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Matrix Metalloproteinase-12 as an endogenous resolution promoting factor following myocardial infarction

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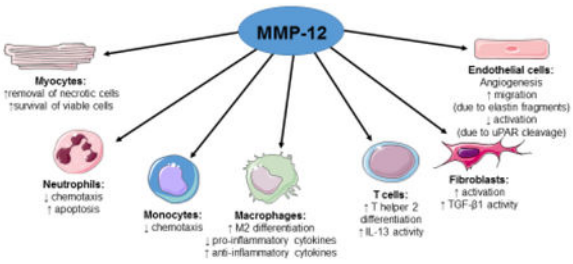
Abstract

Following myocardial infarction (MI), timely resolution of inflammation promotes wound healing and scar formation while limiting excessive tissue damage. Resolution promoting factors (RPFs) are agents that blunt leukocyte trafficking and inflammation, promote necrotic and apoptotic cell clearance, and stimulate scar formation. Previously identified RPFs include mediators derived from lipids (resolvins, lipoxins, protectins, and maresins), proteins (glucocorticoids, annexin A1, galectin 1, and melanocortins), or gases (CO, H_2S, and NO). Matrix metalloproteinase-12 (MMP-12; macrophage elastase) has shown promising RPF qualities in a variety of disease states. We review here the evidence that MMP-12 may serve as a novel RPF with potential therapeutic efficacy in the setting of MI.

Graphical abstract



Keywords

inflammation; extracellular matrix; inflammation resolution; macrophage; neutrophil; fibroblast

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Disclosures. None

1. Introduction

Myocardial infarction (MI) occurs due to blockage of the coronary artery that supplies the left ventricle (LV) with blood, leading to irreversible ischemic damage of the downstream myocardium. Within 30 minutes of ischemia, cardiomyocytes undergo necrosis that release damage-associated molecular factors that initiate an inflammatory cascade.(1) While inflammation is required to initiate a wound healing response, excessive inflammation can exacerbate tissue damage both in the infarct and remote areas of the LV. The infarcted portion of the LV undergoes a wound healing response and is eventually replaced with scar tissue. The wound healing cascade consists of three sequential but overlapping phases: inflammatory, proliferative, and maturation phases.(2, 3) For appropriate scar formation to occur, the necrotic myocytes in the ischemic area must be broken down and new extracellular matrix (ECM) synthesized in a balance of replacement scar formation that provides structure to the infarct while preventing the development of an overly stiff myocardium.(2, 3)

A promising therapeutic strategy for treating MI is to stimulate the production of endogenous inflammation resolution promoting factors (RPFs) to enhance wound healing, generate a stable scar, and limit progression to heart failure.(4-8) RPFs regulate leukocyte trafficking, blunt inflammatory mediator production, and promote necrotic cell clearance and tissue repair. The current RPF catalogue includes lipid mediators (resolvins, lipoxins, protectins, and maresins), proteins and bioactive peptides (glucocorticoids, annexin A1, galectin 1, and melanocortins), and gases (NO, H_2S, and CO).(9-11)

Of the RPFs identified to date, lipid mediators are the most studied. In particular, immune cells rapidly produce resolvins after injury as a means to dampen inflammation.(9-16) Lipid mediator RPFs are enzymatically produced from polyunsaturated fatty acids and are rapidly produced by immune cells.(9-15, 17) Of the polyunsaturated fatty acid-derived resolvins, resolvin D1 binds to the formyl peptide receptor 2, resolvin E1 binds to the chemoattractant receptor 23, and both resolvins bind the leukotriene B4 receptor BLT1.(9) In post-MI mice, resolvin D1 treatment stimulates an earlier neutrophil exit from the LV infarct and spleen, reduces pro-fibrotic collagen I α and tenascin C, and improves fractional shortening.(15) Resolvin D1 also reduces macrophage numbers and stimulates a shift from pro- to antiinflammatory phenotype by downregulating the CC chemokine receptor 5 and CXC motif chemokine ligand Cxcl5 while upregulating mannose receptor c-type 1, arginase-1, and chitinase-like protein 3 (Ym1).(15) Annexin A1 is a small protein expressed by macrophages and neutrophils that serves as an RPF after MI by binding to the formyl peptide receptor-2 and inhibiting neutrophil pro-inflammatory actions.(18) These results provide a template for studies of other RPFs and serve as literature controls for comparisons (Table 1).

