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REVIEW

Matrix metalloproteinases and their inhibitors in cardiovascular pathologies: current knowledge and clinical potential

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Abstract: Matrix metalloproteinases (MMPs) constitute a family of endopeptidases that harbor matrix-degrading potential, but also modulate the proliferation, migration, and apoptosis of resident blood-vessel cells and recruited inflammatory cells. Accordingly, they are proposed to play a major regulatory role in numerous cardiovascular pathologies, including restenosis, atherosclerosis, aneurysms, and post-myocardial infarction remodeling. Collectively, clinical and animal studies have begun to unravel the complex and often diverse effects MMPs and their endogenous tissue inhibitors of metalloproteinases (TIMPs) impart during cardiovascular pathologies. It is apparent that some MMPs are beneficial, while others impose detrimental influences on disease progression. This premise is underscored by evidence that broad-spectrum MMP inhibition fails to provide protection from most cardiovascular diseases. However, recent studies in mice using more selective inhibitors have proved promising. Consequently, there is an immediate need to elucidate the precise roles of individual MMPs and TIMPs in the distinct cardiovascular pathologies in order to facilitate the development and translation of new therapeutic approaches to combat cardiovascular disease, the major cause of death worldwide.

Keywords: MMPs, TIMPs, atherosclerosis, aneurysm, myocardial infarction, restenosis

Introduction

Matrix metalloproteinases (MMPs), also known as matrixins, can collectively degrade all of the extracellular matrix (ECM) components that are commonly found within the blood-vessel wall.[1] Accordingly, they have been implicated in the pathophysiology of numerous cardiovascular pathologies, including restenosis, atherosclerosis, aneurysms, and post-myocardial infarction (MI) remodeling (Table 1), although MMP-17, -20, -21, -23, -25, -26, and -27 remain unstudied. However, the paradigm of MMP function has recently changed. In addition to ECM digestion, they have also been demonstrated to process a number of cell-surface and soluble mediators that can potently affect cell behavior.[2] Consequently, MMPs harbor the potential to modulate the proliferation, migration/invasion, and apoptosis of resident blood-vessel cells, such as vascular smooth-muscle cells (VSMCs),[3] endothelial cells,[4] and several inflammatory cell types, including monocytes.[5]

At present, the MMP family consists of 23 members that share a high degree of homology and can be regulated by inflammatory cytokines, growth factors, hormones, and physical cell–cell and cell–matrix interactions.[1] They are included in the metzincin family together with ADAMs (a disintegrin and metalloproteinase family) and ADAMTSs (ADAM with thrombospondin motifs), as they all contain a zinc atom and a conserved methionine in the catalytic domain.[6] Within the MMP family, subtle

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Table 1 MMPs upregulated in cardiovascular pathologies compared to relevant normal tissues, and cellular sources

MMP	Restenosis	Atherosclerosis	Aneurysms (AAA)	Post-MI remodeling
MMP-1	VSMCs	Mø, VSMCs, ECs, and T-cells	Mø and VSMCs	Myocytes, fibroblasts, and Mø
MMP-2	VSMCs	Mø and VSMCs	VSMCs	Myocytes, fibroblasts, myofibroblasts, Mø, VSMCs, and ECs
MMP-3	VSMCs	Mø, VSMCs, ECs, and T-cells	Mø and VSMCs	Myocytes, fibroblasts, and Mø
MMP-7		Mø		Myocytes and Mø
MMP-8	VSMCs	Mø, VSMCs, and ECs	Mø and VSMCs	Mø and neutrophils
MMP-9	VSMCs	Mø, VSMCs, ECs, and T-cells	Mø and VSMCs	Myocytes, fibroblasts, myofibroblasts, Mø, neutrophils, VSMCs, and ECs
MMP-10		Mø and ECs		
MMP-11		Mø, VSMCs, and ECs		
MMP-12		Mø	Mø	Mø
MMP-13		Mø	VSMCs	Fibroblasts
MMP-14	VSMCs	Mø and VSMCs	VSMCs	Myocytes, fibroblasts, myofibroblasts, and VSMC
MMP-15		No change		
MMP-16		Mø and VSMCs		
MMP-19			Mø	
MMP-24		No change		
MMP-28				Myocytes and Mø

Abbreviations: MMPs, matrix metalloproteinases; AAA, abdominal aortic aneurysm; MI, myocardial infarction; Mø, macrophages; VSMCs, vascular smooth-muscle cells; ECs, endothelial cells.

differences in their domain structure afford them overlapping substrate specificities (Figure 1). Accordingly, MMPs can be subdivided into interstitial collagenases (MMP-1, -8, -13, and -14) that cleave fibrillar collagens, gelatinases (MMP-2 and -9) that efficiently cleave denatured collagen (ie, gelatin), and stromelysins (MMP-3, -7, -10, and -11) that have broad specificity but do not effectively cleave intact fibrillar collagens. Macrophage metalloelastase (MMP-12), as it name suggests, primarily cleaves elastin.[1,7] Moreover, while most MMPs are secreted in a latent form and require activation, numerous MMPs are membrane-bound in an active form (including MMP-14 to -17, -25, and -26) and termed membrane-type MMPs (MT-MMPs).[1,7]

As such, MT-MMPs are considered potent sheddases due to their pericellular location, and can accordingly dynamically regulate cell activities through the modification of membrane proteins, such as growth-factor and cytokine receptors, integrins, and cell–cell contacts.[6] In addition it has also been demonstrated that secreted MMPs can localize to the cell membrane, where their proteolytic actions alongside MT-MMPs can play diverse roles in cell behavior, such as proliferation, phenotypic switching, migration, and apoptosis.[8] Conversely, it has been postulated that cells can fine-tune their MMP expression and activity through sensing the mechanical properties imparted by their surrounding ECM components. For instance, integrin[9] and syndecan[10] family members can relay outside-in signals to modulate MMP expression, localization, and activity. Moreover, growth-factor signaling, such as platelet-derived growth factor, basic fibroblast growth factor, and epidermal growth factor (EGF) can independently or through synergism with integrin signaling mediate vascular cell MMP expression and localization.[11] Finally, complex cross talk between cell–cell/cell–matrix interactions and focal adhesions can modulate the activity and localization of MMPs to the migratory edge of vascular cells.[12] Taken together, these findings demonstrate the complex regulatory processes involved in MMP regulation, which are discussed in more detail in the associated citations.

