Published in final edited form as:
Curr Drug Targets. 2013 March ; 14(3): 276–286.

Matrix metalloproteinases: drug targets for myocardial infarction

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Abstract

Myocardial infarction (MI) remains a major cause of morbidity and mortality worldwide. Rapid advances in the treatment of acute MI have significantly improved short-term outcomes in patient, due in large part to successes in preventing myocardial cell death and limiting infarct area during the time of ischemia and subsequent reperfusion. Matrix metalloproteases (MMPs) play key roles in post-MI cardiac remodeling and in the development of adverse outcomes. This review highlights the importance of MMPs in the injury and remodeling response of the left ventricle and also discusses their potential as therapeutic targets Additional pre-clinical and clinical research is needed to further investigate and understand the cardioprotective effects of MMPs inhibitors.

Keywords

myocardial infarction; left ventricle; extracellular matrix; matrix metalloproteinases; left ventricle remodeling

1 Introduction

Acute myocardial infarction (MI) occurs as a result of myocardial cell death due to prolonged ischemia. Ischemia occurs when the blood supply to the myocardium stops, often due to the formation of a thrombus in the lumen of the artery supplying oxygen. Ischemic heart disease remains a primary contributor to morbidity and mortality, highlighting the need for new drug targets. Following MI, the necrotic myocytes in the myocardium activate an inflammatory response. This response is beneficial and necessary for wound healing, but at the same time can be detrimental because it further damages the left ventricle (LV) to expand the initial region of injury. Tissue remodeling post-MI involves both a cellular component as well as an extracellular matrix (ECM) remodeling component.

The ECM represents an important cardiac element that adapts to coordinate the functional requirements of the myocardium. In addition to providing structural support, cardiac ECM serves as a reservoir to house a variety of cytokines and growth factors, which are surrounded by a hydrated proteoglycan and glycosaminoglycan-rich environment [1]. The ECM possesses a number of physiological properties and functions, but is primarily directed at preserving cardiac integrity and architecture to facilitate and govern cellular activity [2]. The myocardial ECM directs contractile force generated by cardiomyocytes and sustains

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shear stress generated by cardiomyocytes. In addition, the myocardial ECM produces and maintains certain levels of a variety of growth factors, as well as modulates cell proliferation and differentiation, ECM synthesis and remodeling [3–5].

Following MI, the ECM is degraded and synthesized through a process that is modulated by the balance between matrix metalloproteinase (MMP) activity and the function of the main source of most of the ECM, the fibroblast [6]. Presently, 23 human MMPs have been identified, and although they share a common homology, their functions vary tremendously [2]. MMP activity is regulated by two major types of endogenous inhibitors: α2-macroglobulin (a plasma protein that acts as a general proteinase inhibitor) and the tissue inhibitors of metalloproteinases (TIMPs) [2]. Four TIMPs have been identified: TIMP-1, -2, -3 and -4. TIMPs form high-affinity complexes with activated MMPs and neutralize substrate degradation by blocking the MMP catalytic domain [7]. TIMP-1 is known to inhibit most MMPs, with the exception of MMP-14 (MT1-MMP), but has a higher affinity for MMP-9 than MMP-2. TIMP-2 potentially inhibits all MMPs but has a higher affinity to MMP-2 than MMP-9. TIMP-3 has been shown to bind to MMP-1, -2, -3, -9, and -13 and TIMP-4 inhibits MMP-1, -3, -7, and -9 [8].

To better understand the significance of MMPs as drug targets for MI, this review article will summarize the latest developments in the MMP inhibitor arena, focusing on potential applications of MMP inhibitors for post-MI remodeling.

2 LV remodeling following MI

The composite of tissue changes occurring to the LV in response to MI are collectively termed as LV remodeling. LV remodeling modifies LV size, shape, and function, and these changes start immediately after MI and can continue for years [9]. MMPs are involved in all aspects of remodeling, including the cellular and extracellular responses.

2.1 Cellular responses to MI (Table 1)

Prolonged ischemia leads to myocyte death, which occurs by apoptosis and necrosis [10]. Myocyte death stimulates the release of a variety of bioactive substances, including complement components. Complement is an essential component of the humoral defense mechanism and also mediates the inflammatory process [11]. The activation of the complement system is organized *via* interaction between various specific protein components. Certain complexes of complement system are involved in coating of damaged tissue fragments, thereby facilitating their ingestion by phagocytic cells. The other mediate chemotaxis associated recruitment of leukocytes into the infarcted area *via* receptor-mediated mechanisms [12]. The late-acting complement complexes form macromolecular complexes, which express cytotoxic properties to the local cells [13]. Leukocytes produce a variety of biologically active substances, which in turn initiate signaling pathways locally and systemically to provide a robust inflammatory response at the site of injury [14].