Wound healing following MI is a dynamic process that depends on a temporal succession of events, in which matrix metalloproteinases (MMPs) play critical roles.(19, 20) MMPs are a family of protease enzymes with a catalytic zinc ion. Collectively, MMPs degrade a number of ECM and intracellular proteins.(1, 3, 21, 22) Endogenous MMP inhibitors include alpha 2

macroglobulin in the circulation and tissue inhibitor of metalloproteinases (TIMPs) locally that provide feedback to temper MMP proteolytic activity.(3) MMPs and TIMPs are critically involved in ECM remodeling after MI, including having direct and indirect roles in inflammation modification. (3)

To date, no RPF has translated to the clinic, indicating a need to better understand the mechanisms involved and the need to identify additional RPF candidates. MMP-12 (macrophage metalloelastase) cleaves a number of MI-relevant ECM substrates including elastin, fibronectin, heparan sulfate, laminin, type IV collagen, and vitronectin.(3, 23) We have reported that MMP-12 inhibition after MI, using the selective phosphinic peptide inhibitor RXP 470.1, impaired CD44 and hyaluronan interaction to suppress neutrophil apoptosis and prolong inflammation, which worsened LV physiology.(8) This led to the concept that MMP-12 may serve a beneficial role in MI remodeling and may be working as a previously unidentified RPF. To demonstrate that MMP-12 is an RPF, there are a number of fulfillment criteria listed in Table 1 that should be met. Here, we summarize the current knowledgebase on MMP-12 in the post-MI myocardium, with the majority of information deriving from our own inhibition study. Where information is not currently available in the myocardium, we borrow from other fields to provide insight into possible MMP-12 roles in the post-MI LV (Figure 1).

2.1 MMP-12 is elevated after MI and with aging.

MMP-12 increases at MI day 1 and remains elevated through day 7.(8) Of interest, the LV MI neutrophil was identified as a novel MMP-12 source, as circulating blood neutrophils showed no expression and MI day 1 neutrophils isolated from the infarct zone showed robust expression. MMP-12 expression is induced by a number of MI relevant factors, including TGF-β1, IL-4, and hypoxia inducible factor (HIF)-1α, and is decreased by interferon gamma (IFN-γ).(24-27) In humans, MMP-12 is significantly elevated in the serum of patients with carotid atherosclerosis and ST-segment elevation MI, indicating MMP-12 persists through the pathological continuum initiating with atherosclerosis and culminating in MI. (28, 29)

Aging is an important modulator of MMP-12 at baseline and after MI. Aging stimulates LV hypertrophy, inflammation, and fibrosis, resulting in impaired diastolic function.(30-32) Older patients have a higher mortality rate after MI, in part due to baseline differences.(33) In the myocardium, MMP-12 increases in mice with age, and correlates positively with LV mass.(30, 34) MMP-12 increases in the insoluble fraction and decreases in soluble fraction, which may indicate MMP-12 is more associated with insoluble ECM substrates and less associated with soluble substrates such as tumor necrosis factor alpha (TNFα).(35) In response to pressure overload, MMP-12 increases to a higher extent in older mice compared to the younger cohort.(36) The higher MMP-12 in the older pressure-overloaded mice corresponds with less LV remodeling (less hypertrophy and dilation) and reduced mortality rates, indicating MMP-12 serves a protective role in aging hearts with pathology.(36) These effects may be due to MMP-12 cleavage of urokinase-type-plasminogen activator receptor on endothelial cells to inhibit pathological angiogenesis in response to LV hypertrophy.(36) MMP-12, therefore, associates with cardioprotective roles after MI and aging.