Due to the destructive nature of MMPs and their ability to modulate multiple substrates, they are tightly regulated by various nonspecific inhibitors; these include the membrane-anchored reversion-inducing cysteine-rich protein with kazal motifs (RECK), tissue-factor pathway inhibitor-2 (TFPI-2), the pro-collagen C-terminal proteinase enhancer (PCPE), and the plasma protein α_2-macroglobulin.[13] MMPs are, however, most potently inhibited by endogenous tissue inhibitors of metalloproteinases (TIMPs), which are therefore believed to play the major role in regulating their activity physiologically. In vertebrates, four TIMPs have been identified (TIMP-1, -2, -3, and -4), that can form tight complexes with MMP catalytic domains through inhibitory residues present within their N-terminal domain (Figure 1).[13] TIMPs are secreted proteins, but they can also be found on the cell membrane associated with such membrane proteins as MT-MMPs. All the TIMPs can inhibit

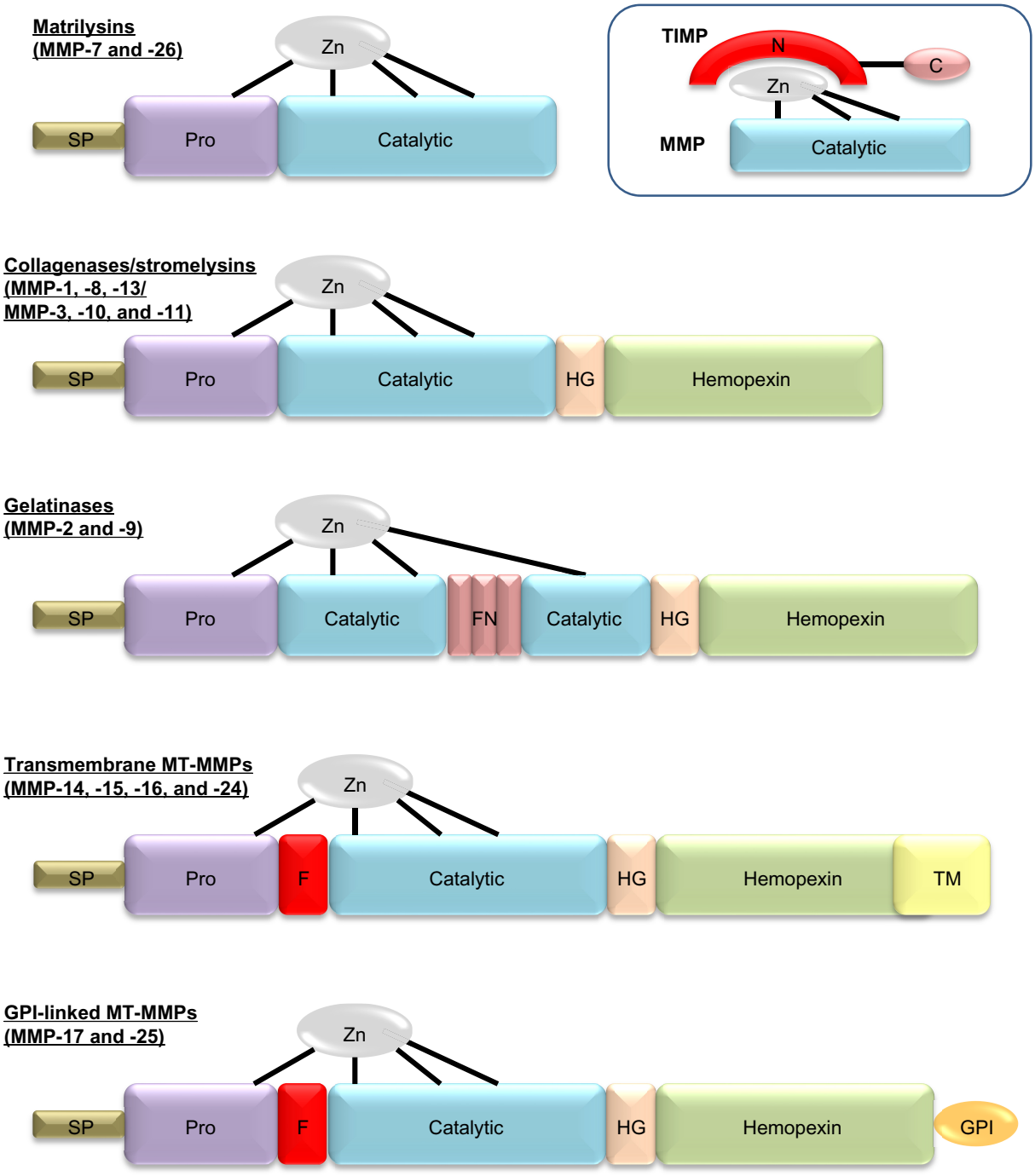

Figure 1 Domain structure for the major classes of matrix metalloproteinases (MMPs). Major domains include the signal peptide (SP), prodomain (Pro), catalytic domain with the active site zinc bound to cysteine residues within this domain and "cysteine-switch" residue in the Pro, the hinge domain (HG), the hemopexin domain, and in some cases either a transmembrane domain (TM) or glycosylphosphatidylinositol (GPI)-anchor domain. A furin-cleavage site (F) between the Pro and the catalytic domain is found in some MMPs. In the gelatinases, fibronectin (FN)-like type II repeats are also present. The schematic within the dotted lines depicts the inhibitory action of tissue inhibitors of metalloproteinases (TIMPs) on MMPs, demonstrating how the N-terminus of the TIMP chelates the active site zinc and blocks MMP activity.
Abbreviation: MT, membrane-type.

the activity of all MMPs; however, TIMP-1 has a poor inhibitory effect on MMP-9, -14, -15, -16, and -24. TIMPs also harbor the ability to inhibit members of both the ADAM and ADAMTS families of proteinases, especially TIMP-3.[1] Moreover, the C-terminal domain of TIMP-3 displays high affinity for ECM proteins, enabling it to accumulate within the pericellular space and prolong its half-life.[13] The balance between MMPs and TIMPs is therefore crucial for homeostasis, and alterations in this balance have been implicated in numerous cardiovascular diseases.[11]

Intimal formation/restenosis

The development of a vascular smooth muscle cell (VSMC)-rich intimal thickening underlies several occlusive cardiovascular pathologies that form as a result of interventions for preexisting atherosclerosis; these include angioplasty, stent deployment, and saphenous vein bypass grafting. Within the healthy blood-vessel wall, VSMCs are restricted to the media in a quiescent state and regulate vessel contractility. Upon injurious insults, such as the aforementioned interventions, medial VSMCs proliferate and migrate into the intima, where their irregular growth can impede lumen patency or serve as a soil bed for superimposed atherosclerosis.[3] It has been proposed that MMPs may directly liberate VSMCs from their normally retentive ECM alongside disruption of cell–cell contacts within the media and therefore facilitate their migration and growth within the developing neointima.[3] Numerous MMPs have been shown to be expressed by various cell types within intimal thickenings (Table 1), and accordingly a plethora of in vivo studies have been undertaken to elucidate which MMPs direct intimal formation (Table 2).[14–36]

Table 2 Results of in vivo animal studies evaluating the effects of modulating matrix metalloproteinases (MMPs) or tissue inhibitors of metalloproteinases (TIMPs) on neointimal and vascular smooth-muscle cell behavior, using recombinant adenoviral overexpression, gene knockout, or pharmacological inhibitors of MMPs (MMPis)