2.1.1 Polymorphonuclear leukocyte infiltration—Polymorphonuclear leukocytes (PMNs) are the first line of defense against foreign bodies and are the first to infiltrate into the infarct region, in the absence of reperfusion. PMNs produce pro-inflammatory cytokines (*e.g.* tumor necrosis factor-alpha (TNF-α) and interleukin 1-beta (IL-1β)), a number of chemokines (*e.g.* IL-8 and macrophage inducible protein 1-alpha (MIP-1α)), and several growth factors (*e.g.* vascular endothelial growth factor (VEGF) and transforming growth factor (TGF) β [15].

The recruitment of PMNs into the infarcted region begins with their adhesion to the endothelial cells in the vessel wall. PMNs migrate to the site of injury and secrete

superoxide anions; myeloperoxidase; MMPs -8, -9, and other proteolytic enzymes (e.g. serine elastase); and TIMP-1. These factors are secreted as a protective measure but actually results in extending the tissue damage [15–17]. MMP-9, in particular, is rapidly released within the early hours post-MI and positively correlates with PMN numbers [16, 18]. Serine elastase, stored within secretory granules of the PMNs, serves as a local MMP-9 activator [19]. By day 5 post-MI, PMNs begin to undergo apoptosis and are phagocytized by macrophages.

2.1.2 Macrophage infiltration—Macrophages originate from circulating blood monocytes, which are derived from CD34+ bone marrow progenitors [20]. The conversion of monocytes into macrophages begins with their adhesion to the vessel wall. This process is followed by the induction of several cytokines, including macrophage colony stimulating factor, TNFα, platelet derived endothelial cell growth factor, TGFα and β, IL-1, and insulin-like growth factor [21]. A predominant function of the macrophage post-MI is to facilitate wound healing and scar formation by phagocytosis of necrotic or apoptotic cells and by secretion of angiogenic molecules and growth factors. Macrophage migration into the injured myocardium is mediated by locally released chemoattractants [22]. Subsequently, activated macrophages produce cytokines, chemokines, and proteases. For example, macrophages are a source of MMPs -1, -2, -3, -7, -8, -9, -12, -14, and -28 as well as TIMPs -1, -2, -3, and -4 [20, 23].

Phagocytosis triggers TGFβ production in macrophages, which in turn downregulates MMP-9 activity by inducing TIMP-1 expression [20]. In addition to phagocytic roles, macrophages also contribute to angiogenesis by secreting factors that directly stimulate endothelial cell proliferation and by releasing MMPs. Moldovan and colleagues reported macrophage-derived MMPs degrade the ECM necessary for the formation of new vessels, which subsequently are inhabited by endothelial cells [24]. ECM degradation and chemoattractant production both stimulate and inhibit angiogenesis in the post-MI setting [25]. Several ECM proteins have angiogenic activities after being degraded into smaller fragments. For example, hyaluronic acid displays neovascularization properties *in vitro* and *in vivo* [26, 27]. Mathematical models show that ECM density influences the velocity of formation and branching of the vessels, while the alignment of ECM fibers dictate the orientation and shape of endothelial cells [28]. Degradation of matrix components at low ECM densities inhibits angiogenesis, whereas matrix degradation at high densities of ECM stimulates angiogenesis [29].

2.1.3 Myofibroblast activation—A major outcome of the inflammatory response is fibroblast activation, which ultimately coordinates scar formation. Activation involves the differentiation of fibroblasts into myofibroblasts (fibroblasts that express contractile proteins) [30]. Myofibroblasts activation can be observed by day 3 post-MI which corresponds to the timing of macrophage infiltration. Moreover, the positive correlation between macrophage number and collagen mRNA levels in the infarcted area was observed in a rat occlusion and reperfusion model 5 days post-reperfusion [31]. At later stages, the maintenance of the scar is coordinated by the continued presence of myofibroblasts [32, 33]. Among the factors that stimulate myofibroblast activation, macrophages are a primary source of activators, such as TGFβ, MMPs and TIMPs [20]. TIMPs stimulate fibroblast proliferation as well as phenotypic differentiation of fibrocytes into myofibroblasts, and this stimulation is independent of its MMP blocking activity [34].

In addition to ECM, fibroblasts and myofibroblasts synthesize many other factors relevant to LV remodeling, including interleukin (IL) -1, IL-6, TGFβ, connective tissue growth factor, tumor necrosis factor α (TNFα), angiotensin II, endothelin I, MMPs, and TIMPs [33, 35–38]. Myofibroblasts, under certain stimuli, activate or express a number of MMP family

subtypes, including MMP-1, -2, -9, -13, and membrane type MMP-14 [33]. MMP-2 secreted by myofbroblasts *in vitro*, and could be further induced by IL-1β, TNFα, TGFβ, mechanical load and oxidative stress [33]. Increased TIMP-2 is associated with increased fibroblast collagen synthesis, while TIMP-4 inhibits cell growth and triggers apoptosis of differentiated myofibroblasts [39]. TIMP-3 facilitates programmed cell death of both normal and injured myofibroblasts to prevent excessive myocardial fibrosis [34].