2.2 MMP-12 regulates leukocyte trafficking.

MI initiates a robust inflammatory response characterized by release of pro-inflammatory cytokines and chemokines and the influx of leukocytes.(2, 37-39) Monocyte infiltration begins first, followed by the influx of neutrophils at a much higher amplitude, such that by 24 h after MI neutrophils are the predominant leukocyte in the infarct region.(40) MMPs regulate the inflammatory response to MI by proteolytic processing chemotactic factors that stimulate leukocyte recruitment.(23, 41) MMP-12 roles in post-MI leukocyte infiltration have not been defined. In the smoke-induced emphysema mouse model, MMP-12 induces rapid monocyte and neutrophil influx into the lung through proteolytic processing of elastin, generating fragments that incite a strong chemoattractant response.(42) In a mouse model of lipopolysaccharide-induced lung injury, MMP-12 null mice had delayed neutrophil resolution.(43) One mechanism of action was through MMP-12 cleavage of the ELR^+ motif at Glu-Leu amino acids to inactivate CXCL1, 2, 3, 5, and 8. MMP-12 also inactivates CCL2, 7, 8 and 13 to discontinue neutrophil recruitment. In the injured cornea, MMP-12 promotes epithelial proliferation and migration and early neutrophil infiltration to promote healing. (44, 45) In summary, MMP-12 is a critical regulator of leukocyte trafficking, and promotes both the initial influx and discontinuation of neutrophils into the site of injury. The net effect as assessed by MMP-12 null mice is to limit the chronic persistence of neutrophils.

2.3 MMP-12 turns off pro-inflammatory signaling.

MMP-12 inhibition after MI prolongs upregulation of pro-inflammatory molecules IL1rl, IL6ra, IL11, and Cxcr5, and worsens cardiac physiology (Table 2).(8) In addition to serving as a proteolytic mediator of inflammation signaling, MMP-12 is a transcription factor.(46) MMP-12 is endocytosed by cardiomyocytes and exerts transcriptional activity at the NFKBIA promoter, supporting interferon-alpha (IFN-α) production and anti-viral activity. (46) As a protease, MMP-12 later cleaves IFN-α to inhibit its activity and promote resolution of inflammation.(47) MMP-12 also possesses intracellular anti-bacterial properties in macrophages through its carboxy-terminal domain.(44) MMP-12 inactivates the complement cascade, one of the earliest stimuli to attract inflammatory cells during injury, and inactivates CCL2, a potent monocyte chemoattractant.(48, 49) Through cleavage of actin and fibrin, MMP-12 promotes clearance of neutrophil extracellular traps (NETs) that serve as neutrophil reservoirs following ischemic injury.(48, 50) In a mouse model of autoimmune encephalomyelitis, MMP-12 improves outcomes through proteolytic cleavage of osteopontin to reduce inflammation.(51) The CD14 receptor recognizes damage-associated molecular patterns released during MI, and MMP-12 sheds membrane bound CD14 to downregulate pro-inflammatory monocyte activity.(52, 53) In summary, MMP-12 turns off pro-inflammation by both direct cleavage of substrates and by serving as a transcription factor.

2.4 MMP-12 stimulates anti-inflammatory signaling.

IL-13 is an anti-inflammatory cytokine expressed by T helper 2 (Th2) cells that promotes healing following MI by enhancing macrophage differentiation to a reparative phenotype. (54) While IL-13 has positive roles in MI remodeling, IL-13 is detrimental in lung injury. In

a mouse model of bleomycin-induced lung injury, MMP-12 mediates many of the pro-fibrotic effects of IL- 13 and supports Th2 cell-derived IL-13 to promote pulmonary fibrosis.(55, 56) IL-13 positively feeds back to further induce MMP-12 expression.(57) MMP-12 is induced by transforming growth factor (TGF)β1, an anti-inflammatory and pro-fibrotic cytokine, and in turn MMP-12 stimulates TGFβ1-induced lung fibrosis.(25) In a mouse model of multiple sclerosis, MMP-12 confers protection by enhancing anti-inflammatory Th2 cell activation, and Th2 cell activation links to decreased MI risk.(58, 59) MMP-12 processes adiponectin from full-length to globular forms, which promotes nitric oxide production by endothelial nitric oxide synthase expression in endothelial cells, and promotes IL-10 expression while inhibiting pro-inflammatory cytokine expression in macrophages.(60, 61) In summary, MMP-12 stimulates anti-inflammatory signals, which in turn stimulate further MMP-12 production.