Modulation	Model (species)	Intimal size	Migration	Proliferation	Reference
MMP-1					
Inhibitor	Wire injury (Ms)	↓	ND	ND	10
MMP-2					
Knockout	Carotid ligation (Ms)	↓	↓	ND	11
Knockout	Carotid ligation (Ms)	↓	↓	ND	12
MMP-3					
Knockout	Carotid ligation (Ms)	↓	↓	ND	13
MMP-8					
Knockout	Wire injury (Ms)	↓	↓	↓	14
MMP-9					
Knockout	Wire injury (Ms)	↓	↓	↓	15
Knockout	Carotid ligation (Ms)	↓	↓	↔	16
Knockout	Carotid ligation (Ms)	↓	↓	↔	13
MMP-12					
Knockout	Carotid ligation (Ms)	↓	ND	ND	13
MMP-14					
Knockdown	Carotid ligation (Ms)	↓	↓	ND	17
TIMP-1					
Knockout	Electric injury (Ms)	↑	↑	ND	18
Overexpression	Balloon injury (Rt)	↓	↓	↓	19
Overexpression	Balloon injury (Rt)	↓	↓	↔	20
Overexpression	Balloon injury (Rt)	↓	↓	↔	21
TIMP-2					
Overexpression	Balloon injury (Rt)	↓	↓	↔	22
Overexpression	Vein graft (Ms)	↓	ND	ND	23
TIMP-3					
Overexpression	Vein graft (Pg)	↓	ND	↑	24
Overexpression	Vein graft (Pg)	↓	ND	ND	25
TIMP-4					
Overexpression	Balloon injury (Rt)	↓	↓	↓	26
MMPi					
Hydroxamate	Balloon injury (Rt)	↓	↓	↓	27
Hydroxamate	Balloon injury (Rt)	↓	↓	↔	28
Hydroxamate	Balloon injury (Rt)	↓	↓	↔	29
Tetracycline	Balloon injury (Rt)	↓	↓	↔	30
Tetracycline	Balloon injury (Rt)	↓	↓	↓	31
Tetracycline	Balloon injury (Rt)	↓	↓	↓	32

Notes: ↓, decreased; ↑, increased; ↔, no change.
Abbreviations: Ms, mouse; Rt, rat; Pg, pig; ND, not determined.

Due to their ability to degrade cellular basement membranes and in vitro evidence implicating them in migration and proliferation of VSMCs,[3] initial work focused on gelatinolytic MMPs, including MMP-2, -9, and -14, in neointima formation. Studies utilizing mouse carotid artery-injury models revealed that gene deletion of MMP-2,[15,16] MMP-9,[17,19,20] and MMP-14[21] retarded intimal formation, primarily through effects on VSMC migration, whereas proliferation was less affected. Recently, MMP-3 has been indirectly implicated, due to its ability to activate MMP-9.[17] Intimal formation was also abrogated in mice receiving an MMP-1 inhibitor[14] or *Mmp8*-knockout (KO) mice[18] after wire-induced injury of the carotid artery. The mechanisms underlying the detrimental effects of MMPs on neointima formation have been discussed elsewhere,[3] and chiefly affect VSMC function through the cleavage of cell–cell and cell–matrix contacts.[3] In particular, N-cadherin represents a major cell–cell adhesion molecule in VSMCs that has been shown to be cleaved by several MMPs (MMP-7, -9, and -12), altering VSMC behavior, including migration, proliferation, and apoptosis.[37,38] Accordingly, controlling N-cadherin function may represent a therapeutic avenue for retarding intimal thickening, as recently intimated in an ex vivo model where inhibition of N-cadherin and its downstream effects retarded intimal thickening via induction of VSMC apoptosis.[39]

In line with MMPs playing an important role, the overexpression of TIMPs has been demonstrated to negate intima formation in various species. TIMP-1 gene transfer was shown to reduce balloon injury-induced intimal formation in the rat,[23–25] while expectedly intimal size was increased in a mouse wire injury model.[22] Similar protective effects have been reported for TIMP-2,[26,27] TIMP-3,[28,29] and TIMP-4,[30] primarily through retarded VSMC migration or apoptosis.

Similarly but less specifically, broad-spectrum MMP inhibitors have been utilized, and demonstrated that both hydroxamate-based[31–33] and tetracycline-derived compounds[34–36] retarded intimal thickening in rodent models. However, the use of broad-spectrum MMP inhibitors in nonhuman primates[40] and man (reviewed by Peterson[41]) has yielded less promising results. Therefore, while other antiproliferative agents have become widely adopted as therapeutic tools to prevent in-stent restenosis, interest in targeting MMPs has waned. Nonetheless, preclinical studies in pigs[28,29] have proven that TIMP-3 gene therapy is effective at reducing vein-graft intimal thickening, and is consequently moving toward a Phase II clinical trial. The use of TIMPs affords a level of specificity above and beyond that of broad-spectrum MMP inhibitors, targeting select MMPs. Accordingly, the development and employment of specific-MMP inhibitors may prove more fruitful as a therapeutic approach for restenosis. Such a tactic may also circumvent the possibility that MMPs may play beneficial and detrimental roles during restenosis and a more selective inhibitory course is required, as recently shown for atherosclerosis.[42,43]

Atherosclerosis

The rupture of an atherosclerotic plaque with associated luminal thrombosis is the major underlying cause of acute coronary syndromes (such as coronary artery disease and ensuing MI) and stroke. Clinically relevant atherosclerotic lesions develop primarily within the coronary and carotid arteries of humans over many decades, and are widely accepted as an inflammatory disease,[44] although VSMCs and endothelial cells also play prominent roles.[3,45] In particular, VSMCs appear to play a divergent role in atherosclerosis; while their phenotypic modulation and growth can precipitate early lesion formation, in advanced plaques they take on a beneficial role through the generation and maintenance of a protective fibrous cap that shields them from plaque rupture.[3,12] Nonetheless inflammatory cells, especially monocytes/macrophages, are considered pivotal to atherosclerotic plaque progression and destabilization (rupture) through their roles in fibrous cap thinning, VSMC loss, lipid/necrotic core expansion and microcalcification, all characteristics associated with rupture-prone plaques.[44,46] A wealth of biochemical and histological studies have highlighted a prominent role for MMPs in atherosclerotic plaque progression and vulnerability (Table 1), particularly those derived from macrophages,[11] except for MMP-15 and -24, whose expression has been shown to be unaltered in human atherosclerotic coronary artery plaques.[47] Accordingly, researchers have turned to animal models to elucidate the contribution of MMPs in atherogenesis and the formation of advanced plaques.

Both transgenic and KO animal models have been utilized to investigate the role of MMPs and TIMPs in the pathogenic steps of atherosclerotic plaque formation, progression, and rupture, notably rabbits and mice. When these animals are rendered hypercholesterolemic, they develop atherosclerotic lesions at multiples sites that resemble the human analogs and progress similarly from fatty streaks to complex advanced lesions.[48] Accordingly, there are numerous empirical factors that can be assessed in addition to plaque size; these include characteristics associated with plaque vulnerability in humans, such as VSMC and macrophage number, collagen content, lipid-core size, neovascularization and intraplaque hemorrhage, and elastin fragmentation.[49] Recent studies have highlighted the potential detrimental

role of neovascularization (a form of angiogenesis) in human atherosclerosis,[50] which is mediated in part by MMPs.[4] However, plaque neovascularization is uncommon in plaques from animal models, and their incidence is rarely reported.[50] Utilizing mainly apolipoprotein E (*Apoe*)-KO mice, and to a lesser degree low-density lipoprotein receptor (*Ldlr*)-KO animals, a large number of studies have been conducted where these mice are either bred with transgenic or KO mice, or treated with potential therapeutic agents. These studies have illuminated the potential roles of MMPs and TIMPs in atherosclerotic plaque progression and stability (summarized in Table 3).[33,42,43,51–67]

