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Regulation and involvement of matrix metalloproteinases in vascular diseases

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Abstract

Matrix metalloproteinases (MMPs) are a family of zinc dependent endopeptidases whose main function is to degrade and deposit structural proteins within the extracellular matrix (ECM). A dysregulation of MMPs is linked to vascular diseases. MMPs are classified into collagenases, gelatinases, membrane-type, metalloelastase, stromelysins, matrilysins, enamelysins, and unclassified subgroups. The production of MMPs is stimulated by factors such as oxidative stress, growth factors and inflammation which lead to its up- or down-regulation with subsequent ECM remodeling. Normally, excess activation of MMPs is controlled by their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs). An imbalance of MMPs and TIMPs has been implicated in hypertension, atherosclerotic plaque formation and instability, aortic aneurysms and varicose vein wall remodeling. Also, recent evidence suggests epigenetic regulation of some MMPs in angiogenesis and atherosclerosis. Over the years, pharmacological inhibitors of MMPs have been used to modify or prevent the development of the disease with some success. In this review, we discuss recent advances in MMP biology, and their involvement in the manifestation of vascular disease.

Keywords

MMPs; TIMPs; miRNA; Epigenetics; Extracellular Matrix; Atherosclerosis; Cardiovascular; Review

2. INTRODUCTION

Vascular diseases are the leading cause of morbidity and mortality worldwide. In general, vascular disease relates to pathological states of the circulatory system including arteries, vein, capillaries, lymph vessels, and blood disorders which affects circulation. One of the major manifestation of vascular disease is atherosclerosis, a plaque build-up containing fat, cholesterol, and other substances within the arterial walls. Over time, the plaque hardens leading to narrowing of the arterial lumen which ultimately decreases blood flow to the

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tissue or organ. The consequence of atherosclerosis can progress to a spectrum of serious health problems including hypertension, stroke, heart attack and death.

The inner lining of blood vessels is composed of endothelial cells (ECs) and damage to ECs by pathogens or oxidative radicals lead to inflammatory response which triggers leukocyte adhesion and transmigration into the vessel wall. As a result, extracellular matrix regulatory peptidases, matrix metalloproteinases (MMPs) become activated leading to vascular smooth muscle cells (VSMCs) proliferation, cell-to-cell tight junction protein alteration and vascular leakage, elastin and collagen derangement, and vascular dysfunction. This review, summarizes the impact of uncontrolled MMP activation in the vasculature and highlights their regulatory mechanisms involved in maintaining physiological function and deviations leading to pathophysiology.

3. GENERAL CONCEPTS OF MMPS

In 1962, Gross and Lapiere discovered an enzyme capable of degrading collagen during the metamorphosis of the anuran tadpole tail (1). The enzyme, a collagenase was found to play a significant role in the normal development and growth in amphibians thus maintaining a balance between tissue synthesis and degradation (1). From this conclusion arose the general concept of MMPs which has been applied continuously in various studies including homeostasis and tissue remodeling under pathological conditions. The MMPs in turn are regulated by a group of enzymes, tissue inhibitors of metalloproteases (TIMPs). The general concept dictates that a balance between TIMPs and MMPs regulates tissue remodeling, repair, and resorption. A dysregulation of the MMP/TIMP ratio may lead to unchecked MMP activity leading to adverse events in tissue homeostasis (2). There are currently 25 MMPs with substrate specificity for a broad spectrum of fibrous structural proteins (2). Many of these substrates are found within the extracellular matrix (ECM) surrounding the blood vessels (3). Indeed, dysregulated MMP activity has been observed in a number of diseases including atherosclerosis, fibrosis, heart failure, emphysema, and chronic obstructive pulmonary disease (COPD) where ECM alteration is a predominant feature (2,4). Since MMP activity is known to play a prominent role in vascular diseases a potential strategy counter would be to reduce MMP activity to ameliorate ECM remodeling.

4. STRUCTURE AND BIOSYNTHESIS

X-ray crystallography and NMR spectroscopy have been used for elucidation of MMP structure in the last 20 years. Prior to this, thermolysin, a bacterial endopeptidase, and astacin, a crayfish endopeptidase, were used to design MMP inhibitors and subsequent structure elucidation. However, the models lacked the information necessary to carry out rational drug design, and the catalytic domain of MMP-1 became the first of the group to undergo structural studies using multiple isomorphous replacements at a resolution of 2.4 Angstroms (5). MMPs have three conserved domains; (i) zinc-containing catalytic domain; (ii) pro-peptide on the amino terminus; (iii) hemopexin-like domain at the C-terminus (Figure 1). The catalytic domain has two zinc ions and at least one calcium ion. Of the zinc ions, only one ion (Z1) is catalytic (2). MMP-23 does not have a catalytic domain (2). The hemopexin-like domain is called as such because of its sequence homology to hemopexin, a

plasma protein involved in heme binding and transport (2). MMPs are a family of zinc endopeptidases present in the extracellular matrix (ECM) or membrane (2). Sequence alignment has confirmed that they belong to a superfamily of zinc peptidases known as metzincins. Among all the MMPs described so far, 25 MMPs have been discovered where MMP-4,-5, and -6 are encoded by MMPs can be either membrane-bound or secreted (2,6,7). Membrane-type MMP is often referred to as simply MT-MMPs (2).

All MMPs are secreted and cleavage of the signal sequence yields a zymogen inactivated by a highly conserved prodomain displaying the consensus sequence PRCGVPDV (Figure 1). This prodomain is often called a switch loop as it contains Cys92 whose thiol coordinates with Z1 in the proenzyme (2,8). The polypeptide linker connecting the catalytic domain to the prodomain can undergo furin cleavage, proconvertase action, sheddase action, or auto-activation to yield the active enzyme (2).

5. TYPES OF MMPS AND THEIR INVOLVEMENT IN DISEASES

MMPs are further divided into subgroups based on their substrate preference (Figure 2). Blood vessels are known to be under the control of hormonal, neuronal, and hemodynamic input. Since the blood vessels are surrounded by ECM, dysregulation of MMP activity may lead to chronic vascular remodeling and vascular disease (9). Table 1 displays the vascular events associated with specific MMPs.

5.1. Collagenases

MMP-1, -8 -13 and -18 are collagenases which mainly cleave fibrillar collagen types I, II and III. In addition, these collagenases exhibit specificity for other substrates such as gelatin, casein, aggrecan, laminin, versican, perlecan, fibronectin, and tenascin (10,11). High levels of MMP-1 have been reported in varicose veins (12). In spontaneously hypertensive rats, DeLano and Schmid-Schonbein showed that cell membrane receptor cleavage by MMP-1 was associated with insulin resistance (13). Elevated MMP-1 and -8 activity in the mesentery were observed in rat models of acute venous hypertension (12). In the same study, upstream of the venous pressure increased vascular endothelial growth factor receptor-2 (VEGRF2) expression was observed, and became more elevated with MMP inhibition (12). In human carotid atheroma, angiotensin II receptor 1 blockage significantly reduced MMP-1 and -8 concentrations within atheroma suggesting the involvement of these MMPs in plaque stability (14). Recent findings suggest that M1 macrophage-mediated MMP-13 expression induced neointima formation after vascular injury in eNOS knockout mice, and that MMP-13 is involved in vascular disease (15). Protease-activated receptor-1 (PAR1) is a G protein-coupled receptor and MMP-13 has been demonstrated to cleave PAR1 resulting in the activation of G-protein signaling pathway in restenosis and atherothrombotic diseases (16). In addition, MMP-13 is an interstitial collagenase and has been shown to have significant renal expression related to ECM remodeling during progressive renal diseases (17,18). In a recent study, we reported that increased expression of MMP-13 in mouse glomerular ECs were mediated by homocysteine, a non-protein amino acid and vascular risk factor (19). Using pharmacological MMP-13 inhibitor, Quillard *et al* showed that the accumulation of collagen in the plaque is associated with resistance to rupture (20).