2.2 Extracellular response to MI

A number of ECM proteins are expressed in normal myocardium, including collagens, laminin, fibronectin, and low levels of matricellular proteins (e.g. thrombospondin-1 (TSP-1)) [40]. These ECM proteins play a central role in the physiological performance of the heart during various stage of development and in response to pathophysiological signals [41–43].

2.2.1 Collagen—The collagen found in normal LV includes types I, III, IV, V and VI [44]. The most abundant collagen type present in the LV is type I, which represents 70% of the total cardiac collagen [45]. Collagen fibers form a complex network to provide strength sufficient to support the three-dimensional structure surrounding cardiac muscle fibers and neighboring vascular tissues [46]. These fibers prevent excessive cardiomyocyte stretching due to the elastic energy that is saved during myocardial contraction. Additionally, collagen fibers allow the LV walls to resist the intracavitary pressure. Collagen is synthetized and secreted by fibroblasts in the form of a collagen precursor, which later is converted to a matured collagen under the effect of specific collagen proteinases [47].

Elevated amounts of collagen III are observed two days post-MI in rats [48]. This increase in collagen III is consistent with an early wound healing response, where collagen III is quickly laid down to provide structural support. However, the production of the main collagen component, collagen I, occurs more slowly. The increase in collagen III continues through the first 21 days post-MI, while collagen I production continues to remain high for more than 90 days post-MI [49, 50]. An increase in collagen contents is observed in both infarcted and distant region of the myocardium, although levels are a magnitude higher in the infarct [48].

The major causes that lead to cardiac rupture after acute MI are the misbalance between ECM degradation and synthesis, and alterations in the cross-linking of collagen.

Post-MI, there is a balance between ECM synthesis and degradation, and the fibroblast contributes to the synthesis part of the equation. If ECM degradation exceeds synthesis, LV aneurysm or rupture can develop. The later usually occurs after transmural MI. It may develop in the early period post-MI as well as in the later stages within the first 7 to 10 days when the infarct region is the most vulnerable [51]. Among many *in vivo* studies directed to determine the possible causes for cardiac rupture, the first place belongs to imbalanced system of collagen production and cross-linking [52]. If ECM synthesis exceeds degradation, increased LV stiffness can lead to heart failure. MMPs and TIMPs regulate both parts of the equation [53]. While many studies suggest that deletion of MMP-9 is beneficial in the early post-MI setting, therapeutic approaches of mediating direct effects on collagen have not been explored [54].

2.2.2 Fibronectin—In the normal myocardium, fibronectin is localized to the basement membrane of endothelial cells, myocytes, and smooth muscle cells [55]. Fibronectin binds growth factors, fibrin, heparin, collagens, and integrins [1]. In the MI setting, increased fibronectin deposition has been observed from 12 hours to 14 days after the infarction [55, 56]. In the MI setting, fibronectin is produced by ischemic cardiomyocytes and local

fibroblasts [55, 57–59]. Fibronectin acts as a chemoattractant for a variety of cell types involved in wound healing [57]. Fibronectin is also degraded by MMPs, and fibronectin fragments have been shown to have biological activity [60]. In particular, fibronectin has been shown an *in vivo* substrate for MMP-7 and the MMP-9 in post-MI LV [61, 62].

2.2.3 Laminins—Like fibronectin, laminin is localized to the basement membrane of endothelial cells, myocytes, and smooth muscle cells in the normal myocardium. Laminin links the extracellular space and the intracellular milieu by binding several cell-surface receptors including the integrins α6β1, α1β1, α2β1, and α3β1 [63]. In addition, laminin binds to sarcoglycans through the α-dystroglycan to form connections with intracellular dystrophin.

Laminin is a well-known MMP substrate associated with early remodeling post-MI [64]. Dinh *et al.* showed that laminin levels are higher in patients with severely reduced LV function and proposed laminin as a surrogate marker of ECM remodeling post-MI [65]. Horstmann and colleagues demonstrated a negative correlation between MMP-9 levels and intact laminin levels in patients with acute stroke, suggesting that laminin processing may be a key event in remodeling [66]. Laminin may help early survival after MI by preventing cardiac rupture but may also inhibit macrophage infiltration, which could delay wound healing [67]. Laminin improved the differentiation of adipose-derived stem cells *in vitro* to become cardiomyocytes, suggesting a role in stem cell biology [68].

2.2.4 Matricellular proteins—Secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin or BM-40, is restricted in adult to tissues that undergo consistent turnover or to sites of injury and disease [69, 70]. The capacity of SPARC to bind ECM, modulate growth factor efficacy, increase MMP expression, and alter cell shape as a counter-adhesive factor highlights the importance of SPARC in the response to injury [71]. SPARC binds to a number of ECM components, including collagen types I, II, III, IV, and V. SPARC binds to growth factors such as platelet-derived growth factor and vascular endothelial growth factor and modulates TGFβ activity to stimulate cell proliferation, migration, and differentiation [72].

