–231.
148. Turner NA, Aley PK, Hall KT, Warburton P, Galloway S, Midgley L, et al. Simvastatin inhibits tnfa-induced invasion of human cardiac myofibroblasts via both mmp-9-dependent and -independent mechanisms. *Journal of molecular and cellular cardiology*. 2007; 43:168–176. [PubMed: 17560598]
149. Li J, Zhao SP, Peng DQ, Xu ZM, Zhou HN. Early effect of pravastatin on serum soluble cd40l, matrix metalloproteinase-9, and c-reactive protein in patients with acute myocardial infarction. *Clin Chem*. 2004; 50:1696–1699. [PubMed: 15265816]
150. Nakaya R, Uzui H, Shimizu H, Nakano A, Mitsuke Y, Yamazaki T, et al. Pravastatin suppresses the increase in matrix metalloproteinase-2 levels after acute myocardial infarction. *Int J Cardiol*. 2005; 105:67–73. [PubMed: 16207547]
151. Yasuda S, Miyazaki S, Kinoshita H, Nagaya N, Kanda M, Goto Y, et al. Enhanced cardiac production of matrix metalloproteinase-2 and -9 and its attenuation associated with pravastatin treatment in patients with acute myocardial infarction. *Clin Sci (Lond)*. 2007; 112:43–49. [PubMed: 16939410]
152. DeLeon KY, de Castro Bras LE, Lange RA, Lindsey ML. Extracellular matrix proteomics in cardiac ischemia/reperfusion: The search is on. *Circulation*. 2012; 125:746–748. [PubMed: 22261193]

Figure 1.

Myocardial wound healing is dependent on the balance between extracellular matrix (ECM) breakdown and synthesis. Matrix metalloproteinase (MMPs) are critical during this process as key regulators of inflammation, fibrosis, angiogenesis, and collagen degradation. Optimal scar formation (left) requires (1) appropriate inflammation, (2) fibroblast differentiation, proliferation, and migration to the wound site, (3) suitable angiogenesis, and (4) proper synthesis, cross-linking, and alignment of collagen at the infarct site. Too much or too little of these events will result in insufficient scar formation (right) and can facilitate in the development of heart failure post-myocardial infarction.

Figure 2.

Therapeutics given to post-myocardial infarction patients either directly or indirectly inhibit matrix metalloproteinase (MMP) activity leading to extracellular matrix (ECM) remodeling of the left ventricle (LV).

Table 1

Summary of MMP substrates and their post-myocardial infarction (MI) functions. See manuscript text for references.

MMP substrates	MI functional roles	Cleaved by MMP
Angiostatin	Angiogenesis inhibitor, cardiomyocytes death, ↑ heart failure	–2, –3, and –9
C-1158/59	increased migration rate of fibroblast cells, ↑ wound healing	–2 and –9
C-terminal telopeptide of collagen I	exaggerated myocardial fibrosis	–1, –2, –8, and –9
CD36	↓ macrophage phagocytosis and neutrophil apoptosis	–9 and –12
Citrate Synthase	↓ mitochondrial function	–9
Endostatin	suppresses proliferation and migration of endothelial cells	–2, –9, and –13
Fibronectin	act as chemoattractant, ↑ inflammation, migration of monocytes	–2, –7, –9, –12, and –13
Galectin-3	↑ collagen deposition, ↓ LVEF	–9
Hyaluronan	↑ inflammation, ↓ neutrophil apoptosis, induce cardiac dysfunction	–9, and –12
Laminin	inhibit migration of macrophages into the inflammatory region	–2
Osteopontin	↑ migration rate of cardiac fibroblast, ↑ wound healing	–2, –3, –7, –9, and –12
Periostin	↑ myocardial fibrosis, ↑ heart failure	–2, –9, –14
SPARC	anti-angiogenic effect, maturation of ECM	–2, –3, –7, –9, and –13
Tenascin-C	unknown	–3, –4, –7 and –9

SPARC-secreted protein acidic and rich in cysteine