Unlike humans, mice do not actively express MMP-1. Nonetheless, a study where human MMP-1 was overexpressed selectively in macrophages of *Apoe*-KO mice unexpectedly showed a reduction in plaque size and collagen content.[51] *Mmp*-KO studies in *Apoe*-KO mice have indicated both protective and detrimental effects. MMP-2-KO mice presented a reduction in plaque size, potentially through a decrease in VSMC accumulation and suggesting plaque stability may be compromised.[52] MMP-3 deletion resulted in larger aortic and brachiocephalic plaques[53,54] associated with fewer medial elastin breaks,[53] but lowered VSMC content and concomitant increase in buried fibrous layers (a surrogate marker of mouse brachiocephalic plaque instability),[54] implying MMP-3 affords greater stability. In agreement, reduced VSMC migration and associated neointimal formation was observed in *Mmp3*-KO mice.[17] In contrast, an increase in VSMC content was observed within brachiocephalic plaques of *Mmp7*-KO mice,[54] consistent with a proapoptotic role of MMP-7 on VSMCs.[37] Lesion size and macrophage numbers were reduced in *Mmp8*-KO mice, suggesting improved stability.[55] Conflicting observations have been reported in *Mmp9*-KO mice; whereas aortic plaque burden and macrophage number were reduced in one study examining the aortic root,[56] increased plaque size, macrophage content, and buried fibrous layers were detected in another focusing on the brachiocephalic artery.[54] In agreement with promoting plaque stability, reduced VSMC migration and associated neointimal formation was observed in *Mmp9*-KO mice.[17] Moreover, macrophage-specific overexpression of pro-MMP-9 did not influence lesion instability in arterial plaques.[57] Conversely, intraluminal overexpression of pro-MMP-9 triggered intraplaque hemorrhage in advanced lesions (but not intermediate plaques) induced in carotid arteries by collar implantation in *Apoe*-KO mice.[58] Additionally, nonphysiological overexpression of a fully autoactivated form of MMP-9 augmented plaque progression.[57]

Mmp12 KO reduced brachiocephalic artery lesion area and number of buried fibrous layers,[54] while also decreasing aortic

Table 3 Results of in vivo animal studies evaluating the effects of modulating matrix metalloproteinases (MMP) or tissue inhibitors of metalloproteinases (TIMPs) on atherosclerotic plaque size and cellular composition, using transgenic (Tg) or recombinant adenoviral (RAd) overexpression, gene knockout (KO), or pharmacological inhibitors of MMPs

Modulation	Model (species)	Site	Size	VSMCs	Mø	Reference(s)
MMP-1 Tg	*Apoe* KO (Ms)	Aorta and root	↓	↔	↔	46
MMP-2 KO	*Apoe* KO (Ms)	Aorta and root	↓	↓	↔	47
MMP-3 KO	*Apoe* KO (Ms)	Aorta/BCA	↑/↑	ND/↓	↔/↓	48, 49
MMP-7 KO	*Apoe* KO (Ms)	BCA	↔	↑	↔	49
MMP-8 KO	*Apoe* KO (Ms)	Aorta	↓	↔	↓	50
MMP-9 KO	*Apoe* KO (Ms)	BCA/aorta	↑/↓	↓/ND	↑/↓	49, 51
MMP-9 Tg	*Apoe* KO (Ms)	Arch, collar	↔	↔	↔	52, 53
MMP-12 KO	*Apoe* KO (Ms)	BCA/aorta	↓/↔	↑/↔	↓/↔	49, 51
MMP-12 Tg	kbt:JW (Rb)	Aorta	↑	↑	↑	54
MMP-13 KO	*Apoe* KO (Ms)	Root	↔	↔	↔	55
MMP-14 KO	LDLR-KO (Ms)	Root	↔	↔	↔	56
TIMP-1 Tg	*Apoe* KO (Ms)	Root	↔	ND	↓	63
TIMP-1 RAd	*Apoe* KO (Ms)	BCA and root	↓/↔	ND/↔	↓/↔	61, 62
TIMP-2 RAd	*Apoe* KO (Ms)	BCA	↓	↑	↓	62
TIMP-1 KO	*Apoe* KO (Ms)	Aorta and root	↔/↓	↔/ND	↔/↑	59, 60
Nonselective MMP inhibitor	LDLR or *Apoe* KO (Ms)	Aorta, BCA	↔	↔	↔	29, 57, 58
MMP-12 inhibitor	*Apoe* KO (Ms)	Aorta, BCA, and root	↓	↑	↓	38
MMP-13 inhibitor	*Apoe* KO (Ms)	Carotid	↔	↔	↔	39

Notes: ↓, decreased; ↑, increased; ↔, no change.

Abbreviations: VSMCs, vascular smooth-muscle cells; Mø, macrophages; *Apoe*, apolipoprotein E; Ms, mouse; Rb, rabbit; BCA, brachiocephalic artery; root, aortic root; LDLR, low-density lipoprotein receptor; ND, not determined.

elastin fragmentation.[56] Additionally, the intraplaque ratio between VSMCs and macrophages was favorably increased toward VSMC content, implying heightened stability, in part through modulation of monocyte/macrophage invasion and apoptosis.[42] In support, macrophage overexpression of an active form of MMP-12 in rabbits increased plaque size and increased inflammation,[59] suggesting that MMP-12 promotes plaque progression and instability. Deletion of MMP-13 or MMP-14 had negligible effects on plaque size and composition, but increased fibrillar collagen content, indicating a role in plaque instability.[60,61] Taken together, these findings indicate that some MMPs (such as MMP-2, -3, and -9) may exert a protective role in atherosclerosis by promoting VSMC growth and associated fibrous cap formation, and therefore enhance plaque stability. Conversely, other MMPs (including MMP-7, -8, -12, -13, and -14) may promote plaque progression through increased matrix degradation, inflammation, and susceptibility to apoptosis, and thus participate in triggering of plaque rupture.

In advocacy, transgenic or gene therapy-directed systemic overexpression of TIMP-1 failed to retard plaque progression,[66,68] although atherogenesis was retarded in another study.[67] Similarly TIMP-1 deficiency had no effect on plaque burden in one study,[64] while increasing lesion size in another.[65] Conversely, both short-term and long-term overexpression of TIMP-2 but not TIMP-1 retarded progression of advanced plaques, in part through inhibiting monocyte/macrophage invasion and their susceptibility to apoptosis.[66] These studies lend further support for pro- and antiatherosclerotic effects of MMPs, as TIMP-1 and -2 display salient differences in their inhibitory efficacies toward specific MMPs, such as MT-MMPs.[13] These findings may explain why the results of in vivo studies utilizing synthetic compounds containing zinc-chelating groups (such as thiol or hydroxamate groups or tetracycline derivates), which serve as broad-spectrum MMP inhibitors, have been so disappointing. Indeed, a hydroxamic acid-based, nonselective MMP inhibitor exhibited no beneficial effects on plaque development or progression in *LDLR*-KO mice[33] or *Apoe*-KO animals.[63] Similarly, the widely used antibiotic doxycycline, which also displays broad-spectrum MMP-inhibitory properties, failed to prevent plaque development in *Apoe*-KO mice.[62] Moreover, treatment with doxycycline in two independent, randomized, double-blind, and placebo-controlled clinical trials in patients with symptomatic coronary and carotid artery disease failed to have any positive effects on plaque phenotype or clinical outcome.[69,70]

