Review

Relevance of matrix metalloproteinases and their inhibitors after myocardial infarction: A temporal and spatial window

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Abstract

The post-myocardial infarction wound repair process involves temporarily overlapping phases that include inflammation, formation of granulation tissue, scar formation, and overall left ventricle (LV) remodelling. The myocardial extracellular matrix (ECM) plays an important role in maintaining the structural and functional integrity of the heart and is centrally involved in wound repair post-myocardial infarction (MI). The main proteolytic system involved in the degradation of the ECM in the heart is the matrix metalloproteinase (MMPs) system. The present review will focus on the importance of the unique temporal and spatial window of MMPs and their inhibitors (TIMPs) within the different wound healing phases post-MI. It summarizes (1) the MMP/TIMP levels at different time points post-MI, (2) the alterations seen in post-MI healing in genetically modified mice, and (3) the effects and limitations of therapeutic MMP-inhibition post-MI.

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1. The normal cardiac matrix

The extracellular matrix (ECM) is a multifunctional complex of proteins and proteoglycans assembled in a highly organized manner that contributes to the structural and functional integrity of the heart [1].

1.1. ECM-proteins

The extracellular matrix (ECM) surrounding the cardiomyocytes, fibroblasts, capillaries and larger vessels is a vital component of the heart. It is composed of basic structural elements such as collagen and elastin, and more specialized proteins, like fibrillin, fibronectin, proteoglycans and matricellular proteins [2]. While the ECM is ubiquitous, its composition varies significantly from organ to organ, and is carefully regulated [3].

The interstitial collagen fibers form a wide network that weaves throughout the myocardium, providing supportive scaffolding for myocytes and blood vessels, thereby preserving myocardial thickness and architecture [4–8]. As a whole the ECM provides an environment for cells to migrate, grow and differentiate, establishing a connection between cell and tissue function [2]. The cardiac fibroblast is the most abundant cell type in the myocardium. Cardiac fibroblasts are the main regulators of ECM levels through at least three mechanisms: (1) by regulating the synthesis and deposition of matrix molecules; (2) by mediating matrix degradation and turnover by production and release of MMPs and TIMPs; and (3) by maintaining mechanical tension on the collagen network [9]. In the normal heart, ECM synthesis and degradation, also called ECM remodelling, is a continuous and tightly regulated process.
1.2. Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteases that are involved in the turnover of the ECM [10]. They mediate a wide variety of biological processes including normal embryonic development and wound healing, as well as pathological processes [11]. The MMP family can be divided into five classes based on their substrate specificity and/or structure (Table 1, reviewed in [11]). The first four groups include the collagenases, the gelatinases, the stromelysins and elastase or MMP-12. These first 4 groups of MMPs represent the secreted MMPs and are produced as a latent proform. Pro-MMPs bind specific ECM proteins and remain enzymatic inactive until the propeptide domain is cleaved through the cysteine switch mechanism [12,13]. Pro-MMPs are activated by serine proteases, trypsin, chymotrypsin, and plasmin [13–15]. In addition, several MMPs are substrate for other pro-MMPs, leading to autocatalytic activation of pro-MMPs. Therefore, activation of a few select enzymes can launch a cascade of proteolytic activity of many others.

The last group of MMPs includes the membrane-type MMPs (MT-MMPs), a unique class of MMPs. Unlike the secretable MMPs, MT-MMPs are activated once positioned in the cell membrane. MT-MMPs retain their propeptide domain, which is required for TIMP binding and also for subsequent MMP activation [16].

A large reservoir of recruitable MMPs exists within the cardiac matrix, which upon activation can result in a rapid surge of ECM proteolytic activity. All cell types found in the myocardium, either under basal conditions (myocytes, fibroblasts, endothelial cells) or in response to an inflammatory stimulus (neutrophils and macrophages) express one or more types of MMP species (Table 1). The present review will focus on their role in the myocardial remodelling process post myocardial infarction.