SPARC levels increase significantly in the post-MI LV, to organize the formation of granulation tissue in the scar. The role of SPARC in LV remodeling follows the TGFβ signaling pathway, indicating a strong interaction with TGFβ [40]. SPARC deletion has beneficial effects in early post-MI LV function [70]. Impaired fibroblast activation in SPARC-deleted mice, however, suggested that long-term deletion would be detrimental. This turned out to be correct, as there was an increase in LV rupture rates in the longer post-MI period [73]. SPARC up-regulates MT1-MMP expression and MMP-2 activation, indicating that its post-MI roles are complex [74].

Thrombospondin-1 (TSP-1) is another matricellular protein with multiple biological functions associated with early remodeling post-MI. TSP-1 is expressed in α-granules of platelets and by endothelial cells and macrophages in a highly regulated manner [75]. TSP-1 possesses protective properties post-MI, however the exact mechanisms remain unclear [76].

TSP-1 increases at days 7–28 after ischemia and reperfusion, and TSP-1 clearly demarcates the infarcted area from the non-infarcted myocardium. TSP-1 deletion led to expansion of the post-MI inflammatory reaction and extension of granulation tissue formation into the non-infarcted remote region [76]. Moreover, TSP-1 inhibited MMP activity in the border region to control excessive ECM degradation [40].

2.2.5 Proteoglycan—Proteoglycans maintain the tensile strength of ECM and provide a reservoir for a number of growth factors. Biglycan, the major small chondroitin sulphate/dermatan sulphate, is involved in the interaction with other matrix components, especially type I collagen, and TGFβ [77, 78]. During MI, the expression of biglycans positively correlates with collagen mRNA expression during the fibrotic process in the LV [79]. Biglycan null mice showed alteration in scar formation in the mouse model of permanent coronary artery ligation 30 days post-MI [79].

Decorin, another proteoglycan base component, is widely distributed in the ECM and is associated with collagen fibrils. Decorin is upregulated during later fibrotic stages. The mRNA expression of decorin positively correlated with type I collagen mRNA levels in the infarct area in the rat model of permanent coronary artery ligation 7, 14 and 28 days post-MI [80]. Decorin was reported to mediate the fibrotic processes *via* suppression of TGFβ1 mRNA expression *in vivo* [81].

Syndecans belong to a family of cell-surface heparan sulphate proteoglycans. Its level is upregulated in the infarcted tissue and is associated with macrophage infiltration [82]. Syndecan null mice exhibited impaired cardiac function and showed increased mortality rate after MI in the model of permanent coronary artery ligation in acute stage post-MI. Although TGFβ1-dependant cell signaling was preserved in these mice, the cell migration, fibronectin-induced cell signaling, and differentiation in cardiac fibroblasts were defective [83].

3 MMPs as therapeutic targets

The generation of the smallest possible scar that does not affect the biomechanics of the heart requires a carefully balanced activity of MMPs and TIMPs in the infarcted heart. Multiple MMPs are elevated post-MI, and roles for several of these MMPs have been elucidated. Well-healed infarcts contain large amounts of ECM, which can occupy up to 80% of the infarct area [84]. MMP-3 is an upstream activator of other MMPs and may contribute to aneurysm formation in the infarcted LV [85, 86]. MMP-7 increases the potential for post-MI arrhythmias, through cleaving connexin-43 [87]. MMP-9 levels increase in multiple animal models of MI and positively correlate with infarct rupture rates in humans [88]. MMP-12 is highly expressed in macrophages and may also play a role in post-MI remodeling [85]. Therefore, there remains a strong rationale to study MMPs as possible therapeutic targets in the MI setting.

3.1 Direct MMPs inhibitors and selectivity

The search for the first orally bioavailable small molecule MMP inhibitor began in the late 1970s and was directed at treating arthritis [89]. At that time, only a few MMPs had been identified, and the first generation of MMP inhibitors (e.g., batimastat and galardin) had poor bioavailability that substantially limited their development [90]. Later, second generation of MMP inhibitors was also reported to possess numerous side effects [91]. In the past decade, both macromolecular MMPs inhibitors (monoclonal antibodies and natural TIMPs) and small molecules (synthetic and natural products) have been tested as potential therapeutic agents [92, 93].

A large body of literature now supports a key role for the two motifs (S1’ subsite and P1’ residue) in the interactions of MMPs with their substrates (or inhibitors). X-ray crystallographic studies have classified MMPs into two broad structural classes dependent on the depth of S1’ pocket, which was suggested as the selectivity pocket for MMP inhibitors [94]. This selectivity pocket was later shown to be relatively deep for some MMPs, but partially or completely blocked for others due to differences in amino acid

chains forming the pocket. Therefore, developing selective inhibitor of MMPs was rather limited in the application towards deep pocket enzymes over short pocket enzymes, *via* incorporation of an extended P1' group. In this case, the presence of the smaller P1' group led to wide spectrum selectivity (Figure 1).