Although the expression of MMP-18 has been reported in a variety of human cell lines, it has not been associated with any disease (21,22).

5.2. Gelatinases

MMP-2 and MMP-9 are gelatinases highly expressed in varicose veins (9). Increased MMP-9 activity has been demonstrated in the mesenteric veins of acutely hypertensive rats (12). In a meta-analysis focusing on characterizing the expression profile of low grade inflammation in patients with coronary artery disease, MMP-9 levels were found to be elevated suggesting its use as a potential biomarker, however, further studies are required to conclude the causality of low grade inflammation in vascular diseases (23).

The receptor activation of NF-kB was studied by using receptor activator of nuclear factor kappa-B ligand (RANKL) /Osteoprotegerin ratio in a cohort study consisting of patients with severe carotid artery stenosis and was observed to correlate directly with MMP-9 activity (24). Hydroxytyrol is commonly found in olive oil and is associated with cardioprotection. It has been suggested that this molecule inhibits monocyte activation of cyclooxygenase 2 which generates eicosanoids capable of suppressing MMP-9 activity (25). The proposed mechanism of action is inhibition of the protein kinase C alpha and beta 1 pathways conferring anti-atherosclerotic and anti-inflammatory properties (25). High serum MMP-9 is associated with increased intimal thickness and plaque instability (26). Tumor necrosis factor-induced activation of eNOS along with MMP-9 and protein kinase B activation are markers for endothelial dysfunction which is mitigated by treatment with apigenin, an estrogen receptor agonist (27). The formation of calcified aortic valve is influenced by a number of cardiac risk factors, molecular signaling pathways, and hemodynamics (28,29). A model for fluid shear stress (FSS) showed increased ECM degradation due to elevated MMP-9 and MMP-2 activity was associated with FSS (30). In patients suffering from cardiac disease, increased expression and binding of CD40 ligand/ receptor has been associated with activation of MMP-9 and pro-angiogenesis (31). The upregulation of soluble CD40 ligand (sCD40L) occurs via CD40/CD40L/ TRAF axis and the stimulation of sCD40L has been shown to induce the phosphorylation of p38 MAPK and to increase the release of MMP-9 in endothelial progenitor cells (31). In a recent study, vitamin C deficiency directly correlated with stress-induced cardiac damage which was associated with increased activity of MMP-2 and -9 (32).

The cardiac matrix was shown to regulate physiological processes involved in angiogenesis, hypertrophy, and cardiac fibrosis through the differential microRNA profile (33). A recent review article reports the current mechanistic understanding on the effects of reactive oxygen/nitrogen species effect on MMP-2 expression (34).

MMP-2 was also shown to induce VSM relaxation in the inferior vena cava of rats leading to venous dilatation, varicose veins and insufficiency (35). Treatment with L-NG-nitroarginine methyl ester (L-NAME) and indomethacin showed that elevated levels of nitric oxide (NO) or prostacyclin was not involved because inhibition of nitric oxide synthase (NOS) and cyclooxygenase did not stop vascular smooth muscle (VSM) relaxation (8,35). Iberiotoxin treatment was successful in stopping VSM relaxation through the action of blocking large

conductance Ca^{2+}-activated K^+ channels, suggesting a role in the VSM hyperpolarization pathway (8).

In patients with chronic ischemic stroke it has been demonstrated that decreased plasma concentrations of MMP-2 and homocysteine were more closely associated with intracranial atherosclerosis (ICAS) than extracranial atherosclerosis (ECAS) suggesting that MMP-2 may play a role in the development of ICAS (36). In another clinical study, Shimizu *et al* reported the progression of intracranial large artery atherosclerosis (ILA) in 12.5% patients with acute ischemic stroke, and these patients exhibited decreased MMP-2 and increased MMP-9 along with increased IL-6 in their serum (37). Although the authors did not conclude on the role of MMPs in this study, it is possible that both MMPs may have role in ILA progression along with IL-6. It is also known that carotid artery atherosclerotic plaque rupture can lead to thromboembolism and stroke. In fact, Heo *et al* conducted a study to determine the relationship between the expression of MMP-2 and -9 in patients with atherosclerotic plaque instability. Their findings demonstrated a significant correlation between increased expression of MMP-2 and -9 and cap rupture suggesting their involvement in plaque instability (38).

Cell-to-cell gap junction proteins play a pivotal role in vascular remodeling and disease progression. In a pressure overload rodent model, our group demonstrated that gap junction proteins, connexins-37 and -43 were decreased in TIMP-2 knockout mice with ascending aortic banding (AB), a model of pressure overload-induced left ventricular dysfunction and heart failure (39). In addition, decreased expression of pro-angiogenic MMP-2, VEGF and increase in anti-angiogenic factors exacerbated abnormal left ventricular remodeling in these animals suggesting a possible relationship between MMP-2, connexins-37 and -43 in heart failure (39).

Unlike gap junction proteins, caveolae are lipid rafts within plasma membrane and contains caveolins which are involved in endocytosis, transcytosis and signal transduction in vascular health and disease. In bleomycin-induced caveolin-1 knockout mice, Shivshankar *et al* demonstrated that MMP-2 and -9 expression was reduced and this was associated with attenuated pulmonary injury and collagen deposition in caveolin-1 knockout mice (40). On the other hand, loss of caveolin-1 has been reported to upregulate MMP-2 and -9, tight junction proteins, and enhanced blood brain barrier (BBB) permeability in focal cerebral ischemia and reperfusion injury (41). These above experimental evidences suggest that gap junction proteins and collagenases (MMP-2 and -9) may have a role in BBB permeability as observed in caveolin-1 knockout mice where one modulates another and vice versa leading to vascular pathogenesis. Furthermore, our group has demonstrated that hyperhomocysteinemia enhanced cerebrovascular permeability through activation of MMP-9 and increased the formation of fibrinogen-β-amyloid complex within the brain (42). Additionally, increased cerebrovascular permeability and memory loss was also observed with increased MMP-9 activity which was ameliorated by MMP-9 ablation (43).

5.3. Stromelysins

Stromelysin-1, -2, and -3 subcategorize MMP-3, MMP-10, and MMP-11 respectively. Among them, MMP-3 and -10 are intestinal proteases, and are established key players in the

development of ulcers in inflammatory bowel disease (44). In addition, although in chronic human hypertension elevated activity of MMP-3 has been reported (45), MMP-10 experimentally has been shown to regulate tumor cell migration, invasion and EC tube formation (46). In a recent report, Toni *et al* documented that increased circulating MMP-10 was associated with increased microvascular disease risks including diabetic retinopathy in type 1 diabetes (47). In addition, MMP-10 has been reported to play a critical role in muscle regeneration during injury and muscular dystrophy (48). Using a MMP-11-deficient mice model, Tan *et al* showed that during postnatal mammary gland development ductal tree, alveolar structure and milk production were reduced suggesting a paracrine function of MMP-11 (49). MMP-11 is a negative regulator of adipogenesis which reduces and even reverts adipocyte differentiation, and has been shown to require correct collagen IV folding for fat tissue cohesion and adipocyte function (50).