1.3. TIMPs, the endogenous MMP inhibitors

Because MMPs degrade various components of the ECM, a tight regulation of MMP activity is essential to prevent excessive matrix degradation. A group of endogenous proteins, tissue inhibitors of metalloproteinases (TIMP-1, -2, -3 and -4), firmly regulate MMP activity (Table 1) [17–19]. TIMPs bind to the active site of the MMPs in a stoichiometric 1:1 molar ratio, thereby blocking access to extracellular matrix substrates. Although the TIMPs are expressed in a variety of cells in different organs, TIMP-4 shows a high level of expression in human myocardial tissue, and is therefore also called cardiac inhibitor of MMPs (CIMP) [18,20].

The primary action of TIMPs is to inhibit matrix metalloproteinases, but numerous studies have reported cell growth-promoting, anti-apoptotic, steroidogenic and anti-angiogenic activities (reviewed in [11,21]), which are in part independent of MMP inhibition. Importantly, both TIMP-1 and TIMP-2 may stimulate the growth of fibroblasts in vitro [11,21,22] apart from their MMP inhibition. In vitro, TIMP-
2 has a predominant role over TIMP-1 in stimulation of collagen production by cardiac fibroblasts, independent of its ability to inhibit MMPs. Thus, TIMPs may favour cardiac fibrosis not just by inhibiting MMPs, but also by separate direct pro-fibrotic mechanisms.

1.4. Matricellular proteins and MMPs

Matricellular proteins are a group of proteins that modulate the cell-matrix interactions, and appear to be the local effectors of a number of chemical and physical stimuli during cardiac stress. Their expression is low to absent in local effectors of a number of chemical and physical stimuli modulate the cell-matrix interactions, and appear to be the best described members of the matricellular proteins concerning their importance in the injured heart [24,25]. Interestingly, some matricellular proteins have the ability to regulate the expression of MMP’s. OPN is able to inhibit interleukin-1beta induced MMP activity in cardiac fibroblasts [26], whereas others have demonstrated that OPN increases MMP activity in non-cardiac cells [27,28]. The exact role of OPNs in MMP regulation after MI, however, requires further investigation. TSP2 deficient hearts show increased pro-MMP-2 and -MMP-9 activity after angiotsin II infusion, compared to wild-type mice [25]. TSP2 is capable of binding both pro-MMP-2 and MMP-2, and this complex can be endocytosed via LRP-1 [29]. This may explain the increased activity of pro-MMP-2 and -MMP-9 after angiotensin II infusion in TSP2 null mice, and the cardiac rupture and dilatation seen in TSP2 null mice after angiotensin II infusion and MI.

2. MMPs and TIMPs after myocardial infarction: “a temporal and spatial window”

Acute myocardial infarction (MI) is one of the most common diseases in the developed world [30]. MI occurs when a previously atherosclerotic coronary artery becomes totally occluded due to thrombus formation, resulting in irreversible cell death and tissue necrosis [31]. Complex architectural alterations following MI, also called LV remodelling, involve both the infarcted and non-infarcted LV myocardium. LV remodelling determines myocardial performance and residual LV function [32]. This is a process that progresses over months and even years. In short term after MI endogenous molecular, cellular and physiological responses are triggered. This acute remodelling process is involved in cardiac failure, life-threatening arrhythmias and even fatal cardiac rupture. In the long term, remodelling leads to LV dilatation, resulting in increased myocardial wall stress and work and ultimately causing decreased functional reserve and progressive congestive heart failure (CHF) [33–35]. Chronically after MI, heart failure has an escalating cardiovascular burden worldwide, and the 1-year mortality remains high at 25% to 40% [36]. Therefore, novel therapeutic strategies to prevent this negative outcome are compulsory.

2.1. Expression studies

Cardiac repair after a MI is a highly complex process, that involves temporarily overlapping phases that include inflammation, new tissue formation and tissue remodelling [37,38] (Fig. 1). A unique temporal and spatial profile of MMPs and TIMPs on the remodelling process has been determined through the use of several post-MI animal models, and is described in detail below (Table 2).