Two major classes of inhibitors were identified from these structural assessments: hydroxamate-based inhibitors and non-hydroxamate-based inhibitors. The main idea was based on a creation of a compound that would substitute the active site of the active MMP with a peptide-like structure [92]. In hydroxamate-based inhibitors, most of the small molecules use hydroxamate as their zinc-binding site. Hydrogen bonds between hydroxamate-NH group and carbonyl oxygen Ala128 this interaction is also known to contribute to the binding. The interactions observed were reported to be productive without any adverse effect [95]. Hydroxamate inhibitors are further grouped into substrate-analogue peptides, such as succinyl, sulphonamide, phosphinamide hydroxamates [96]. Non-hydroxamate inhibitors have limited use due to a general lack of specificity.

Another step in the MMP inhibitor field has been to develop inhibitors based on mechanism. Mobashery *et al.* demonstrated a novel approach to highly selective gelatinase inhibition through coordination of the thiirane group of the inhibitor with the active zinc-site of the MMP [97]. This coordination caused conformational change of the MMP and the covalent attachment of inhibitor to the active-site Glu of the MMP [98]. From the many MMP inhibitors tested to date, only doxycycline (Periostat) has been approved by the FDA [99].

3.2 The MMP inhibitory properties of currently used post-MI medications

While selective and specific MMP inhibitors have not been successfully tested and applied to the post-MI setting, many of the drug therapies currently used to treat MI have indirect MMP inhibition effects (Figure 2). These effects are summarized below in Table 2.

3.2.1 Thrombolytic agents and anticoagulants—In clinical guidelines, acute vascular events such as acute MI and acute ischemic stroke share similar treatment approaches, namely the timely use of thrombolytic agents. MMP-3, -9, and -14 levels increase in the serum or plasma following treatment with tissue plasminogen activator after acute ischemic stroke in both humans and a rat model [66, 100]. Alteplase treatment increases MMP-2 and MMP-9 concentrations in patients with ST segment elevation acute MI [101]. The rise in MMP-9 levels suggested that MMP activity may be responsible for the failure or thrombolytic agents [102].

Thrombolysis is often accompanied with anticoagulant therapy. Three main classes of anticoagulants are used for MI therapy: heparins, synthetic heparins, and direct thrombin inhibitors [103, 104]. Anticoagulant therapy increases MMP-9 in blood samples of stroke patients [105, 106]. At the same time, anticoagulant therapy increases TIMPs levels in the plasma. Manello *et al.* reported that heparin directly activates MMPs and also increases the release of TIMP-2 to block their activity [107].

3.2.2 ACE inhibitors and angiotensin II receptor inhibitors—Angiotensin converting enzyme (ACE) inhibition is an effective post-MI treatment [108]. Because the regions close to the zinc in ACE are very similar to analogous regions in other metalloproteases, several ACE inhibitors have high affinities for MMPs, suggesting a direct inhibitor role. Yamamoto *et al.* demonstrated strong MMP-9 inhibition by ACE inhibitors in a post-MI animal model [109, 110]. ACE inhibitors and angiotensin II receptor inhibitors: ACE inhibitors directly bind to MMP-9 at the S1' subsite, which forms a deep hydrophobic pocket compatible with hydrophobic moieties present in ACE inhibitors. The Yamamoto lab has also shown that different ACE inhibitors have varying levels of inhibitor activity

depending on their affinities. Lisinopril is stabilized in the active site of MMP-9 by specific hydrogen bonds and hydrophobic interactions, while imidapril possesses a higher affinity to MMP-9, probably due to a stronger interaction with the S1 site [110]. This team has shown that captopril directly binds to the MMP-9 active site [111]. Perindopril decreases MMP-9 activity and cytokine production in peripheral blood in the acute period of ischemic stroke and MI, while trandopril and valsartan supresses MMP-9 activity and cardiac remodeling post-MI [112].

In addition to ACE inhibition, blocking the angiotensin II receptor has also been shown to attenuate remodeling. Harada *et al.* demonstrated that angiotensin II type 1A receptor null mice displayed less LV remodeling and improved survival post-MI [113]. Irbesartan, an angiotensin II receptor antagonist, inhibits MMP activity in patients with symptomatic carotid artery stenosis [114]. Inhibiting both angiotensin II type 1 and type 2 receptors with Sar1-Ile8-Ang II reduces collagen type I and elastin deposition but also increases vascular stiffness, fibronectin, and MMP-2 activity [115]. Olmesartan improves LV remodeling in apo E null mice by inhibiting nuclear factor κ-B (NF-κB) and MMP-9 activities [116]. Yang and colleagues reported that valsartan decreased levels of MMP-2, -3, and -9 post-MI [117]. More studies are needed, however, to further explore the long-term effects of these inhibition strategies.