5.4. Membrane-type MMPs

MMP-14, -15, -16, -17, -24 and -25 are membrane type or membrane bound enzymes. MMP-14 was the first MMP discovered possessing a transmembrane domain cloned from lung tumor cells conferring their invasiveness and metastasis (51). A study focusing on ischemia-reperfusion in the spinal cord injury of rats reported that TIMP-2 binding to MMP-2 activates MMP-14 (52). Furthermore, MMP-14 has been found to be involved in neuroinflammation (53). In another study, elevation of MMP-14 and MMP-2 correlated with abnormal aortic remodeling in sheep fetus development under hypoxic conditions. Furthermore, aortic intimal proliferation was associated with increased expression of cell adhesion molecule, E-Selectin suggesting interaction between endothelial cells and leukocytes (54).

In diabetic retinopathy, MMP-14 induced MMP-2 activation has been associated MMP-2 interaction with integrin and promotion of apoptosis leading to impaired retinal pericyte survival (55). In an in vitro study using VSMCs, MMP-14 induced ApoE degradation was associated with migration of VSMCs in both lipid-free and lipid-loaded treatment (56). Further, proteomic studies has shown that ApoA1, a lipid-free lipoprotein is a substrate of MMP-14 and more susceptible to cleavage than the lipid-loaded lipoprotein suggesting that degradation of high-density lipoprotein (HDL) can severely hamper lipid metabolism and possibly induce vascular disease (57). In salt-sensitive rats, elevation of MMP-14 was seen in late phase of chronic hypertension and left ventricular remodeling (59).

The ischemia-reperfusion (IR) model was applied to the left rat lung, and showed upregulation of several MMPs, including MMP-2 and MMP-9. Uninhibited protease activity was observed during the early phase of reperfusion which was demonstrated to arise from plasma via protein extravasation instead of *de novo* synthesis within the pulmonary tissue. Preconditioning rats with NO was shown to mitigate protease activity suggesting the mitigation IR injury (58). In another study, IL-6 induced upregulation of MMP-14 has been reported to contribute in carotid artery plaque formation involving Raf-MEK-ERK1/2-AP-1 pathway leading to ECM collagen degradation (61). In group X secretory phospholipase A2-deficient double knockout mice treatment with angiotensin II failed to induce MMP-2, -13,-14 and was associated with decreased progression of abdominal aortic aneurysms in

this model suggesting a pathogenic role for MMP-14 (62). Elevated MMP-14 has been observed in early phase venous thrombosis. However, its role in thrombus formation or resolution has not been defined (63). In age-related macular degeneration, MMP-14 and basigin mediated increase in MMP-2 activity was associated with ECM dysregulation and sub-retinal pigment epithelium deposits (64).

MMP-14 has been shown to cleave brain-specific angiogenic inhibitor-1 to yield vasculostatin-40 a potent angiogenesis inhibitor (65). Early stage hypertension is associated with increased MMP activities including MMP-14 and enhanced NAPDH oxidase activity suggesting that tissue remodeling occurs from the onset of hypertension and is linked to oxidative stress (66). This study further suggests that vascular remodeling associated with the early phase of hypertension may be mitigated through the administration of MMP inhibitors or antioxidants (66).

In hepatic ischemia reperfusion injury (IRI), fibronectin- α4β1 integrin interaction with macrophages leads to increased MMP-9 and -14 levels worsening the injury (67). Using a peptide, connecting segment-1, CS-1 the authors showed that the levels of both MMPs decreased offering protection to the liver (67). Furthermore, the pharmacological inhibition of p38 MAPK pathway via SB203590 also mitigated the MMP-14 expression suggesting the involvement of this pathway in hepatic IRI (67).

In tumor pathology, angiostatin mediated inhibition of angiogenesis was found to be dependent on MMP-2 and MMP-14 expression (68). This was associated with an increase in hypoxia-induced VEGF which was sufficient in protecting against angiostatin-induced apoptosis (68).

In another study, osteopontin upregulation directly correlated with MMP-14 expression in a rat model of balloon-injured carotid artery suggesting a pathogenic role. One study showed that MMP-14 expression levels increased with respect to osteopontin upregulation in balloon-injured rat carotid arteries suggesting that osteopontin may be involved in the signaling leading to MMP-14 expression (69). The study suggested that osteopontin may be a potential target for avoiding arterial restenosis (69). Sirtuin-1, deficiency in mice was shown to decrease MMP-14 expression promoting a fibrotic phenotype which was associated with vascular dysfunction and diminished angiogenesis (70).

There is limited literature on the role of MMP-15 in vascular diseases. One study reported the upregulation of MMP-15 in chronic inflammatory diseases and malignant tumors (71). It is reported that VEGF-A upregulates ADAMSTS-1 (a Disintegrin And Metalloproteinase with Thrombospondin motifs-1) and increases the development of large ‘mother’ vessels in human cancers (71). In the above study, VEGF-A was found to upregulate MMP-15 and ADAMTS-1 which together contributed to pathological angiogenesis (71).

MMP-16 levels were reported to be upregulated in patients with Henoch–Schönlein purpura (72). Another study focusing on the MMP expression profile in traumatic deep vein thrombosis (TDVT) in rats reported low expression of MMP-16 and -24 in early thrombotic stage but was upregulated during the resolution stage (73). The role of MMP-17 in vascular

disease has not been described so far, however, it has been reported to stimulate tumor growth and facilitate a permissive microenvironment for metastsis (74).

MMP-25 expression was shown to be downregulated in the aortic wall of patients suffering from abdominal aortic aneurysm after the administration of doxycycline (75). Furthermore, increased MMP-25 expression was observed in classically activated macrophages, and increased mRNA expression was observed in alternate activation of macrophages (76).

5.5. Matrilysins

MMPs-7 and -26 are matrilysins. MMP-7 has been shown to be involved in adverse left ventricular remodeling post-myocardial infarction and proteomic analysis revealed fibronectin and tenascin-C as its substrate (77). Thyroid cancer-1 gene was suggested to activate MMP-7 and endothelial growth factor downstream of the Wnt/β-catenin signaling pathway to enhance non-small-cell lung cancer in patient (79).

In patients with Kawasaki's disease, increased expression of integrins α4 and αM on macrophages and myofibroblasts were associated with increased MMP-7 activation and collagen type 1 α1 expression in coronary artery stenosis (80).

In another study involving coronary artery disease patients, the expression of MMP-7, osteopontin, IFN-gamma, and osteopontin were found to be increased suggesting its potential use as biomarkers (81). MMP-7 has been reported to be increased by over 100-fold in patients with atherosclerotic carotid plaques and associated with plaque instability (82). In addition the upregulation of MMP-7 correlated with overexpression of inflammatory genes, RANKL and CD68 (82). In spontaneously hypertensive rats, the increase in MMP-7,-9 and elastase expressions has been demonstrated to cleave ICAM-1 in the glomeruli leading to renal inflammation (83). Using a protease-activated receptor 1 antagonist, F16688, Chieng-Yane et al demonstrated that downregulation of MMP-7 and TNF-alpha levels mitigated post angioplasty restenosis of carotid artery in rats (84). Similarly, using RNA interference against MMP-7 and TACE, Odenbach *et al* demonstrated mitigation of MMP-2 mediated angiotensin-II-induced cardiac pathology (85). Taken together, the above studies suggest a significant role for MMP-7 in various vascular pathologies. It is known that β_2 adrenergic receptor (β_2 AR) agonists mediate vasodilatation of blood vessels (87). In rats, when MMP-7 and -9 were injected into the superior mesenteric artery the diameter of arterioles and venules in the mesentery were reduced and these effects have been attributed to MMP-7 and -9 mediated cleavage of β_2 AR (87).