2.1.1. Early wound healing: 0–7 days post-MI

When a previously atherosclerotic coronary artery becomes totally occluded due to thrombus formation, the LV tissue becomes hypoxic and a MI occurs (Fig 1) [31]. During this stage of healing, activated MMPs degrade the pre-existing ECM, disrupting the fibrillar collagen network and allowing inflammatory cells to migrate into the infarct tissue to remove necrotic myocytes [38,39]. Subsequently these inflammatory cells release MMPs, cytokines, growth factors and angiogenic factors (Fig 1, Tables 1 and 2). MMP-9 expression is present in its active form within 24 h following myocardial infarction in mouse, and it is mainly expressed in infiltrating neutrophils and macrophages of the infarct area [40–42]. On day 3, MMP-9 activity further increases in non-infarcted, border and infarcted myocardium of mice [43]. Neutrophils are thought to be the predominant source of MMP-9 during the early inflammatory response [37,41,42,44]. After reaching its peak-activity, MMP-9 gradually decreases, whereas MMP-2 activity starts to increase rapidly at 4 days, reaching a maximum by 7 days, remaining elevated afterwards [37,41,42,44]. During the early healing process after MI, activated macrophages, fibroblasts as well as myocytes appear to be the source of MMP-2 [41,45,46]. MMP-3 expression is also up-regulated shortly after MI, however not until 48 h after injury [46]. In rabbits, MMP-3 expression reaches its maximum at 4 days post-MI and remains upregulated throughout the 14-day time-course after MI [46]. Here both MMP-9 and MMP-3 expression are detected in myocytes within the infarct 2 days after coronary artery occlusion. In rats, MMP-1 mRNA increased markedly at the infarct-site on day 3 and declined to normal levels by day 7 [47]. This increase is reflected in the time course of cardiac MMP-1 activity after MI, which significantly increases on day 3 and reaches a peak on day 7. Fibroblast-like cells are the major source of MMP-1 in rats [48]. No elevation of MMP-1 was observed at later time points.

Despite their possible beneficial effects in post-MI healing, activation of MMPs may also promote detrimental actions on infarct healing. MMP-9 and MMP-2 activity increases in a time-dependent manner and is temporally related to cardiac rupture [41], an acute lethal complication accounting for 5–30% of in-hospital mortality after MI [30].
This deleterious effect of MMPs may be the result of an inappropriate removal of myocardial ECM components and disruption of the myocyte–matrix interface network, causing myocyte misalignment and slippage. The latter may not only result in cardiac rupture, but more importantly also cause LV dilatation and dysfunction [49–52].

A loss of TIMP-mediated control has been reported in LV remodelling following MI (Table 2). In both mice and rats, expression of TIMP-1 mRNA significantly increases within 3 days following MI [37,47,53] and reaches a peak by day 7. The protein level of TIMP-1, however, only increases in a later stage of post MI healing, at 2 and 16 weeks post-MI [47,53], suggesting post-translation processing of TIMP-1 in the heart. No elevation is seen in the non-infarcted myocardium [47]. In rabbits, however, protein expression of TIMP-1 is reduced in the infarcted tissue for the first 4 days following infarction and then returns to its normal level [46].

Like TIMP-1, TIMP-2 mRNA significantly increases during the early phase post-MI, and TIMP-2 protein levels do not change until a later time point, on 2, 5 and 16 weeks post-MI in rats [53], also indicating post-translation processing of TIMP-2. TIMP-4 mRNA does not change after MI, but its protein levels drop substantially at 1 week post-MI, where after it restores to its basal level [54].

There seem to be some discrepancies in the expression and/or activity pattern of MMPs and TIMPs between different species after MI [41,46,53]. In contrast to persistent MMP-2 and -9 upregulation in mice within 7 days, MMP-9 activity returned to basal level in rabbits at 4 days with only a minor MMP-2 upregulation [46]. In rats, MMP-2 protein levels were already elevated within 24 h post-MI, whereas MMP-9 was elevated until 16 weeks post-MI [53].

All together, these studies suggest a shift of the MMP/TIMP balance towards increased proteolytic activity and
ECM degradation within the first few days following MI. In particular, increased MMP-9 and MMP-3 within the first 24–48 h after MI may be involved in the initial proteolytic degradation of the infarcted heart, contributing to the rapid matrix degradation and overall dilatation following MI [46,52,55].