3.2.3 Aldosterone antagonists—Aldosterone antagonists are recommended for acute MI patients who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction. According to the National Institutes for Health and Clinical Excellence recommendations, treatment with an aldosterone antagonist should be initiated within 3–14 days post-MI, preferably after ACE inhibitor therapy has been initiated [118].

Aldosterone induces MMPs activity through the activation of mineralocorticoid receptor, protein kinase, and reactive oxygen species dependent activation of mitogen/extracellular signal-regulated kinase and extracellular signal-regulated kinase pathway [119]. Aldosterone antagonists demonstrate indirect effects on MMP activity and collagen deposition post-MI. Spironolactone prevents cardiac collagen deposition post-MI in rodents [120]. Spironolactone and hydrochlorothiazide both demonstrated an ability to reduce vascular MMP-2 activity and expression in a model of renovascular hypertension [121]. Moreover, prolonged treatment with spironolactone for 24 weeks in patients with heart failure decreased the level of MMPs and improved cardiac function [122].

3.2.4 Beta-blockers—Beta-adrenergic antagonists are another class of medications commonly used in post-MI patients with developing heart failure. Beta-blockers possess antioxidant, anti-proliferative, and free radical scavenging effects, which may alter MMP abundance [123]. Carvedilol reduces plasma MMP-9 levels in younger patients with idiopathic dilated cardiomyopathy and improves LV remodeling in a mouse model of acute myocarditis [124, 125]. While carvedilol has been shown to inhibit MMP-2 and -9, it also increases MMP-8 and -13, indicating that the connection between β blockers and MMP activity is complex [126, 127]. Atenolol in supra-therapeutic doses reduces MMP activity and prevents ventricular stiffening in a dog model of pacing-induced cardiac dysfunction [128]. Short-term beta-adrenergic blockade decreases MMP-9 promoter activity in the human ECV304 endothelial cell line and plasma gelatinase activity in patients with heart failure [129].

3.2.5 Statins—Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are broadly used to treat patients with high cholesterol levels [130]. Statins also block the synthesis of isoprenoid intermediates, which serve as lipid attachments for a variety of intracellular signaling molecules. In particular, the rho-family small GTP-binding

proteins, whose proper membrane localization and function are dependent on isoprenylation, are blocked by statins. [131]. Statins improve endothelial cell function, inhibit proliferation and migration of smooth muscle cells, and decrease vascular inflammation. Statins inhibit MMPs by suppressing macrophage infiltration [132]. Luan *et al.* demonstrated that statins stabilize the atherosclerotic plaque by inhibiting several MMPs, including MMP-1, -2, -3 and -9 [133]. Statins, however, can also trigger the upregulation of macrophage elastase (MMP-12) [134]. Pravastatin reduces serum soluble CD40L, C-reactive protein, MMP-2, and MMP-9 levels in post-MI patients [135–137]. Turner *et al.* demonstrated that simvastatin suppresses TNF-α-induced invasion of human cardiac myofibroblasts by both MMP-9-dependent and -independent mechanisms, indicating that statins likely have effects on MMPs through multiple pathways [138].

3.2.6 Non-steroid anti-inflammatory drugs (NSAIDs)—NSAIDs occupy an important place in treatment of patients presenting with acute MI. NSAIDs suppress gene expression of MMPs SP1 transcription factor binding site [139]. Experimentally, however, no studies have been performed to investigate the potential use of NSAIDs as MMPs inhibitors in the MI setting. Aspirin, the most commonly used NSAID among patients with myocardial infarction and heart failure, suppresses MMP-1 in isolated human coronary endothelial cells but did not affect MMP-2 or -9 levels [140, 141].

4 Conclusion

LV remodeling post-MI involves MMP activity at every step. MMPs coordinate key biological activities, including inflammation and scar formation. The alteration in MMP and TIMP expression may lead to undesired consequences, resulting in the development of a variety of possible complications, including sudden cardiac death, LV rupture, or the development of congestive heart failure. The potential roles of MMPs as therapeutic targets in the MI setting, therefore, are warranted. Many direct inhibitors of MMP transcription and activity have been tested; however, none of these inhibitors have translated to clinical relevance for the post-MI patient. At the same time, many of the currently used medications to treat MI influence MMP and TIMP activity. Identifying selective MMP inhibition strategies for the post-MI patient, particularly therapies that limit the progression to heart failure remain a highly desired goal.

Acknowledgments

We acknowledge support from NIH/NHLBI HHSN 268201000036C (N01-HV-00244) for the San Antonio Cardiovascular Proteomics Center and R01 HL075360, the Max and Minnie Tomerlin Voelcker Fund, and the Veteran's Administration (Merit) to MLL.