Accordingly, selectively targeting MMPs with a clear detrimental role represents a more effective approach for retarding atherosclerotic plaque progression. In point of fact, two recent studies employing selective inhibitors to MMP-12[42] or MMP-13[43] have supported this tactic. Selective MMP-12 inhibition blocked plaque progression and improved stability through reduction of lipid-core expansion and macrophage apoptosis, increased VSMC-to-macrophage ratio, decreased plaque calcification, and attenuated elastinolysis.[42] All these effects, together with a reduction of buried fibrous layers in brachiocephalic plaques, mirrored those observed in *Mmp12*/*Apoe* double-KO mice.[54] Similarly a highly specific inhibitor toward MMP-13[43] retarded intraplaque collagenolytic activity, preserving fibrillar collagen levels in plaques, which would confer increased plaque stability, and resembled the effects previously observed in *Mmp13*-KO mice.[60] Therefore, these proof-of-principle studies in mice provide motivation to translate selective MMP-inhibitor treatment to human patients harboring atherosclerosis. Two more recent studies have highlighted the potential of targeting micro-ribonucleic acids that modulate MMP/TIMP expression as novel therapeutic avenues for preventing plaque progression, miR-24 regulation of macrophage MMP-14 expression,[71] and miR-712 modulation of endothelial cell TIMP-3 levels.[72]

An array of studies in cells, animal models, and humans has decisively established that MMPs play a central role in the development, progression, and rupture of atherosclerotic plaques. Additionally, the functions of MMPs in all vascular cell types and the subsequent consequences for atherosclerosis have been further elucidated. Together, this panoply of work has highlighted that modulation of MMP activity can reverse atherosclerosis, but that broad-spectrum MMP inhibition cannot replicate these properties, possibly owing to effects on both beneficial and detrimental MMPs. Consequently, it is now accepted that inhibitors with restricted specificity toward individual MMPs, such as MMP-12 and -13, are desirable for translation to man, particularly in the context of atherosclerotic plaque stabilization.

Abdominal aortic aneurysms

Although found at various locations throughout the vascular tree, abdominal aortic aneurysms (AAAs) demonstrate predominance, and it is estimated that up to 8% of men aged over 65 years and up to 2.2% of women of the same age harbor aneurysms.[73] Patients with AAAs frequently have atherosclerosis, and associations have been shown in meta-analysis studies.[73] Moreover, intimal atherosclerosis is commonly present in AAA lesions,[74] although the composition is different compared to coronary and carotid plaques, and medial elastin fragmentation is more prevalent.[73] Consequently, AAAs are considered

a form of atherosclerosis with subtle differences in etiology to those observed in nascent atherosclerosis, and are regularly referred to as "atherosclerotic aneurysms".[73,75,76] Pathological observations suggest that ECM remodeling in unison with inflammatory cell infiltration, including macrophages at both the adventitial and medial aspects is a striking feature of human atherosclerotic AAAs,[74,77] particularly the transition of small "silent" aortic dilatations to large clinically relevant AAAs.[76] Similarly, macrophage accumulation is a common feature in animal models of AAAs, irrespective of species or stimuli, and throughout all stages of development.[78] Moreover, imaging of the abdominal aorta of angiotensin (Ang)-II-infused *Apoe*-KO mice demonstrated an association between persistent macrophage accumulation and AAA pathogenesis.[79]

It is considered that the principal detrimental role of macrophages in AAAs is their release of proteolytic enzymes, which are responsible for the excessive loss of ECM, especially elastin and fibrillar collagens, which characterize AAA progression and rupture.[77] MMPs have been demonstrated to be abundantly expressed by macrophage infiltrates within AAAs.[80] There is already substantial evidence that increased expression and activity of various MMPs play an important role in the pathogenesis of AAAs.[78,81] For instance, expression of MMP-1, -2, -3, -8, -9, -12, -13, and -14 is increased in aneurysmal tissues compared to control nondiseased arteries (Table 1).[82] Furthermore, plasma levels of MMP-9 are elevated in patients with AAAs compared with controls.[83]

Accordingly, a plethora of in vivo studies have been undertaken to elucidate which MMPs modulate AAA formation (Table 4).[33,53,84–104] It was shown that MMP-2,[84] MMP-3,[53] MMP-9,[84–86] MMP-12,[85,87,88] MMP-13,[89] and MMP-14 KO mice[90] exhibit attenuated experimental aneurysm formation (assessed principally as aortic dilatation)

Table 4 Results of in vivo animal studies evaluating the effects of modulating matrix metalloproteinases (MMPs) or tissue inhibitors of metalloproteinases (TIMPs) on abdominal aortic aneurysm formation and cellular composition, using recombinant adenoviral (RAd) overexpression, gene knockout (KO), or pharmacological inhibitors of MMPs (MMPis)

Modulation	Model (species)	Aneurysm formation	Reference
MMP-2 KO	$CaCl_2$ (Ms)	Reduced	79
	$CaCl_2$ (Ms) – BMT	No effect	79
MMP-3 KO	*Apoe* KO (Ms) – HFD	Reduced	48
MMP-9 KO	$CaCl_2$ (Ms)	Reduced	79
	$CaCl_2$ (Ms) – BMT	Reduced	79
	Elastase (Ms)	Reduced; ↓ inflammation and MMP activity	80
	Elastase (Ms) – BMT	Reduced	80
	$CaCl_2$ (Ms)	Reduced; despite ↑ MMP-2 activity	81
MMP-12 KO	Elastase (Ms)	No effect	80
	$CaCl_2$ (Ms)	Reduced; ↓ inflammation	82
	AngII + TGFβ (Ms)	Reduced	83
MMP-13 KO	Elastase (Ms)	Reduced	84
MMP-14 KO	$CaCl_2$ (Ms) – BMT	Reduced; ↓ MMP activity, ↔ inflammation	85
TIMP-1 KO	Elastase (Ms)	Increased	86
TIMP-1 RAd	Xenograft (Rt)	Reduced; ↓ MMP activity	87
TIMP-2 KO	$CaCl_2$ (Ms)	Reduced; ↓ MMP-2 activity	88
TIMP-3 KO	AngII (Ms)	Increased; MMP-2 independent	89
MMPi (Dox)	Elastase (Ms)	Reduced; ↓ inflammation and MMP activity	80
MMPi (Dox)	Elastase (Ms)	Reduced; ↓ MMP activity, ↔ inflammation	90
MMPi (Dox)	Elastase (Ms)	Reduced; ↓ inflammation and VSMC proliferation	91
MMPi (Dox)	Elastase (Rt)	Reduced; ↔ inflammation or MMP expression	92
MMPi (Dox)	$CaCl_2$ (Ms)	Reduced	93
MMPi (Dox)	$CaCl_2$ (Ms)	Reduced; ↓ MMP activity	94
MMPi (Dox)	*Apoe* KO (Ms) + AngII	Reduced; ↓ MMP activity	95
MMPi (Dox)	*Apoe* KO (Ms) + AngII	Reduced; ↔ MMP-2 and -9 expression	96
MMPi (Dox)	*Apoe* KO (Ms) + AngII	Reduced; ↓ inflammation	97
MMPi (Hyd)	*Apoe* KO (Ms) – HFD	Reduced	29
MMPi (Hyd)	Elastase (Rt)	Reduced; ↓ inflammation	98
MMPi (Hyd)	Elastase (Rt)	Reduced; ↔ inflammation	99