2.5 MMP-12 promotes cell clearance.

MMP-12 may also promote resolution of inflammation by mediating clearance of inflammatory cells. Neutrophil clearance is critical for inflammation resolution, as the persistent presence of neutrophils impairs resolution and healing.(4, 53, 62) Mice lacking MMP-12 show a continuation of neutrophils in arthritic joints.(48) A similar phenotype is seen in the post-MI LV where MMP-12 inhibition prevented neutrophil apoptosis and in vitro where MMP-12 directly stimulates neutrophil apoptosis by caspase 3 activation.(8) In tumor cells, MMP-12 promotes apoptosis by activating TNF-related apoptosis-inducing ligand.(63) MMP-12 also cleaves hyaluronic acid to promote its binding to CD44 in neutrophils, leading to their apoptosis.(8) At MI day 7, MMP-12 inhibition reduced CD44 and increased hyaluronic acid levels, halting neutrophil apoptosis due to inadequate CD44-hyaluronic acid binding.(8, 64) CD18 (β2 integrin), a cell adhesion molecule that suppresses neutrophil apoptosis, is elevated when MMP-12 is blocked.(8)

MMP-12 inhibition also reduces the phagocytic marker CD36 at MI day 7, decreasing the ability of macrophages to engulf apoptotic neutrophils.(8) Macrophage phagocytosis is a necessary component for optimal neutrophil removal and activation towards a pro-reparative state.(65, 66) In macrophages, the absence of MMP-12 prevents migration and ECM degradation.(3, 67) In the injured liver, MMP-12 is more highly expressed in Ly6C-low M2 macrophages, which play anti-inflammatory and pro-reparative roles following MI, compared to Ly6C-high M1 macrophages.(40, 68)

These results highlight the significant influence of MMP-12 on reducing apoptotic and necrotic cells within inflammed tissue.

2.6 MMP-12 promotes scar formation and angiogenesis.

Following MI, optimal scar formation requires an adequate inflammatory response, timely resolution of inflammation, and collagen synthesis and organization that does not infiltrate the remote, non-infarcted area.(39) Inadequate ECM synthesis paired with increased degradation can lead to LV rupture, while excessive ECM synthesis paired with insufficient breakdown can lead to elevated LV wall stiffness and progression to heart failure.(69) MMPs

stimulates ECM degradation directly and ECM synthesis indirectly, and MMP-12 presents a unique protease mediating both processes.(2, 3)

MMP-12 has cardioprotective and wound healing properties after MI (Figure 2), as MMP-12 inhibition worsened MI outcomes including increased LV wall thinning, dilation, and hypertrophy.(8) In a mouse model of acetaminophen-induced liver injury, fibrinogen-induced MMP-12 protects against hepatocyte necrosis; whether MMP-12 is protective against myocyte necrosis following MI remains to be determined.(70) MMP-12 generates elastin-derived peptides with therapeutic relevance to the myocardium, as these peptides protect from ischemia by enhancing nitric oxide production.(71, 72)

In addition to potentially protecting viable myocardium from ischemic injury, there are other mechanisms by which MMP-12 may promote scar formation. MMP-12 degrades the sarcomeric protein titin to participate in the degradation of necrotic myocytes and contribute to their removal and replacement with scar tissue.(73) MMP-12 may limit excessive tissue degradation by other MMPs, as MMP-12 inhibition after MI results in compensatory upregulation of MMP-8, −10 and −14.(8) Mice deficient in MMP-12 have increased MMP-2, −9 and −13 following lung injury.(8, 55) MMP-12 cleaves fibronectin, whose fragments promote macrophage secretion of fibroblast growth factor-1, insulin-like growth factor-1, and leukemia inhibitory factor to protect cardiomyocytes from ischemic injury.(74, 75) MMP-12 promotes the motility of mesenchymal stem cells, which serve as a cardiac fibroblast source after MI.(76, 77)

MMP-12 influences cardiac fibroblasts, the major cell type responsible for ECM synthesis after MI.(78, 79) MMP-12 is expressed by myofibroblasts in the cornea to assist in the removal of damaged ECM components and support TGFβ1 activity.(80) Angiogenesis is a critical component of MI healing to re-vascularize the infarcted myocardium.(81) MMP-12 generated elastin fragments have pro-mitogenic effects on dermal fibroblasts and are chemotactic for endothelial cells, implicating a role for MMP-12 in scar formation and angiogenesis.(82) MMP-12 also promotes angiogenesis by degrading the basement membrane component collagen IV.(83) At the same time, fibroblast-derived MMP-12 inhibits angiogenesis by cleavage of urokinase-type-plasminogen activator receptor on endothelial cells.(84) This may be a later signal to turn off angiogenesis, when wound healing completes. Overall, MMP-12 promotes scar formation by regulating expression of other MMPs, promoting timely resolution of inflammation, and direct stimulation of fibroblasts and endothelial cells.