2.1.2. Granulation and early remodelling phase: 7–21 days post-MI

Granulation tissue formation constitutes a critical step in infarct repair. Macrophages phagocytose the necrotic myocardium, and, concomitantly, myofibroblasts and endothelial cells proliferate and migrate into the infarct zone [38,56–59]. The necrotic cardiac tissue is then replaced by granulation tissue, a provisional tissue with a matrix rich of collagens, proteoglycans and matricellular proteins such as osteopontin [23] and fibronectin [60,61]. As repair proceeds, myofibroblasts deposit a network of collagen, and the provisional matrix is reabsorbed. Extensive apoptosis of granulation tissue cells finally results in a thin, hypocellular scar [62,63]. Concomitantly there is a hypertrophic response of the non-infarcted cardiac myocytes, further influencing the myocardial performance (Fig. 1).

After reaching their peak within the first 7 days post-MI, both MMP-9 and MMP-2 activity decreases, but still remains significantly elevated between 7 and 14 days post-MI compared with baseline, both in mouse and rat [41,45,53,64]. Proliferation and infiltration of myofibroblasts may result in increased levels of MMP-2 at 14 days post-MI [41,45]. MMP-3 and MMP-13 activity remains elevated within this time-window post-MI [46,65], but the source of these MMPs remains unclear. MMP-8 protein levels, localized to neutrophils, increases starting at 2 weeks post-MI, staying elevated on 5, 8 and 16 weeks post-MI [53,66].

Following MI in rats, TIMP-1 and TIMP-2 mRNA stays markedly elevated on day 14 and 21 at the site of MI and the inflamed pericardium, but not in non-infarcted myocardium [47,53,67]. TIMP-1 and TIMP-2 protein levels do not increase until 2 weeks post MI, but then gradually decrease. In rabbits, TIMP-1 protein expression stays at his basal levels on 7 and 14 days post-MI [46].

2.1.3. Late remodelling phase:>21 days post-MI

Left ventricular (LV) regional remodelling is a continuous process that last for months to years after the acute injury [32,33,68–71], and which will eventually lead to the development of CHF. MMPs and TIMPs continue to have an important role in the process of chronic LV remodelling (Fig. 1 and Table 2).

In a sheep model of post-MI the regional levels of myocardial MMPs and TIMPs have been screened in detail 8 weeks post MI [66]. A region specific portfolio of MMPs is induced after MI and is accompanied by a decline in TIMP levels, indicative of a loss of MMP-inhibitory control. MMP-1 and MMP-9 levels are significantly reduced within the border and MI regions at 8 weeks post-MI, whereas MMP-2 levels increases substantially within the border and MI regions [66], suggesting that MMP-9 mainly is associated with early post-MI events [40–42]. In contrast to the acute MI setting, a different set of MMPs emerges at 8 weeks after...
MI. Interestingly, MMP-8, localized to neutrophils, is increased by over 6-fold within the border and MI regions at 8 weeks after MI [66], suggesting that MMP-8 is associated with a more chronic inflammatory response [35,38]. The levels of the collagenses MMP-13, and MT1-MMP are increased by nearly 3-fold in both border and MI region 8 weeks post-MI. MMP-3 is reduced within the MI region and MMP-7 falls within the border and MI regions 8 weeks post-MI. TIMP abundance decreases significantly in the border region after MI, and TIMP-1, -2 and -3 fall to undetectable levels within the MI region. Similar results are obtained by the use of a pig model of MI [72,73].

Together, these data clearly demonstrate that targeting of the regional imbalance between specific MMPs and TIMPs within the post-MI myocardium holds a therapeutic potential. However, future studies that directly modify regional expression of MMPs and TIMPs will be necessary to define the relationship between MMP activation and expression and regional expansion after MI.

2.2. Genetic evidence

The particular importance of MMP-9, MMP-2, MMP-1, TIMP-1 and TIMP-3 during different phases of myocardial healing and remodelling after MI have been established by the use of knockout and transgenic mice (Table 1).

MMP-9 deficiency in mice retarded the wound healing process after MI [45], marked by reduced leukocyte influx into the infarct and by larger residual necrotic areas. The lack of proteolytic activity of MMP-9 almost completely protected against infarct rupture. Others demonstrated that targeted deletion of MMP-9 also attenuated LV cavity enlargement until at least 15 days after experimental MI in mice [65]. Limited LV dilatation was accompanied by a reduced inflammatory response and a decrease in collagen deposition in the infarct of MMP-9 deficient mice, suggesting that MMP-9 may mediate the molecular organization of the collagen network. As with all knockout experiments, however, these results do not necessarily imply that inhibition of MMP-9 post-infarct will lead to improved LV remodelling [74]. Un-operated MMP-9 deficient mice had increased expression of MMP-3 and MMP-13 in ventricular tissue compared to wild type [65]. Presence of compensation by MMPs and overlapping MMP substrates should encourage caution when MMP deletion experiments are interpreted.