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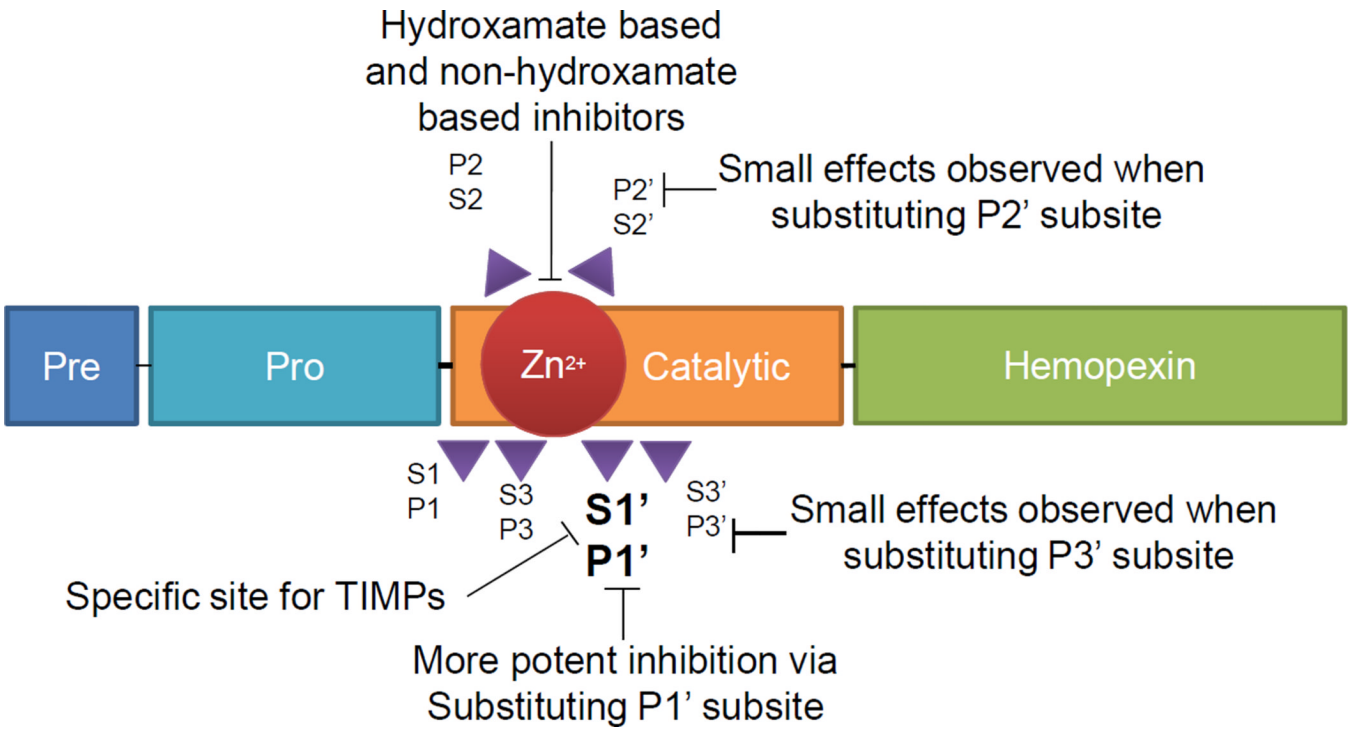

Figure 1.
MMP subsites as targets for different classes of MMP inhibitors. Pre – a signal sequence pre-domain, Pro – pro-catalytic domain, Catalytic – catalytic domain, Zn2+ - metal center of the catalytic domain, Hemopexin – hemopexin-like domain (absent in MMP-7 and MMP-26) [142, 143].