Notes: ↓, decreased; ↑, increased; ↔, no change.
Abbreviations: Ms, mouse; Rt, rat; VSMC, vascular smooth-muscle cell; BMT, bone marrow transplantation; *Apoe*, apolipoprotein E; HFD, high-fat diet; AngII, angiotensin II; Dox, doxycycline; Hyd, hydroxamic acid.

compared to wild-type controls. This evidence suggests that MMPs are vitally important in the formation of aneurysms, and that MMP inhibition may be a potential therapeutic strategy for aneurysms. In fact, a multitude of studies have evaluated the effects of MMP inhibitors or pleiotropic compounds with MMP-inhibitory properties in human aneurysmal samples, organ culture, or animal models of AAAs.[81] For instance, animal studies with doxycycline, a tetracycline analog that reduces both MMP-9 expression and activity attenuated aneurysm formation in elastase-induced,[85,95–97] calcium chloride application,[98,99] and AngII-induced[100–102] rodent models. Results from three preliminary human studies suggest that these experimental findings may also apply to human disease.[105–107] CGS 27023A, batimastat, and RS132908, all hydroxamate-based broad-spectrum MMP inhibitors, also suppressed the expansion of experimental AAAs in murine models.[33,103,104] However, other studies have reported more modest effects or no reduction in AAAs after MMP inhibition.[78,81]

Nonetheless, an endogenous tissue inhibitor of metalloproteinases, TIMP-1, appears to have a protective effect on AAA formation, since *Timp1*-KO mice have larger aneurysms than wild-type mice,[91] and overexpression of TIMP-1 prevents elastin degradation, aneurysm formation, and rupture in a rat model of AAAs.[92] Conversely, KO of TIMP-2 reduced AAA formation, although this may have been through reduced MMP-2 activation.[93] Interestingly, TIMP-3 expression has been shown to be elevated in plasma from AAA patients[108] and aneurysmal tissues, primarily in macrophages,[109] and is considered a positive-feedback mechanism that reflects an effort to counteract MMP activity.[110] In support, a recent study in nonatherosclerotic mice demonstrated that *Timp3* gene deletion triggered adverse remodeling of the abdominal aorta in response to AngII, in part through increased inflammation and associated proteolytic activity,[94] suggesting that restoring TIMP-3 levels may be protective against AAA progression and rupture.

The promising results observed in single-MMP or TIMP-modified animal models, alongside the more ambivalent findings seen with broad-spectrum MMP inhibitors in both mice and humans, again suggest that the roles of individual MMPs are of more relevance, and thus selective MMP inhibition is required for therapeutic modulation of AAA progression and rupture. It must also be noted that the majority of the clinical trials reported were underpowered and exhibited other ambiguities in experimental design.[111] Nonetheless, two large, pivotal trials are in progress, and their outcomes are eagerly anticipated.[112]

Post-myocardial infarction remodeling

Patients who have had a previous MI have an increased susceptibility to heart failure, due primarily to aberrant structural and functional changes to the left ventricle, termed post-MI remodeling. The myocardial damage rendered subsequently to an MI and ensuing ischemic injury triggers a number of cellular and ECM events. These include the expression of a multitude of inflammatory mediators and chemokines, recruitment and infiltration of inflammatory cells (such as neutrophils and monocytes), proliferation and transdifferentiation of cardiac fibroblasts, and the initiation of ECM synthesis and proteolysis pathways.[113] Moreover, at the injury site, macrophages themselves orchestrate a myriad of responses, including removal of necrotic cardiac myocytes and apoptotic neutrophils; secretion of cytokines, chemokines, and growth factors; and modulation of phases of the angiogenic response.[114] Indeed, neovascularization is an important aspect of effective post-MI remodeling, and consequently promoting angiogenesis is considered a therapeutic strategy to prevent heart failure. Intriguingly, MMP activity is considered a vital determinant during the initiation and growth of angiogenic vessels.[4] Together, these processes are considered a homeostatic wound-healing response that becomes maladaptive due to dysregulated ECM turnover and defective inflammation resolution, resulting in adverse post-MI remodeling and progression to heart failure.[115] In particular, recruited inflammatory cells secrete numerous proteases, including MMPs, which facilitates their margination while also degrading the recently formed ECM at the periphery of the infarct, and it is this overlapping balance between inflammation-mediated proteolysis and fibrosis-driven remodeling that is fundamental for efficient healing and scar formation.[114] Accordingly, there has been considerable interest in the spatial and temporal expression patterns of MMPs during post-MI remodeling. Indeed, a myriad of MMPs are upregulated post-MI by both resident cardiac cells and newly recruited inflammatory cells (Table 1), and are also detectable in the circulation.[116] More recently, researchers have utilized salient animal models to elucidate the contribution of MMPs during post-MI remodeling (Table 5).[117–137]

Inhibition of MMP-2 activity through gene deletion was shown to improve survival rates after left anterior descending coronary artery ligation-induced MI, compared to wild-type control animals.[117] This benefit was afforded primarily due to inhibition of cardiac rupture, despite negligible effects on infarct size and heart function. Similar findings were reported by Matsumura et al[118] employing either *Mmp2*-KO mice or

Table 5 Results of in vivo animal studies evaluating the effects of modulating matrix metalloproteinases (MMPs) or tissue inhibitors of metalloproteinases (TIMPs) on post-MI remodeling, using recombinant adenoviral (RAd) overexpression (Ovex), gene knockout (KO [KO* = heterozygote]), gene knockdown (KD), transgenic (Tg), or pharmacological inhibitors of MMPs (Inhib)