3.1 Therapeutic relevance.

There is strong logic for testing MMP-12 for RPF roles after MI. At the same time, both MMP-12 deletion and inhibition limit atherosclerosis progression,(23) which brings into question the clinical relevance of using MMP-12 to treat patients with MI. Acute (days) administration of MMP-12 in the immediate post-MI setting would target the initial inflammatory phase and stimulate efficient conversion of immune cells to repair phenotypes and limit the effects potentially seen with chronic (months) administration. MMP-12 is highly induced by statin use, which has anti-inflammatory properties. Statins are standard of

care for patients with MI, and MI patients who discontinue statin use have a higher one-year mortality rate.(85, 86) Thus, the effects of commonly used pharmacological agents on MMP-12 should be taken into consideration when evaluating therapeutic efficacy.

A second strategy to promote MMP-12 beneficial effects while limiting detrimental effects would be to target a particular MMP-12 substrate, rather than MMP-12 itself. While the atherosclerosis environment is macrophage and smooth muscle cell predominant, the MI environment is dominated by neutrophils, macrophages, and fibroblasts. The substrate environment, therefore, is different for the two pathologies. A better understanding is needed to evaluate MMP-12 and MMP-12 substrate treatment timing and effect on different cell types. Following this process will allow us to develop a mechanistic foundation on which to test translational applications. With the recent development of a number of guidelines for cardiovascular research, experimental designs that incorporate rigor and reproducibility will enlighten us on the potential therapeutic relevance of MMP-12.(87-90)

3.2 Conclusions.

MMP-12 displays several features of an RPF in the post-MI setting, including blunting excessive infiltration and promoting clearance of inflammatory cells, preventing excessive cytokine and chemokine activity, promoting anti-inflammatory activities of macrophages and T cells, and stimulating ECM remodeling and fibroblast function to promote scar formation. Our studies and others build a foundation upon which to test MMP-12 as an RPF for the treatment of MI.

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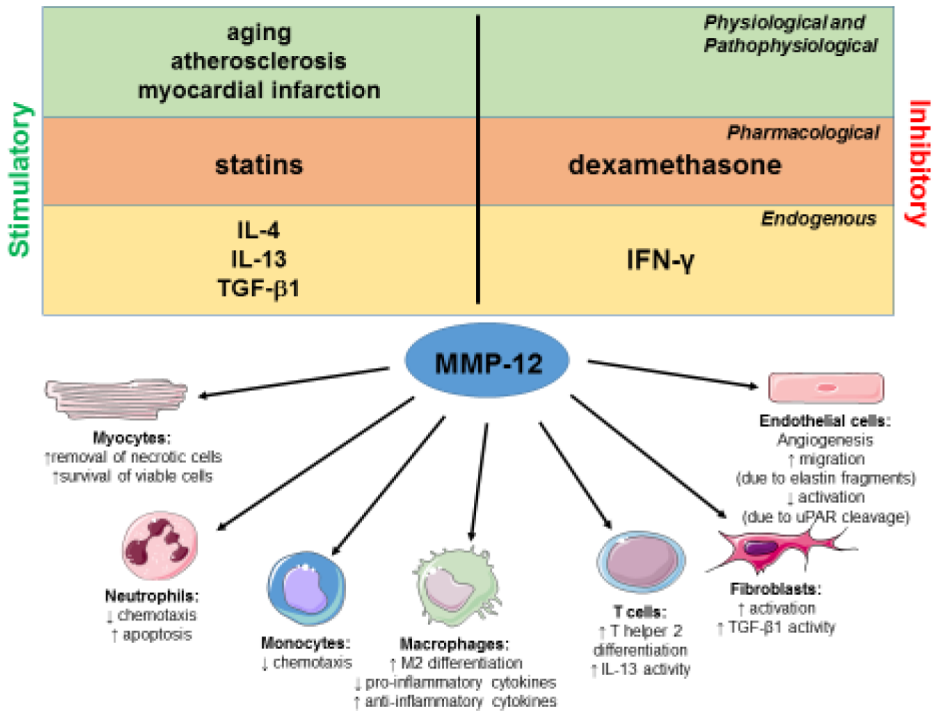

Figure 1. Actions by MMP-12 as a potential resolution promoting factor following MI.