A study focusing on endothelium regeneration post-vascular injury reported a decrease loss of pertussis toxin-induced endothelial derived relaxation factor mechanisms as well as an increase in MMP-7 expression (86).

In wound healing, MMP-26 expression is associated with chronic wound healing (88). In an *in vitro* study using human macrophages, Krishnatry *et al* observed that acute nitroglycerin exposure decreased MMP-26 expression along with testican-1, integrin α-1, thrombospondin-3, fibronectin-1 suggesting that nitroglycerin modulates ECM by changes

in the activities of proteases (89). Furthermore, MMP-26 was found to be associated in patients with cerebral amyloid angiopathy (90).

5.6. Enamelysin

MMP-20 is a protease secreted during teeth development and functions mainly in the deposition of minerals in the dental matrix. There is not reported literature on its vascular effects.

5.7. Metalloelastase

MMP-12 is a metalloelastase originally discovered in alveolar macrophages of cigarette smokers (91). In a mouse model of brachicephalic artery atherosclerosis, MMP-12 was found to be detrimental to plaque stability (230). Using a MMP-12 inhibitor, RXP470.1, Johnson et al demonstrated a significant reduction in plaque formation, necrosis, calcification and macrophage apoptosis. Furthermore, this was associated with increased smooth muscle cell: macrophage ratio leading to a loss of thickness of fibrous plaque and slowing of atherosclerosis (92).

Henoch-Schönlein purpura (HSP) is a IgA mediated immune complex disease characterized by small vessel vasculitis of the skin, gastrointestinal tract, kidneys, joints and rarely the respiratory and central nervous system. Increased MMP activity has been implicated in the pathogenesis of HSP (93). In a recent study, patients with HSP receiving steroids showed negative correlation of MMP-12 suggesting a role of this MMP-12 in HSP (72). Further, a recent study identified MMP-12 as a potential biomarker in patients with Stanford-A Acute Aortic Dissection (94). In a mice model of angiotensin-II induced abdominal aortic aneurysm, 3, 4-Benzopyrene, a compound present in cigarette was found to increase macrophage infiltration, upregulation of MMP-2, -9 and -12 and apoptosis of vascular smooth muscle cells (95). Further, MMP-12 levels were found to be elevated in patients with aortic dissection and coronary artery disease suggesting its use as a potential biomarker and effect of treatment (96).

In patients with abdominal aortic aneurysm (AAA), elevated leptin, a hormone involved in ECM degradation was associated with increased MMP-12 (97). Further, when ApoE−/− mice were treated with local leptin, the expression of MMP-12 and MMP-9 increased by several fold which was associated with medial degeneration of aorta suggesting a link between leptin and AAA (97). MMP-12 ApoE−/− mice increased levels of MMP-12 and exacerbated degeneration of the aortic wall in Ang-II-induced abdominal aortic aneurysm was detected which further demonstrated enhanced degeneration upon endogenous leptin induction (97).

Osteopontin, an atherosclerotic factor, can be cleaved by MMP-12 into an N-terminal and C-terminal fragment where the former is associated with high-risk carotid plaque formation in hypertensive patients (98). In another clinical study carotid atherosclerotic plaques were found to be associated with MMP-12-expressing foam cells and increased MMP-12 is linked to plaque instability (99,100).

Using MMP-12 knockout mice, Li et al demonstrated decreased macrophage infiltration in oxygen-induced retinopathy (101). Furthermore, it reduced adverse neovascularization and promoted non pathological revascularization of the retina (101). Increased MMP-12 has been associated with disruption of blood brain barrier following intracerebral hemorrhage (102). Furthermore, in a neonatal hypoxic-ischemic brain injury, increased MMP-12 expression was observed in neurons suggesting its participation in immature brain injury (103).

Elevated MMP-12 was observed in systemic sclerosis patients and associated with the classical symptoms of scleroderma including peripheral vascular damage (104). Aortic dilation induced by congenital bicuspid aortic valves is associated with increased MMP-12 levels among other MMP and TIMP levels (105). Spleen tyrosine kinase leads to JNK and p38 signaling leading to glomerular injury which enhances pro-inflammatory expression of MMP-12 (106). Certain MMP-12 haplotype are associated with elevated risk of aneurysm in patients suffering from Kawasaki disease (107). Mice susceptible to atherosclerosis showed cigarette smoke-induced COPD vascular effects as well as increased activity of MMP-12 (108). Furthermore, pentraxin-3, a modulator of inflammation, was upregulated upon cigarette smoke as well as an increase in MMP-12/TIMP-1 ratio (109). Expression of MMP-12 was found to be elevated in deep vein thrombosis in rats (73).

5.8. Unclassified MMPs

Some MMPs such as, MMPs-19, -21, -23, -27 and – 28 remain uncategorized. In patients with tricuspid aortic valves, elevated MMP-19 has been associated with thoracic aortic aneurysms (110). Furthermore, a human study has revealed immunoreactivity against MMP-12 in cerebral blood vessels in cerebral amyloid angiopathy (90). A study focusing on the acute and chronic manifestations of myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalitis in mice showed that VEGF levels directly correlated with demyelination of lesions which was associated with increased MMP-19 (111). MMP-19 has been extracted from the synovium of patient suffering from rheumatoid arthritis and was found to be localized to smooth muscle cells in the media of blood vessels (112).

Since its original description in ovarian serous tumors, the role of MMP-21 has now expanded to include invasiveness in breast cancer cells and early melanoma development (113). Apart from tumor progression, MMP-21 activity is associated with embryogenesis (114,115,117). Also, MMP-21 may be a marker for keratinocytes as demonstrated by a study which showed increased MMP-21 upon keratinocyte differentiation in cell culture (116). Increased MMP-21 expression was suggested to play a role in invasiveness of human colorectal cancer and progression in human gastric cancer (118, 119).

MMP-23 is encoded by two genes, MMP23A and MMP23B (120, 121). MMP23A is a pseudogene which is duplicated on chromosomal region 1p36.3, while MMP23B is the protein encoding gene. In a study involving DVT in rats, the expression of MMP-12 was found to be low during thrombus formation but increased during resolution suggesting a wound healing role than pathological (73). MMP-23 expression has been described in

reproductive tissues such as, testis, prostate and ovaries however, their exact role remains unknown (11).

MMP-27 was first discovered as epilysin expressed in response to injury, and in testis and keratinocytes (122). The role of MMP-27 in vascular disease has currently not been identified. MMP-27 is expressed in B-cells, bone and kidney tissues of rats (123). In humans, MMP-27 has been implicated in osteogenesis (231). Although mutations in MMP-27 have been identified in thyroid cancers, it has not been suggested to play a role in tumorigenesis (124).