Modulation	Model (species)	Infarct size	HF	Inflammation	Survival	Reference
MMP-2 KO	LAD CA ligation (Ms)	↔	↔	NR	↑	112
	LAD CA ligation (Ms)	↔	↔	$\downarrow^{E}$; $\leftrightarrow^{L}$	↑	113
MMP-2 Inhib	LAD CA ligation (Ms)	↔	↔	$\downarrow^{E}$; $\leftrightarrow^{L}$	↑	113
MMP-3 KO	LAD CA ligation (Ms)	↔	NR	↔	↔	114
MMP-7 KO	LAD CA ligation (Ms)	↔	↑	NR	↑	115
MMP-9 KO	LAD CA ligation (Ms)	↔	NR	↓	↑	114
	LAD CA ligation (Ms)	↔	↑	↓	↔	116
	LAD CA ligation (Ms)	↔	↑	$\downarrow^{E}$; $\leftrightarrow^{L}$	↔	117
MMP-9 Tg	LAD CA ligation (Ms)	↔	↑	↔	↔	118
MMP-12 KO	LAD CA ligation (Ms)	↔	NR	↔	↔	114
MMP-14 KD	LAD CA ligation (Ms)	↔	↑	NR	↑	119
	LAD CA ligation (Ms)	$\leftrightarrow^{E}$; $\downarrow^{L}$	↑	↓	↑	120
MMP-14 Tg	LAD CA ligation (Ms)	↔	↓	NR	↓	119
	LAD CA ligation (Ms)	NR	↓	NR	↓	121
MMP-25 KO	LAD CA ligation (Ms)	NR	↓	↓	↓	122
TIMP-1 KO	LAD CA ligation (Ms)	↔	↓	↔	↔	123
	LAD CA ligation (Ms)	NR	↓	NR	NR	124
TIMP-1 (RAd)	LAD CA ligation (Ms)	↓	NR	↓	↑	114
TIMP-2 KO	LAD CA ligation (Ms)	↑	↓	↑	↔	125
TIMP-2 (RAd)	LAD CA ligation (Ms)	↔	↑	↓	↑	126
TIMP-3 KO	LAD CA ligation (Ms)	NR	↓	NR	↓	127
	LAD CA ligation (Ms)	↑	↓	↑	↓	128
	LAD CA ligation (Ms)	↔	↔	NR	↓	129
TIMP-3 Ovex	LAD CA ligation (Pg)	↓	↑	↓	NR	130
TIMP-4 KO*	LAD CA ligation (Ms)	↑	↓	↑	↓	131
TIMP-4 Tg Ovex	LAD CA ligation (Ms)	↔	↑	↓	↔	132
TIMP-4 RAd Ovex	LAD CA ligation (Ms)	↔	↑	↔	↔	132

Notes: ↓, decreased; ↑, increased; ↔, no change.
Abbreviations: MI, myocardial infarction; Ms, mouse; Pg, pig; HF, heart function; LAD, left anterior descending; CA, coronary artery; E, early (≤7 days post-MI); L, late (≥14 days post-MI); NR, not reported.

an MMP-2-selective inhibitor. However, it was noted that MMP-2 loss/inhibition reduced the inflammatory infiltrate at early time points, potentially resulting in failed clearance of necrotic cardiomyocytes. It should also be highlighted that the MMP-2 inhibitor used was not selective and also targeted other MMPs.[118] Deletion of *Mmp3* had insignificant effects on post-MI remodeling and survival.[119] Cardiac rupture and mortality were attenuated in *Mmp7*-KO mice alongside an improvement in cardiac function, potentially due to a novel role for MMP-7 in modulating connexin-43 levels.[120]

While modulation of MMP-9 failed to impact on infarct size, benefits on heart function and reduced inflammation have been reported,[119,121–123] although improved survival rates were observed in only one study.[119] The beneficial effects of reduced MMP-9 levels are considered to be through modulating fibrosis[121] and improving post-MI angiogenesis,[122] although MMP-9 has also been shown to promote angiogenesis after ischemic injury.[138] Intriguingly, macrophage-specific overexpression did not influence macrophage accumulation at the infarct site, but did favorably alter the inflammatory milieu and limit ECM synthesis to improve left ventricular (LV) function post-MI.[123] *Mmp12* deletion did not influence infarct size, inflammation, or survival subsequent to left anterior descending coronary artery ligation.[119]

Several studies utilizing either *Mmp14* heterozygote gene-knockdown mice[124,125] or cardiac-restricted overexpression of MMP-14[124,126] have collectively demonstrated that perturbed MMP-14 expression and activity affords a distinct survival advantage associated with improved cardiac function through preservation of the fibrillar collagen network in a TGFβ-dependent manner, although reduced inflammation and scar size was also noted.[125] *Mmp28* deficiency aggravated post-MI remodeling and resulted in decreased survival, due to increased cardiac rupture rates and worse function compared with wild-type controls. *Mmp28* deletion also resulted in a reduced inflammatory response, as well as decreases in

cardiac fibroblast numbers, ECM deposition, and collagen cross-linking, attributable to impaired M2 macrophage activation in the absence of MMP-28.[127] Intriguingly, this study suggests that similar to other cardiovascular pathologies, MMPs play divergent roles in the MI setting, and MMP-28 may represent a beneficial protease.

Studies employing animal models of post-MI remodeling where TIMPs were modulated have further supported a deleterious role for MMPs, although differences in changes in myocardial structure were observed. Experimental MI induction in *Timp1*-deficient mice accelerated adverse LV remodeling, resulting in abrogated heart function,[128,129] due in part to decreased ECM structural integrity linked to increased MMP activity. Indeed, broad-spectrum MMP inhibition could partially rescue the *Timp1*-KO phenotype,[129] while adenoviral-directed increased plasma levels of TIMP-1 improved post-MI survival alongside retardation of the infarct inflammatory response.[139] Accelerated post-MI remodeling was observed in *Timp2*-KO mice compared to wild-type controls, which was associated with increased inflammation and infarct size, although no effects on survival were observed.[130] Moreover, *Timp2* deficiency resulted in decreased MMP-2 activity after MI induction, while overall myocardial collagenolysis was increased due to heightened MMP-14 activity, underscoring the selective regulation of adverse MMP-14 remodeling by TIMP-2.[130] In support, adenoviral-mediated myocardial delivery of the TIMP-2 gene reduced MMP activity and improved post-MI survival, while limiting inflammatory cell recruitment and adverse LV remodeling.[131]

Three independent studies have demonstrated that MI induction in *Timp3*-KO mice was associated with increased cardiac rupture and reduced survival.[132–134] The mechanisms underlying these profound effects were postulated as accelerated ECM degradation and inflammatory cytokine activation,[132] heightened and persistent myocardial inflammation,[133] and via EGF/EGF receptor (EGFR) signaling and downregulation of $TGF\beta_1$ expression and collagen synthesis.[134] Indeed, it was demonstrated that inhibition of EGFR by cetuximab, an EGFR-neutralizing antibody, protects against cardiac rupture and improves survival in *Timp3*-KO mice.[134] Eckhouse et al exploited the high affinity TIMP-3 has to the ECM by delivering to the myocardium recombinant TIMP-3 that was encapsulated in a hyaluronic acid-based gel.[135] This approach retarded infarct expansion and LV remodeling, providing proof of principle that targeted delivery of TIMPs may have therapeutic potential for adverse post-MI remodeling. Finally, *Timp4*-KO mice were more susceptible to MI-induced dysfunctional LV remodeling and increased mortality, in part through elevated inflammation and MMP activity, as coadministration of a broad-spectrum MMP inhibitor rescued the observed phenotype.[136] Concomitantly, myocardial targeted adenoviral or transgenic TIMP-4 overexpression perturbed adverse LV remodeling post-MI in mice, which was associated with reduced MMP activity, while fibrillar collagen synthesis and content was increased.[137]

Due to the overwhelming evidence outlined implicating MMPs as orchestrators of adverse post-MI remodeling, the hypothesized beneficial effects of MMP inhibition have been explored. A multitude of animal studies have been conducted where global MMP inhibition has been assessed pre-, during, and post-MI, demonstrating in most studies that broad-spectrum MMP inhibition afforded protection from adverse post-MI LV remodeling, while infarct size and mortality were rarely affected.[140] Despite the plethora of in vivo findings in relevant animal models, only a limited number of approaches have been advanced to the clinical arena. Firstly, the PREMIER study evaluated the potential beneficial effect of a hydroxamate-based broad-spectrum MMP inhibitor (PG11680) in patients who had suffered an MI.[141] Disappointingly, adverse LV remodeling and clinical outcomes were unaffected, despite previously observed beneficial effects in a preclinical animal model with a similar compound.[142] The inefficacy of the PREMIER trial may be attributable to a myriad of factors, including an inadequate dosing regime and a poorly selected end point. Indeed, the plasma profiles achieved in patients receiving PG11680 were not reported, casting further doubt on the validity of the study. Further potentially confounding factors include inhibition of possible beneficial MMPs, spatial and/or temporal effects on MMP activity, and indiscriminate effects on different resident and infiltrating cell types. Encouragingly, a very recent trial (TIPTOP) has yielded more promising results.[143] Administration of submicrobial doses of doxycycline given to patients postreperfusion subsequent to an MI improved heart function and reduced infarct size compared to placebo controls.[143] Although encouraging, larger clinical trials are warranted to further validate these preliminary findings and to test chemically modified tetracycline derivatives, which express a safer clinical profile.