MMP-12 expression is regulated by several pathophysiological, pharmacological, and endogenous factors. MMP-12 has diverse actions on cardiomyocytes, neutrophils, monocytes and macrophages, lymphocytes, fibroblasts, and endothelial cells that may promote inflammation resolution and scar formation. Cell images were obtained from Servier Medical Art© (http://www.servier.com/).

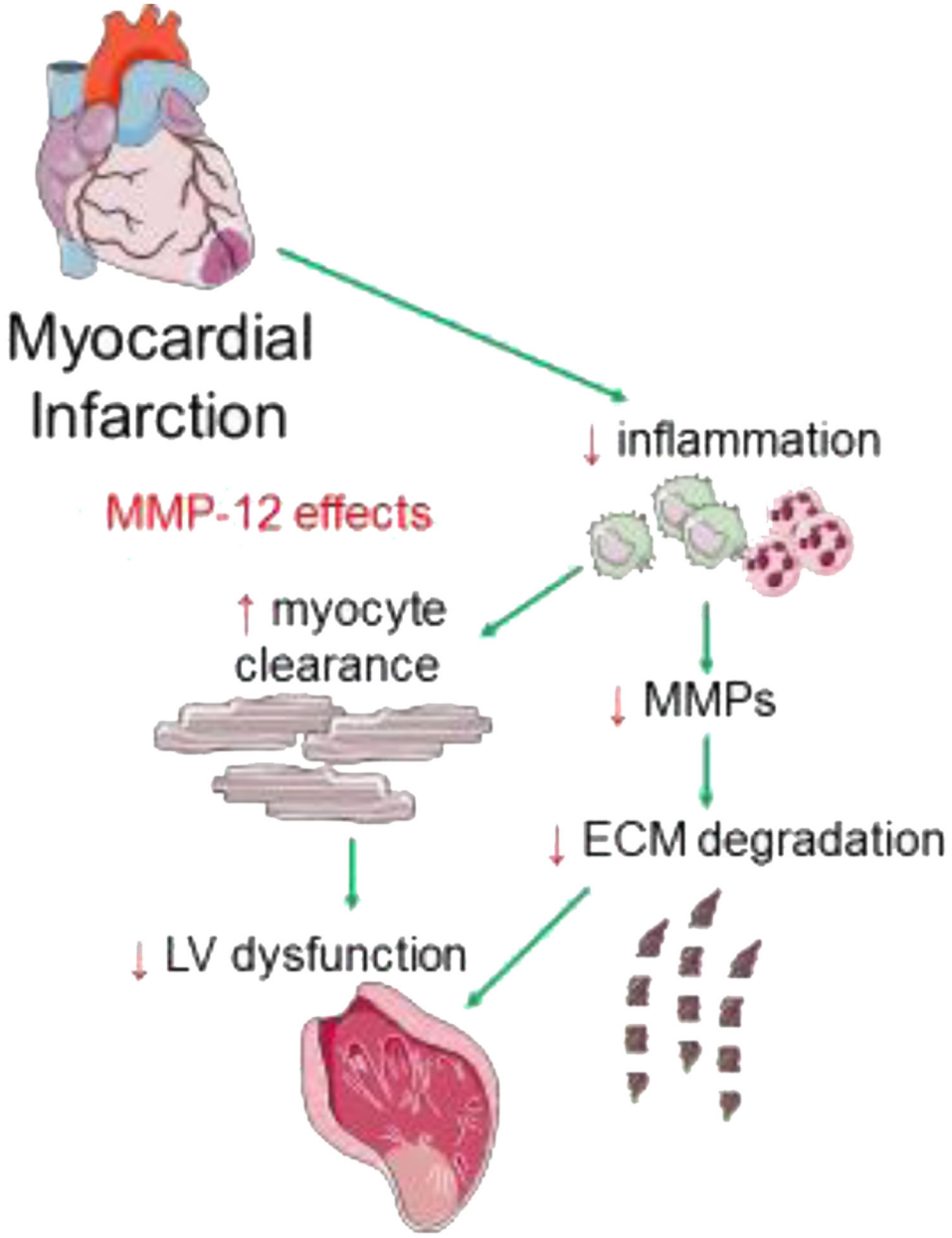

Figure 2. Left ventricular remodeling following MI and potential therapeutic effects of MMP-12.
Following MI, inflammatory cells in the left ventricle clear dead myocytes and release matrix metalloproteinases (MMPs) that degrade the extracellular matrix (ECM), leading to wall thinning and LV dysfunction. MMP-12 may be beneficial after MI by preventing excessive inflammation while promoting more efficient removal of dead cells, decreasing other MMPs, and preserving ECM integrity.

Table 1.

Criteria for classification as a resolution promoting factor (RPF) and comparison of matrix metalloproteinase (MMP)-12 to known RPFs

	MMP-12	Resolvins	Annexin A1
Increases after MI	Yes[8]	Yes[91]	Yes[92]
Regulates leukocyte trafficking	Yes	Yes	Yes
	↑ monocyte/ neutrophil chemotaxis after injury[42, 44]	↓ neutrophil transendothelial migration[93] ↓ neutrophil chemotaxis from spleen[15]	↓ CD68+ macrophages after MI[92] ↓ neutrophil transendothelial migration[94]
Reduces proinflammation	Yes	Yes	Yes
	↓ IL1rl, IL6ra, IL11, and Cxcr5 after MI[8] ↓ IFN-α, CCL2, complement proteins, NETS, OPN, CD 14 [46, 48, 49, 51, 52]	↓ cytokine and chemokines[95] ↓ NF-κB, STAT3, MAPK activity[95]	↓ pro-inflammatory and pro-thrombotic cytokines[94]
Increases antiinflammation	Yes	Yes	Yes