MMP-2 deficient mice had a significantly better survival rate than wild type mice after MI, which was mainly attributed to the inhibition of early cardiac rupture and development of subsequent LV dysfunction at 28 days after MI [64]. Targeted deletion of MMP-2 attenuated the degree of post-MI LV dilatation during the late phase, but did not alter the expansion of the infarct. MMP-2 deficiency also decreased phagocytic removal of necrotic cardiomyocytes, and suppressed degradation of ECM components, including laminin and fibronectin [75]. No differences were seen in the incidence of cardiac rupture, leukocyte infiltration and collagen deposition within the first 14 days post-MI in MMP-3 and MMP-12 knock out mice [45].

Next to the MMM-9, -2, -3 and MMP-12 knockout mice, a transgenic mouse that constitutively expressed human MMP-1 in the heart was created (adult mice do not express MMP-1 protein) [76]. Initially, at 6 months of age, these mice developed compensatory myocyte hypertrophy and an increase in cardiac collagen due to an elevation in transcript levels of collagen type III. Later, at 12 months of age, these mice had a decrease in interstitial collagen accompanied by ventricular dysfunction. This model specifically demonstrated that overexpression of at least one MMP can cause cardiac dilatation and dysfunction.

On the other hand, gene deletion of TIMP-1 in mice caused spontaneous LV dilatation at 4 months of age, suggesting that constitutive TIMP-1 expression participates in the maintenance of normal LV myocardial structure [77]. Fourteen days after MI, TIMP-1 deficient mice displayed an exacerbated healing response, with increased end-diastolic pressure and volume, increased LV weight and myocyte cross sectional areas [78]. This loss of regulatory role in the post-MI remodelling induced by TIMP-1 gene deletion and the subsequent accelerated myocardial remodelling was pharmacologically “rescued” by MMP inhibition [79]. Thus, TIMP-1-deficient mice showed an amplified hypertrophic response and adverse LV remodelling, thereby emphasizing the importance of local endogenous control of cardiac MMP activity by TIMP-1 in the early post-MI remodelling process [78–80]. Finally, loss of TIMP-3 function in mice triggered spontaneous LV dilatation, cardiomyocyte hypertrophy, and contractile dysfunction [81].

In conclusion, these studies clearly provide evidence that disruption of the balance between ECM synthesis and degradation plays a critical role in the post-MI healing process and LV remodelling.

3. MMP/TIMPs and their therapeutic angle

Left ventricular (LV) remodelling after MI leads to progressive ventricular dilatation, fibrosis and decreased cardiac performance [4,82]. The degree of the detrimental remodelling predicts morbidity and mortality [32,83]. Despite the use of agents such as angiotensin converting enzyme-inhibitors (ACEI), angiotensin II type 1 receptor blockers (ARBs) and β-adrenergic-blocking agents, heart failure can still progress. One of the major therapeutic goals of modern cardiology is to design strategies aimed at minimizing myocardial necrosis and optimizing cardiac repair and remodelling following myocardial infarction. One such strategy is matrix metalloproteinase (MMP) inhibition, based on the extensive evidence on their role in remodelling of the infarcted and the remote non-infarcted area of the heart after MI. Recent data show that the use of the existing therapeutical agents are associated with changes in...
the MMP/TIMP balance (Table 3). However, the main challenge and difficulty of MMP-inhibition after MI is to target a specific portfolio of MMPs at specific time points after MI.

3.1. Broad-spectrum MMP-inhibition (MMPi)

Orally active non-selective MMP inhibitors, termed broad spectrum MMP inhibitors (MMPi) [67,73,84–87], as well as selective MMP inhibitors (sMMPi) [42,72,88] were the first to be used in several animal models of MI, resulting in attenuation of the LV remodelling process.