Taken together, the numerous findings discussed highlight that potential therapeutic strategies to modulate adverse post-MI remodeling may be more effective when inhibiting select subsets or individual MMPs rather than global inhibition,

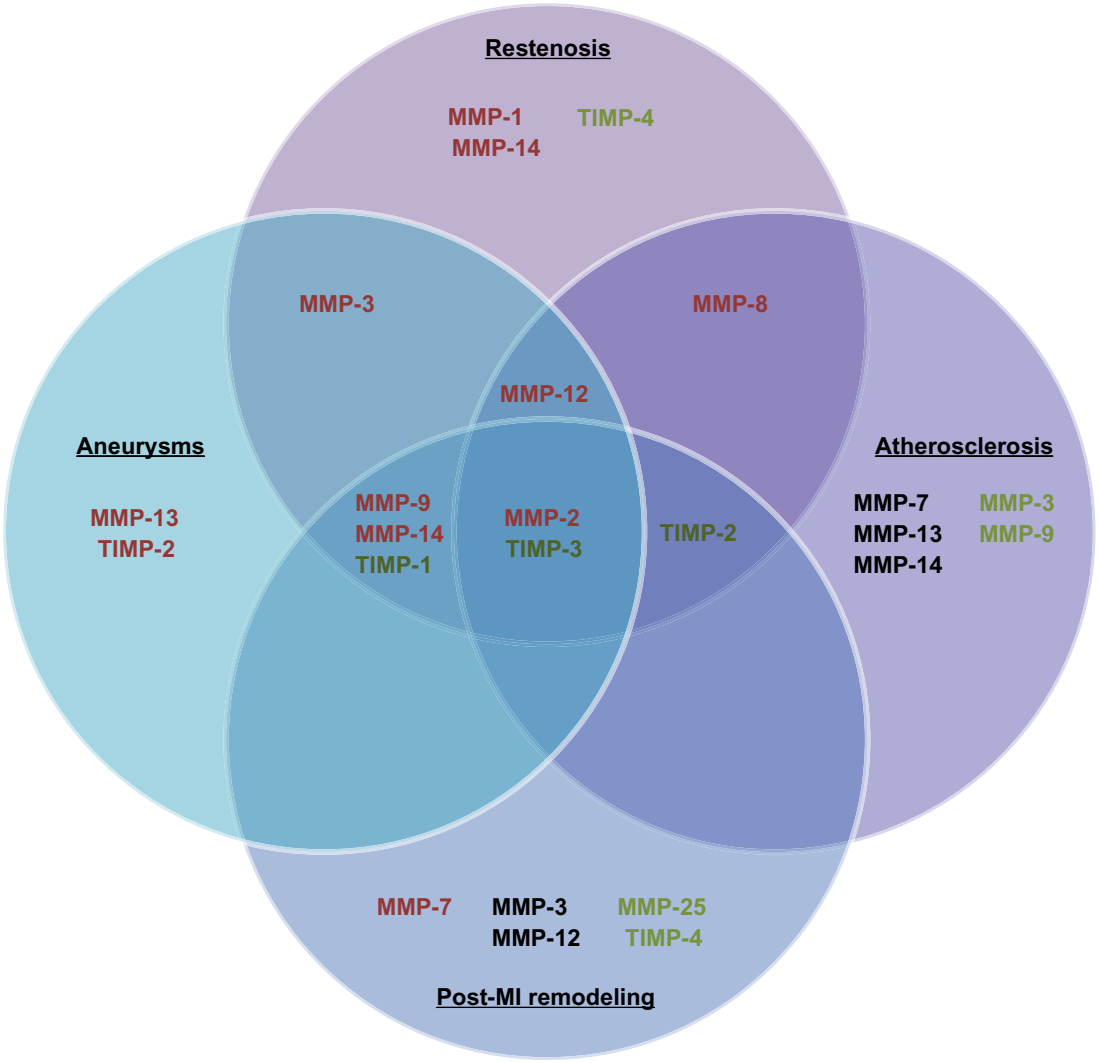

Figure 2 This diagram illustrates the matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) determined detrimental (red), neutral (black), or beneficial (green) in animal models of intimal formation, abdominal aortic aneurysms, atherosclerosis, and post-myocardial infarction (MI) remodeling.

with MMP-28 a notable exception.[127] Moreover, stratagems to direct inhibition toward specific sites within the myocardium at precise time points and within select cell types may prove most efficacious.

Conclusion

MMPs and their endogenous inhibitors play fundamental roles in the progression of pertinent cardiovascular pathologies, including intimal formation, atherosclerosis, AAAs, and adverse post-MI remodeling (Figure 2). Genetic manipulation studies primarily performed in mice, alongside associative studies in human pathological tissues, have established the roles and functions of individual MMPs. Accordingly, varying methodologies to restore or overexpress TIMPs have proven effective in reducing MMP activity in vivo and rescuing pathological phenotypes. Lamentably, the utilization of broad-spectrum MMP inhibitors has not consistently replicated the effects observed with TIMPs in pertinent preclinical models or in clinical trials in man. Such poor translation may be due in part to the beneficial as well as detrimental effects MMPs exert in numerous cardiovascular pathologies, alongside divergent effects on differing cell types. Accordingly, prominence has moved toward the development of MMP inhibitors that display restricted specificity, as recently demonstrated in the atherosclerosis-research field with inhibitors directed toward MMP-12[42] and MMP-13.[43] Additionally, consideration of the temporal and spatial expression of MMPs and their activity in the differing cardiovascular pathologies is necessary to ensure maximal efficacy of any potential inhibitor-based therapeutic approaches. Furthermore, it may be advantageous to target specific cell types, such as macrophages, which may spare

the positive actions of certain MMPs within beneficial cell types, although attention to the stage of disease progression is paramount, as some cell-specific MMPs will have divergent effects dependent on the disease stage. Consequently, in spite of caveats in the translation of findings in animal models to human pathologies, the reviewed studies instill a renewed impetus for future clinical trials of selective MMP inhibitors in prominent cardiovascular pathologies. Indeed, there are several clinical trials under way assessing the potential of elective MMP inhibitors in several cardiovascular diseases, including atherosclerosis, AAAs, and post-MI remodeling.

Disclosure

The author reports no conflicts of interest in this work.

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