The role of MMP-28 in vascular diseases is yet to be defined. However, in a recent study MMP-28-deficient mice worsened left ventricular remodeling to the point of rupture as a result of inhibiting the type 2 subpopulation of macrophages (125). In a clinical study focusing of MMP/ TIMP profile in children with Henoch-Schönlein purpura, decreased MMP-28 expression was observed in soft tissue edema and the levels of MMP-19 was decreased during convalescent stage compared to its level in the acute stage (72). Treatment with steroid mitigated the changes in MMP and TIMP expression in these patients (72).

6. REGULATION OF MMPS IN VASCULAR DISEASES

MMP expression and their biological function are regulated by a variety of factors that include biological effectors, endogenous inhibitors, epigenetic regulators, miRNAs and pharmacological agents. A summarized chart is presented in Table 2. Below, we discuss how these factors regulate MMPs in normal and pathophysiological conditions.

6.1. Biological activators of MMPs

Oxysterols, a promotor of oxidative stress through Nox2 activation, has been shown to enhance the effects of MMP-9 (126). On the other hand, E2F1 is a transcription factor that modulates cell cycle regulation, proliferation and apoptosis, and has shown to enhance MMP expression (127).

6.2. Natural inhibitors of MMPs: tissue inhibitor of metalloproteinases (TIMPs)

A number of inhibitors for MMPs have been described over the years. The most common include endogenous inhibitors known as TIMPs. This family consists of four protease inhibitors TIMP 1–4 which exist as glycosylated or unglycosylated form. TIMPs are 21 to 29 kDa protein consisting of an N-terminal oligosaccharide/oligonucleotide binding (OB)-fold of ~125 amino acids, 5 beta-barrels, and a C-terminal portion ~60 amino acids long forming a beta-turn (128–130). The N-terminal domain interacts strongly with the catalytic domains of MMPs (129). In some cases, however, the C-terminal domain can further enhance the MMP/TIMP interaction (131). Furthermore, TIMPs can also interact to form complexes with pro-gelatinases suggesting that the C-terminal domain interacts with the hemopexin-like domain (131).

TIMP-2: proMMP-2 complex has an important role in both activation and inhibition of MMP-2 (132). A ternary model for TIMP-2: proMMP-2 interacting with MT1-MMP has been proposed (2). Thus, studying MMP/ TIMP ratios enable to define the collective role of

TIMPs in vascular disease. A time course study performed in rats demonstrated that besides the expression of MMP-9 protein and mRNA the MMP-9: TIMP-1 ratio correlated with brain water content (BWC) following acute cerebral infarction (133). TIMP-1 concentration alone did not correlate BWC in this cerebral edema model suggesting that there was no disenable relationship between TIMP-1 concentration and edema (133).

An epidemiology study concluded that certain polymorphism within the promoter regions of MMP-9 and TIMP-2 is statistically associated with varicose vein development within a subset of the Chinese population (134). In another study focusing on obesity increased plasma concentrations of MMP-9 and MMP-9: TIMP-1 ratio and MMP-8 and MMP-8: TIMP-1 ratio was observed in obese women versus lean women suggesting their association with obesity (135). In addition, MMP-9 levels and MMP-9:TIMP-1 ratio was associated with healing in diabetic foot ulcers (136). However, there was only a slight variation in TIMP-1, TIMP-2, and MMP-2 when comparing good vs. poor healing outcomes (136).

TIMP-1 has been used in gene therapy by viral and plasmid delivery systems. Hybridization of TIMP-1 to urokinase receptor decreased neointimal formation in vein cultures (137). Furthermore, in an *in vivo* model of venous graft interposition to carotid artery, TIMP-1 urokinase protein reduced graft thickening suggesting its potential as a therapeutic agent (138). TIMP-4 was shown to mitigate MMP-2 expression in an ischemia-reperfusion injury rat model of myocardial infarction (139). In addition, monocytes isolated from abdominal aortic aneurysm (AAA) were shown to have a greater capacity for transmigration and EC adhesion along with increased MMP-9 and decreased TIMP- 4 levels (140). Furthermore, intermittent hypobaric hypoxia has been shown to ameliorate the effects of ischemia-reperfusion by decreasing MMP-2 activation, and increasing TIMP-4 (141).

A study focusing on ataxia telangiectasia, mutated heterozygous kinase knockout (ATM hKO) mice showed decreased levels of TIMP-4 within the infarct tissue which was associated with increased MMP-9 expression and fibrosis (142). In another study, fibrinogen induced caveolae formation as well as caveolin protein 1 expression, and its phosphorylation was mitigated in presence of the TIMP-4 and MMP-9 modulation (143).

Sirtuin1 (SIRT1) is a protein/histone deacetylase known for its protective effects against development of pulmonary emphysema in smokers (144). In a study by Yao et al, SIRT1 deficiency was associated with decreased TIMP-1 and increased MMP-9 activity in human subjects suffering from COPD and in the lungs of mice exposed to cigarette smoke, whereas increased SIRT1 in transgenic mice was associated with decreased MMP-9 activity (144). The above study did not demonstrate changes in the levels of MMP-2, -12 and TIMP-2, -3 or -4 were observed (144). Additionally, in an *in vitro* rat cardiac fibroblast model, El Hajj *et al* demonstrated that ethanol exposure up-regulated TIMP-1, -3, and -4 levels with no significant changes in MMP profile (145). They concluded that MMP/TIMP imbalance favors collagen accumulation in the development of myocardial fibrosis and cardiac dysfunction in chronic alcohol abuse (145).

6.3. Epigenetic regulation of MMPs

Epigenetics is defined as reversible events and consists of gene silencing mechanisms which stabilize gene expression without modifying the DNA sequence. In mammalian cells, the major epigenetic mechanism includes, DNA methylation, histone modification, and small non-coding RNA (146). DNA methylation is carried out by three DNA methyltransferases (DMNT): DNMT 1, DNMT3, and DNMT 3b. Although epigenetic regulation of MMPs have not been extensively studied in vascular diseases much of what is known has been uncovered through cancer research. Several cancers have overlapping vascular pathology which we discuss in the following paragraphs. In a recent study, methylation of cytosine within the promoter region of dystrophin was examined by using Duchenne muscular dystrophy (DMD) knockout mice, and this deficiency was shown to increase MMP-2 expression levels (150). In breast cancer cells MD-MB-231, high glucose led to the phosphorylation of histone 3 at the Ser10 residue while dephosphorylating the Ser9 residue (151). This event correlated with the increase in DNMT1 expression (151). Silencing GSK-3β by siRNA inhibited the phosphorylation of H3, and thus decreasing DNMT1 expression (151). Furthermore, phospho-H3 levels were directly correlated with MMP-7 expression (151).

MMP-14 was suggested to be a regulator of H3K9ac in adipogenic collagenolysis (152). Another study suggested that proMMP-1 expression is influenced by epigenetics in human fibrosarcoma cells even though its promoter is not believed to possess CpG islands, yet proMMP-1 expression increased under 5-aza-dC treatment which was mitigated with cycloheximide suggesting epigenetic regulation through some other intermediate product (153). Enzymes involved in the pathology, mainly MMP-9 and superoxide dismutase 2, of diabetic retinopathy have been reported to be under the epigenetic regulation of histone lysine demethylase 1, (LSD1) and DNMT (154). Our lab has recently demonstrated that changes in the levels of MMP-9, TIMP-1 are regulated by DNMT1, 3a, Methyl CpG-Binding Domain Protein 2 (MBD2), and H3K9 contributing to aortic remodeling during hyperhomocysteinemia (156).