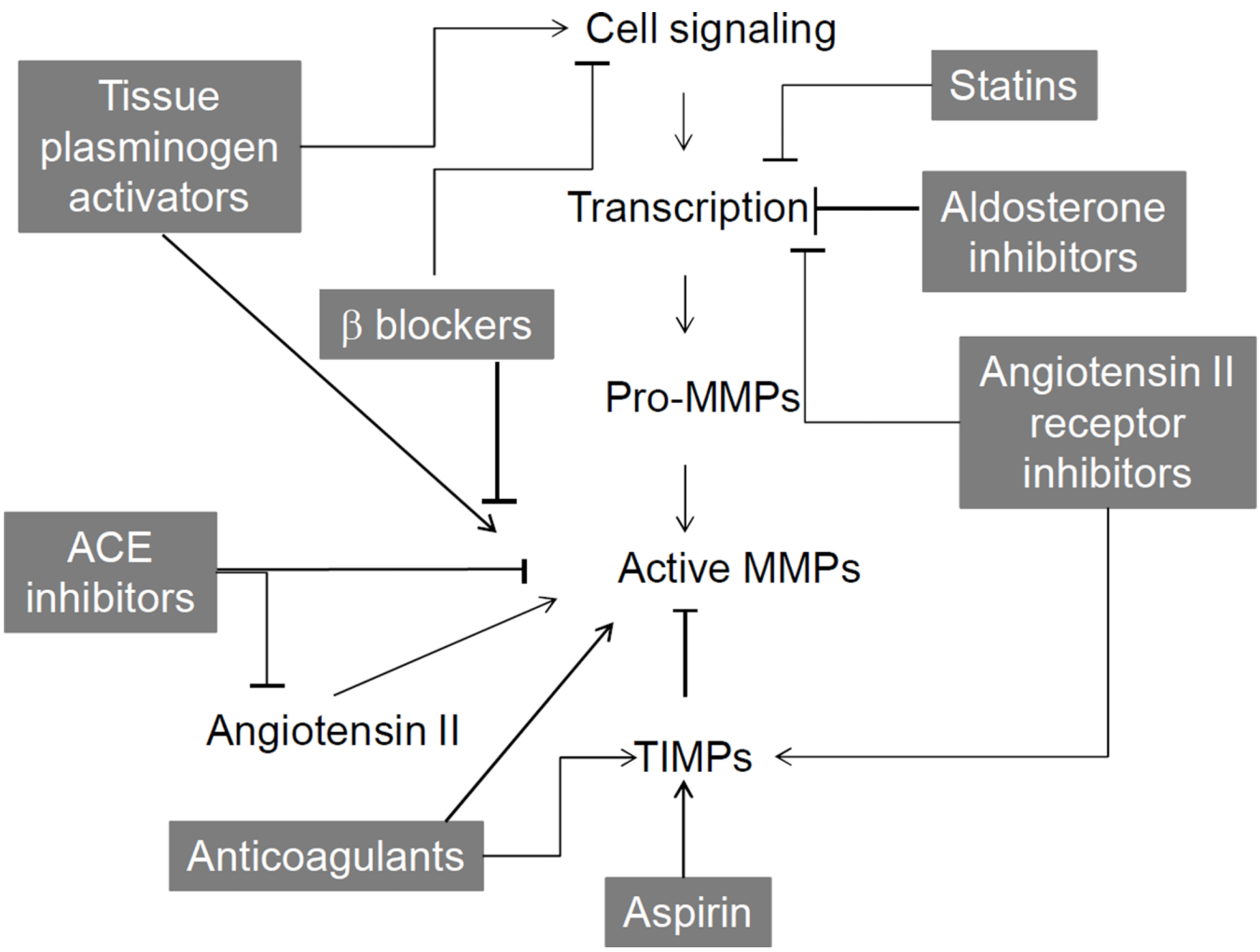

Figure 2.
Medications used post-MI that directly or indirectly affect MMP production or activity.

Table 1

Cell functions in the post-MI left ventricle (LV) [20, 30, 33, 144–152].

Cell type	Functions
Neutrophils	▪ produce pro-inflammatory cytokines, chemokines, and growth factors ▪ release proteolytic enzymes, including MMPs-8 and -9 ▪ mediate tissue damage ▪ produce TIMP-1
Macrophages	▪ phagocytose necrotic myocytes and apoptotic neutrophils ▪ produce cytokines and growth factors ▪ secrete angiogenic molecules ▪ produce TIMPs ▪ trigger myofibroblast differentiation and activation
Fibroblasts	▪ produce extracellular matrix, including interstitial collagens, necessary for scar formation ▪ contract the LV infarct zone ▪ produce MMPs, cytokines, growth factors ▪ produce TIMPs

Table 2

Medications used in post-MI patient management, their applications, and effects on MMPs and TIMPs [23, 58, 116, 92, 94, 95, 100–102, 105, 107, 109, 110, 117, 120, 143–150, 153–160].

Medication	Applications	MMP Effects
Thrombolysis- tissue plasminogen activators	Catalyze the conversion of plasminogen to plasmin, the major enzyme responsible for clot breakdown	↑ MMP-1, -2, -3, -9, -12, -14 ↑ TIMP-1, -2
Anticoagulants	Bind to and activate anti-thrombin III. Activated anti-thrombin III inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa.	↑ MMP-2 and -9 release in blood ↑ TIMP-2 ↓ TIMP-1
Angiotensin converting enzyme Inhibitors	Inhibit the angiotensin-converting enzyme to lower blood pressure	↓ MMP-1, -2, -3, -9 ↑ TIMP-1
Angiotensin II receptor inhibitors	Modulate the renin-angiotensin-aldosterone system to lower blood pressure	↓ MMP-2, -3, -9 ↑ TIMP-1
Aldosterone antagonists	Antagonize aldosterone at the mineralocorticoid receptor level	↓ MMP-1, -2, -9 ↑ TIMP-2
Beta-blockers	Block endogenous catecholamines, including epinephrine (adrenaline) and norepinephrine (noradrenaline)	↓ MMP-2, -9 ↑ TIMP-1, -2, -3
Statins	Inhibit HMG-CoA reductase to lower cholesterol levels; anti-inflammatory effects	↓ MMP-1, -2, -9, -12 ↑ TIMP-1
Non-steroidal anti-inflammatory drugs (aspirin)	Irreversibly inhibit COX-1-mediated platelet aggregation	↓ MMP-1 ↑ TIMP-1