Rhode et al. [84] were the first to demonstrate that in vivo MMP inhibition attenuated early left ventricular dilatation and dysfunction that occurred over a period of 4 days post-MI. Furthermore, pigs given an MMP inhibitor at 5 days post-MI had attenuated LV dilatation at 14 days that persisted throughout the 8-week evaluation. At 2 months post-MI, with continued treatment, the regional MI size remained smaller and LV dilatation was reduced compared to the non-treated pigs [73].

These studies demonstrate that modulating MMP activity represents a potential therapeutic target in the context of LV remodelling and myocardial infarction. However, long-term inhibition of all MMP species will likely interfere with normal tissue remodelling processes and give rise to undesirable systemic effects (musculoskeletal syndrome), thus limiting clinical utility [89–93]. Although the cause of this syndrome is unclear, inhibition of particular MMPs, namely that of the interstitial collagenase (MMP-1) [90–93], as well as other non-matrix metalloproteinases, may be responsible [93]. Importantly, clinical studies using more selective MMP inhibitory profiles have shown that MMP inhibition may be achieved in the absence of adverse musculoskeletal effects [93].

3.2. Selective MMP inhibition (sMMPi)

Lindsey et al. [42] used a selective MMP inhibitor (sMMPi) that does not inhibit MMP-1 in rabbits, but still attenuates left ventricular remodelling and even increases neovascularization in the subendocardial layer of the infarct region. In pigs, MMP-inhibition, without inhibition of MMP-1 or -7 favourably influenced LV remodelling after MI [88]. Moreover, temporal differences exist with respect to the timing of sMMPi institution (3 days before versus 3 days after MI) and patterns of regional and global myocardial remodelling after MI. LV chamber volume was reduced to similar degrees in both pre-MI and post-MI sMMPi groups compared to the MI-only group. However, stroke volume, ejection fraction and fibrillar collagen content within the remote and border zones of the pre-MI sMMPi group differed from the post-MI sMMPi group. These data provide clear evidence of a temporal window for initiation of MMP inhibition.

Because more than 20 distinct MMP species have been identified and cloned [94], continued efforts to narrow the portfolio of MMPs targeted for post-MI inhibition may hold significant therapeutic potential. Based on pre-clinical animal experiments, clinical studies in patients with MI are warranted to investigate the clinical utility of temporal administration of specific MMP-inhibitors in preventing cardiac dilatation and dysfunction after MI.

4. The future of MMP-inhibition after MI

Recently, promising results have been made with the use of broad spectrum and selective MMP-inhibition in several post-MI animal models. However the challenge and the remaining difficulty of MMP-inhibition after MI are to target a specific portfolio of MMPs with respect to their temporal and spatial expression/activity window after MI. To elucidate new pharmacological purposes for MMPs, future studies that examine the temporal and spatial profile of MMPs and TIMPs in the post-MI healing phases are warranted. Next to that, a more extensive unraveling of the mechanisms involved in the release and activity of MMP/TIMP is needed. By the latter, key players at particular time points can be identified. This research should finalize in novel MMP-inhibitors that optimize cardiac repair, remodelling and prevents progressive heart failure after MI.

Table 3
The effect of ACEI, ARB and β-blockers on the MMP/TIMP activity

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
<th>Animal model</th>
<th>Effect on MMPs/TIMP s versus no-treatment</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>Ramipril</td>
<td>Rat, MI</td>
<td>MMP-2, TIMP-4</td>
<td>[101]</td>
</tr>
<tr>
<td></td>
<td>Trandolapril</td>
<td>Rat, MI</td>
<td>MMP-2</td>
<td>[102]</td>
</tr>
<tr>
<td></td>
<td>Quinapril</td>
<td>Rat, SHHF</td>
<td>MMP-2, MMP-9, TIMP-1 and -2</td>
<td>[103]</td>
</tr>
<tr>
<td>ARB</td>
<td>Valsartan</td>
<td>Dog, IR</td>
<td>TIMP-3, thus improved TIMP3/MMP9 ratio</td>
<td>[104]</td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
<td>Hamster, CC</td>
<td>MMP-1, -2, -9; TIMP-1 en-2</td>
<td>[105,106]</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>Propanol</td>
<td>Rat, MI</td>
<td>MMP-9</td>
<td>[107]</td>
</tr>
</tbody>
</table>


♀ decreased versus no-treatment.
♂ increased versus no-treatment.
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