The expression of MMP9 is inhibited by trichostatin A (TSA), a HDAC inhibitor, by its action on thrombospondin-1 (TSP-1), an adhesive glycoprotein (147,148). TSP-1 stabilizes the ECM and also suppresses VEGF release thus regulating angiogenesis (148).

Proto-oncogene c-Fos was also shown to be linked to MMP-2/MMP-9 expression (160). Treatment of cells with OxLDL caused c-Fos activation to decreased histone deacetylase 1 (HDAC1) expression levels (160). Also, shRNA-mediated knockdown of c-Fos restored HDAC1 mRNA and protein expression (160). The increased acetylation and decreased methylation of H3K9 had disappeared in the knockdown of c-Fos treated with OxLDL suggesting that c-Fos was necessary for histone modification and lead to MMP-2/MMP-9 overexpression further downstream of the signaling pathway (160). Furthermore, since c-Fos can activate transcription factor AP-1, a link between OxLDL, AP-1, miRNA-29b, and cardiovascular disease had been suggested (160). MMP-9 has also been shown to be regulated epigenetically (161).

6.4. miRNA regulation of MMPs

MicroRNAs (miRs) are small non-coding RNAs which regulate transcriptional and post-transcriptional gene expression (157). MicroRNA-29b (miRNA-29b) has been shown to be an epigenetic regulator of pro-atherogenic genes (158). OxLDL was shown to up-regulate miRNA-29b expression in a dose-dependent and time-dependent manner within human aortic smooth muscle cells (HASMCs) (158). *In vivo* studies suggest that increased miRNA-29b levels reduced the expression of DNA methyltransferase 3b in primary human aortic smooth muscle cells, and subsequently lead to reduced MMP-2/MMP-9 silencing (158). These results suggested a mechanism for OxLDL to induce HASMC migration via miRNA-29b/DNMT 3b/MMP-2 and MMP-9 pathway (158). These findings reveal that miRNA-29b may generate atherosclerosis (158). Furthermore, increased miRNA-29b levels were shown to dysregulate ECM homeostasis by impacting the expression of collagen (Col1A1 & Col3A1), and elastin (159).

Among miRs, miR133a, miR133b, and miR145 target SP-1 transcription factor which in turn decreases MMP-9 expression in renal cancer (162). In oral squamous cell carcinoma, miR2 targeted STAT3 which in turn decreased MMP-2 in WP1066 treated cells (163). Propofol administration was shown to induce miR-143 which targeted MMP-13 in an osteosarcoma cell line (164). This was shown to inhibit the cell proliferation and invasion which facilitated apoptosis (164). Moreover, miR-143 levels indirectly correlated with MMP-13 levels, which were restored with the application of anti-miR-143 (164). Under hypoxic conditions, neovascularization and therefore MMP-9 and VEGF were suggested to be under the control of miR-126 in monkey chorioretinal vessel ECs (RF/6A) (165). The miR21 expression was suggested to be induced by Ang II which induced MMP-2 expression in mouse cardiofibroblasts (166). TNF- α signaling leading to IL-6, iNOS, and MMP-9 expression and endothelial dysfunction was suggested to occur when miR-149 was down-regulated in a p38MAPK-dependent manner (167). MMP-14 was suggested to be downregulated by miR-9 expression (168). Finally, miR-98 is reported to inhibit tumor angiogenesis and invasion in part by targeting MMP-11 (169).

6.5. Pharmacological inhibitors of MMPs

Pharmacological inhibitors of MMP fit into two classes: non-specific and specific. The non-specific inhibitors act by chelating the catalytic Zn^{2+} ion (170,171). These inhibitors include but are not limited to batimastat, marimastat, ilomastat, PD-166793, and ONO-4817 (172,173). Peptide inhibitors containing motifs HWGF, CRRHWGFEFC and CTTHWGFTLC provide targeted inhibition of MMP-2 and MMP-9 (174). Antibiotics have also demonstrated the ability to inhibit MMPs, such as the tetracycline class (175). Furthermore, chemically modified tetracyclines maintain MMP inhibition in the absence of antimicrobial activity (33).

Statins are a class of drugs used to lower cholesterol levels and have been shown to inhibit MMP-2, MMP-7, and MMP-9 (11). Although cerivastatin was withdrawn from the market due to cases of muscle breakdown, it has exhibited dose-dependent inhibition properties for MMP-1, MMP-3, and MMP-9 secretion in human VSMC (176). Lovastatin inhibited the inducible activity of MMP-1, -3 and -9, while it blocked the MMP-2 constituent activity in

rabbit SMC whereas, TIMP-1 and -2 secretions remained uninhibited (176). Both cerivastatin and lovastatin inhibited the secretion of MMP-1, -3, and -9 in rabbit foam cells with cerivastatin demonstrating greater inhibition (176). In a study, aortic mRNA expression demonstrated elevated levels of MMP-1, MMP-9, and MMP-12 in rabbits that were fed a high cholesterol diet which was decreased but not normalized upon fluvastatin treatment (177). Although MMP-2 level remained the same for normal diet, and cholesterol diet with or without fluvastatin, MMP-12 showed a pronounced decrease with fluvastatin treatment (177).

Interestingly, a recent study focused on a series of MMP inhibitors known as α-sulfone hydroxamates which were conjugated to various dyes for visualizing cells that express MMPs for as a way to measure their synthesis and potency in disease conditions (178). In particular, N-O-Isopropyl sulfonamido-based hydroxamates have shown to be selective inhibitors of MMP-12 and -13 (179,180).

Sulphonamides are another class of inhibitors which have been shown to inhibit MMP activity *in vitro* (181). However, their inhibitory effect *in vivo* remains known as it may be dependent on intracellular signaling and crosstalk between different compounds (181).

In order for proMMP-2 to become activated, the hemopexin domain has to interact with the C-terminal domain of TIMP-2 (182). Using recombinant technology, the activation of proMMP-2 was successfully blocked by TIMP-2 (*C*-TIMP-2) (182). The *C*-TIMP-2 was shown to interact with the inactive MMP-2^{E404A} and hemopexin domain of MMP-2 in a dose-dependent manner (182). Furthermore, *C*-TIMP-2 was shown to compete with TIMP-2 in its interaction with proMMP-2 (182).5-hydroxy,5-substitute-pyrimidine-2,4,6,-triones demonstrate high potency in their IC_{50} values for gelatinases (183). Also, 5-hydroxy moiety may enhance the pharmacokinetics of this inhibitor (183).

A new class of inhibitors has been identified with the ability to selectively inhibit MMP-13 (184). This class of pharmacological inhibitors is unique because they are non-zinc chelating (184). The structure-activity relationships (SAR) studies on this lead compound revealed that reducing the lipophilic property conferred metabolic stability, and lowered clearance rate *in vivo* (185).

Methyl rosmarinate derivatives have also been identified as a potential class of inhibitors for MMP-1 (186). A molecular scaffold has been identified and tested with SAR studies identifying potential lead compounds with IC_{50} on micro molar scale (186). Alendronate and EDTA, divalent chelators, have been shown to inhibit MMP-9 activity irreversibly via plasmin-mediated inactivation (187). Cryptic plasmin degradation sites within the catalytic domain of MMP-9 become accessible to form hemopexin-domain fragments which have the inhibitory property (187).