	↑ IL-13 activity[55, 56] ↑ TGF-β1 activity[25] ↑ IL-8 secretion[96] ↑ Th2 cell activity[58] ↑ globular adiponectin[60]	↑ SIRT1 expression[95] ↑ M2 markers—Mrc1, Arg1, Ym1[15]	↑ IL-10 expression[92] ↑ TGF-β secretion[97] Activation of lipoxin A4 receptor[98]
Promotes cell clearance	Yes	Yes	Yes
	↑ neutrophil clearance from arthritic joints[48] ↑ neutrophil apoptosis after MI[8] ↑ macrophage phagocytosis[65]	↑ neutrophil efflux after MI(99) ↑ neutrophil apoptosis[100]	↑ macrophage phagocytosis of apoptotic neutrophils[101]
Promotes scar formation and angiogenesis	Yes	No	Yes
	↑ degradation of myocyte debris[73] ↑ ECM turnover and remodeling[8, 25] ↓ tissue degradation by other MMPs[8, 55] ↑ TGF-β1 activity in myofibroblasts[80] ↑ fibroblast proliferation[82]	↓ fibrosis/collagen accumulation after MI[15]	↑ fibroblast activation and collagen deposition[102]

Arg 1- arginase 1; CCL- CC chemokine ligand; CD- cluster of differentiation; CXCR- CXC chemokine receptor; ECM- extracellular matrix; IFN- interferon; IL-interleukin; MAPK- mitogen activated protein kinase; MRC1- mannose receptor C type 1; NET- neutrophil extracellular trap; NF-κB- nuclear factor kB; OPN- osteopontin; Stat- signal transducer and activator of transcription; TGF- transforming growth factor; Ym1- chitinase-like protein 3

Table 2.

MMP-12 inhibitor treatment worsens MI day 7 LV geometry and physiology.Adapted from (8).

	MI day 7 Saline (vs day 0 no MI)	**MI day 7 MMP-12 inhibitor (vs day 0 no MI and Ml day 7 MI Saline)**
Infarct wall thickness (mm)	↓	↓↓
End diastolic volume (μL_)	↑	↑↑
End systolic volume (μL)	↑	↑↑
Ejection fraction (%)	↓	↓↓
Remodeling index (end diastolic volume/ LV mass)	↑	↑↑