Cilostazol inhibits MMP-9 in a dose-dependent manner and on the transcriptional level by suppressing its promoter and blocking the translocation of NF-κB (188). Treatment with Cilostazol, reduced MMP-9 activity on and decreased transcript and protein expression (188). The study above presents a mechanism for anti-atherosclerosis by inhibiting monocyte invasion and further differentiation by modulating MMP-9 and TIMP-1 (188).

Anti-hypertensive drug captopril has been shown to inhibit MMP-2 and -9 in a rat model of right ventricular hypertrophy (189), and to decrease plasma MMP-9 in acute myocardial infarction patients (190). Similarly, serum MMP-9 levels were found to decrease in patients with candesartan treatment (191). However, a recent study focusing on the inhibitory action of captopril and lisinopril using purified MMP-2 concluded that these two ACE inhibitors do not act as pharmacological inhibitors of MMP-2 (192).

Hydroxysafflor yellow A, an active ingredients of Chinese herb *Carthamus tinctorius* L, was also shown to inhibit MMP-2 and MMP-9 activity, and also reduces associated apoptosis which helps to mitigate the effects of left ventricular remodeling within the hypertensive heart (193). In addition, kaempferol has shown to act as a pharmacological inhibitor of MMP-2 through the inhibition of the ERK1/2 as well as activator protein-1 pathway making it a good candidate for cardiac disease and cancer (194). Recently, we have shown that hydrogen sulfide treatment confers vascular protection within the kidney and neuronal tissues of hyperhomocysteinemic mice as observed through the decrease of MMP-2 and MMP-9 levels (195–197). Furthermore, phosphinic peptide RXP470.1. is a selective inhibitor of MMP-12 which was shown to mitigate plaque instability in ApoE KO mice (92).

7. SUMMARY AND CONCLUSION

MMPs in general have a fundamental role in matrix homeostasis of vascular health. In disease conditions, MMP activity is altered causing a dysregulation in ECM synthesis and degradation. As a result, vessels become weaker in performing their normal physiological function, such as maintaining blood pressure. In order to keep up with the increased metabolic demand of tumor cells, angiogenesis is facilitated by MMPs in cancer. Similarly, cardiovascular diseases including atherosclerosis, inflammation and ischemia are influenced by MMPs activity. The endogenous inhibitors, TIMPs regulate the expression of MMPs however, they lack specificity. Our current knowledge on interventions to modify MMP activity by pharmacological agents, genetic manipulation and/or by biological agents for prevention or even cure of vascular diseases are limited. Therefore, more research is needed to develop strategies to regulate specific MMPs in a particular disease without affecting other MMPs that are vital for maintaining normal physiological functions.

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Abbreviations

AAA	Abdominal aortic aneurysm
AT1	Angiotensin II receptor type1
BBB	Blood brain barrier
BWC	Brain water content
COPD	Chronic obstructive pulmonary disease

DNMT1	DNA methyltransferase 1
DVT	Deep-vein thrombosis
E2F1	is a transcription factor
ECAS	Extracranial atherosclerosis
ECM	Extracellular matrix
ECs	Endothelial cells
FRET	Fluorescence resonance energy transfer
FSS	Fluid shear stress
H3K9	Histone 3 tri-methylated at lysine
9H3K9ac	H3 lysine 9 acetylation
HDAC1	Histone deacetylase 1
HDL	High-density lipoprotein
HSP	Henoch-Schönlein purpura
ICAS	Intracranial atherosclerosis
ILA	intracranial large artery atherosclerosis
L-NAME	L-NG-Nitroarginine Methyl Ester
LSD1	Lysine-specific demethylase 1
MBD2	Methyl binding domain 2
NO	Nitric oxide
NOS	Nitric oxide synthase
Nox2	NADPH oxidase 2
OxLDL	Oxidized low-density lipoprotein
PLA2	Phospholipase A2
RANKL	Receptor activator of nuclear factor kappa-B ligand
siRNA	silencing of GSK-3β inhibited the phosphorylation of H3SIRT1: Deacetylase Sirtuin-1
TACE	Tumor necrosis factor-a-converting enzyme (also known as ADAM17)
TFPI2	Tissue factor pathway inhibitor 2
TIMPs	Tissue inhibitor of metalloproteinases

TSA	Trichostatin A
TSP-1	Thrombospondin-1
VEGF	Vascular endothelial growth factor
VEGRF2	Vascular endothelial growth factor receptor-2
VSMC(s)	Vascular smooth muscle cell(s)

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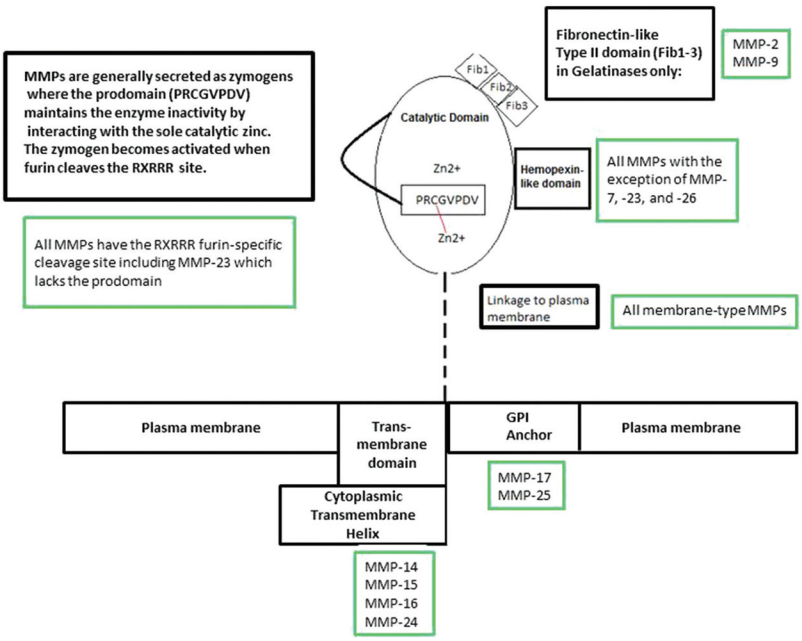

Figure 1.

Schematic of generalized structure of MMPs. The Prodomain has a cleavage site at RxRRR which activates the subsequent autocatalysis of the pro-enzyme. Although MMP-23 has the cleavage site, it is the only one that lacks a prodomain. The catalytic domain is common across all MMPs consisting of two Zn^{2+} ions where one is purely structural, while the other is involved in catalytic activity. The catalytic zinc interacts with a cysteine residue (cysteine switch) within the prodomain to remain inactive. The Hemopexin-like domain and catalytic domain are connect by a linker peptide, and is observed at the C-terminus of all MMPs except for MMP-7,-23, and -26. Its sequence homology resembles that of hemopexin, a protein with heme-binding capabilities. It enhances substrate recognition and specificity in stromelysins and collagenases, but not required for elastase activity in metalloelastase. Lastly, TIMP: proenzyme interactions are facilitated by this domain in gelatinases. The Fib1-3s are fibronectin-like type II domains found only in gelatinases.

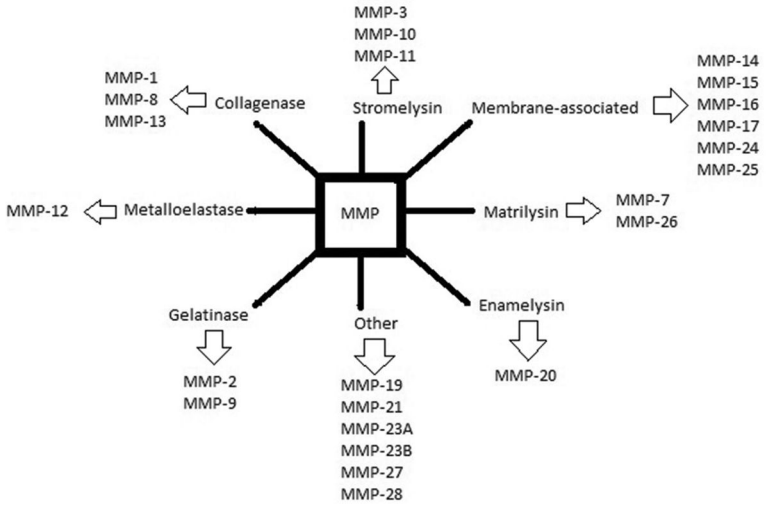

Figure 2.
Subgroup classification of MMPs.

Table 1

MMPs in vascular health and disease

Type	Enzyme	Other name (s)	Associated vascular events (Ref.)
Collagenases	MMP-1	Interstitial collagenase Fibroblast collagenase	Venus hypertension (10) Carotid atheroma (14) Insulin resistance (13)
	MMP-8	Neutrophil collagenase	Carotid atheroma (14)
	MMP-13	CLG3; MANDP1; Collagenase-3	Neointima formation (198) Restenosis/atherothrombosis (16) Renal Disease (17, 18)
	MMP-18	Collagenase-4 Xenopus collagenase	Not known
Gelatinases	MMP-2	Gelatinase A	ICAS, thrombosis, heart and renal disease (12,36,39,197)
	MMP-9	Gelatinase B	Hypertension (12) Carotid stenosis (25) Cardiac and renal disease (31,197)
Stromelysins	MMP-3	Stromelysin-1	Inflammatory bowel disease (44)
	MMP-10	Stromelysin-2	Inflammatory bowel disease (44) Tumor growth and progression (46) Microvascular disease in diabetes (47) Muscular dystrophy (48)
	MMP-11	Stromelysin-3	Mammary gland development (49)
Membrane type	MMP-14	MT1-MMP	Lung tumor (51) Neuroinflammation (53) Neointima formation (54) Pressure overload (59) Macular degeneration (64) Hypertension (66)
	MMP-15	MT2-MMP	Inflammatory disease (71)
	MMP-16	MT3-MMP	HSP and deep vein thrombosis (72,73)
	MMP-17	MT4-MMP	Tumor growth and metastasis (74)
	MMP-24	MT5-MMP	Deep vein thrombosis (73)
	MMP-25	MT6-MMP	Abdominal aortic aneurysm (75)
Matrilysins	MMP-7	PUMP1	Myocardial infarction (77) Kawasaki disease (80) Coronary artery disease (81) Hypertension (83,87)
	MMP-26	Matrilysin-2 Endometase	Wound healing (88) cerebral amyloid angiopathy (90)
Enamelysin	MMP-20	Enamel metalloproteinase	No report
Metalloelastase	MMP-12	Macrophage metallo-/elastase (MME or ME)	Atherosclerosis (92,99) Aortic dissection (96) Retinopathy (101) Intracerebral hemorrhage (102) Peripheral vascular damage (104) COPD (108) Deep vein thrombosis (73)
Unclassified	MMP-19	RASI-1	Thoracic aortic aneurysms (110) Cerebral amyloid angiopathy (90) Rheumatoid arthritis (112)
	MMP-21	Xenopus MMP (XMMP)	Melanoma development (113) Tissue remodeling/embryogenesis (114,115,117)
	MMP-23	MMP-23A/B	Thrombosis (73)

Type	Enzyme	Other name (s)	Associated vascular events (Ref.)
			Reproductive system (11)
	MMP-27	Epilysin	Not known
	MMP-28	Epilysin	Left ventricular remodeling (125) Soft tissue edema (72)

Abbreviations: CLG3, collagenase-3; MANDP1, Metaphyseal anadysplasia 1; ICAS, Intracranial atherosclerosis; HSP, Henoch–Schönlein purpura; COPD, Chronic Obstructive Pulmonary Disease

Table 2

Regulators of MMPs and examples of their targets

Category	Type	Class	Name	Target MMPs (Ref.)
Biological	Activator	Oxidized derivatives of cholesterol	Oxysterols	MMP-9 (126)
	Inducer	Transcription factor	E2F1	MMP-9, -16 (127)
Natural	Inhibitor	TIMPs	TIMP-1	MMP-8, -9 (135,144)
			TIMP-2	MMP-2, -14 (199–201)
			TIMP-3	MMP-9 (202)
			TIMP-4	MMP-2, -9 (139–143)
Epigenetic	Modulator	Methylation	Dystrophin	MMP-2 (150)
miRNAs	Gene regulator	-	-	MMP-2, -9, -11, -13 (158,162,164–167,169)
Pharmacological	Inhibitor	Anti-cancer drug	Batimastat	MMP-2, -14 (203–205)
			Marimastat	MMP-1, -2, -3, -7, -9 (172,206)
			Ilomastat	MMP-2, -9 (207, 208)
			Cipemastat	MMP-2, -9 (205)
	Inhibitor	Statins (cholesterol lowering drug)	Cerivastatin	MMP-1, -2, -3, -9 (209–211)
			Simvastatin	MMP-1, -3, -9 (209,212–216)
			Lovastatin	MMP-1, -3, -9 (209,216)
			Fluvastatin	MMP-9 (217–219)
	Inhibitor	Hydroxamates	R-phosphonate	MMP-8 (220)
			Sulfone hydroxamates	MMP-1, -2, -9, 13 (221)
	Inhibitor	Sulfa drugs	Sulphonamides	MMP-8, -12, -13 (222)
Unclassified	Inhibitor	Recombinant	C-TIMP-2	MMP-2 (182)
	Inhibitor	Pyrimidine	5-hydroxy, 5-substitute- pyrimidine-2,4,6,-triones	MMP-2, -9 (183)
	Inhibitor	Methyl rosmarinate derivatives	(R)-10n	MMP-1 (223)
	Inhibitor	Divalent cation chelators	Alendronate and EDTA	MMP-1, -3, -9, -13 (187,224)
		Quinolinone-derivative	Cilostazol	MMP-1, -9 (188,225–227)
	Inhibitor	Anti-hypertension drug	Captopril	MMP-2, -9 (189,190)
			Candesartan	MMP-9 (191)
	Inhibitor	Herbal	Hydroxysafflor yellow A	MMP-2, -9 (193)
	Inhibitor	Flavonoid	Kaempferol	MMP-2 (194)
	Inhibitor	Gasotransmitter	Hydrogen sulfide	MMP-2, -9 (195–197)
	Inhibitor	Phosphinic peptide	RXP470.1.	MMP-1, -2,-3,-8,-9, -10,-12, -13, -14 (228)
			RXP470, Compound 4	MMP-1, -2, -3,-7, -8, -9, -10, -12, -13, -14 (229)

Abbreviations: R-phosphonate, (1-(4′-methoxybiphenyl-4-sulfonylamino)-2-methylpropyl) phosphonate; EDTA, Ethylenediaminetetraacetic acid.