Published in final edited form as:
EXS. 2012 ; 103: 209–279.

Matrix Metalloproteinase Inhibitors as Investigative Tools in the Pathogenesis and Management of Vascular Disease

Mina M. Benjamin and **Raouf A. Khalil**
Vascular Surgery Research Laboratory, Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA 02115

Abstract

Matrix metalloproteinases (MMPs) are proteolytic enzymes that degrade various components of the extracellular matrix (ECM). MMPs could also regulate the activity of several non-ECM bioactive substrates, and consequently affect different cellular functions. Members of the MMPs family include collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs and others. Pro-MMPs are cleaved into active MMPs, which in turn act on various substrates in the ECM and on the cell surface. MMPs play an important role in the regulation of numerous physiological processes including vascular remodeling and angiogenesis. MMPs may also be involved in vascular diseases such as hypertension, atherosclerosis, aortic aneurysm, and varicose veins. MMPs also play a role in the hemodynamic and vascular changes associated with pregnancy and preeclampsia. The role of MMPs is commonly assessed by measuring their gene expression, protein amount, and proteolyic activity using gel zymography. Because there are no specific activators of MMPs, MMP inhibitors are often used to investigate the role of MMPs in different physiologic processes and in the pathogenesis of specific diseases. MMP inhibitors include endogenous tissue inhibitors (TIMPs) and pharmacological inhibitors such as zinc chelators, doxycycline and marimastat. MMP inhibitors have been evaluated as diagnostic and therapeutic tools in cancer, autoimmune and cardiovascular disease. Although several MMP inhibitors have been synthesized and tested both experimentally and clinically, only on MMP inhibitor, i.e. doxycycline, is currently approved by the Food and Drug Administration. This is mainly due to the undesirable side effects of MMP inhibitors especially on the musculoskeletal system. While most experimental and clinical trials of MMP inhibitors have not demonstrated significant benefits, some trials still showed promising results. With the advent of new genetic and pharmacological tools, disease-specific MMP inhibitors with fewer undesirable effects are being developed and could be useful in the management of vascular disease.

Keywords

TIMP; endothelium; vascular smooth muscle; extracellular matrix; angiogenesis; atherosclerosis; hypertension; aneurysm; varicose veins; pregnancy; preeclampsia

2. INTRODUCTION

Extracellular matrix (ECM) is the extracellular component of animal tissue that provides support and anchorage for cells, segregating tissues from one another, regulating cell movement and intercellular communication, and providing a local depot for cellular growth factors. Formation of ECM is essential for biological processes involved in maintaining

Correspondence and proofs should be sent to: Raouf A Khalil, MD, PhD, Harvard Medical School, Brigham and Women's Hospital, Division of Vascular Surgery, 75 Francis Street, Boston, MA 02115, Phone: 617–525–8530 Fax: 617- 264–5124, raouf_khalil@hms.harvard.edu.

tissue integrity and regeneration including wound healing and fibrosis. ECM consists mainly of fibers, proteoglycans and polysaccharides. Fibers are mostly glycoproteins and include collagen and elastin. Collagen is the main extracellular protein while elastin, which is exceptionally unglycosylated, provides flexibility for the skin, arteries and lungs. Proteoglycans are glycoproteins containing more carbohydrate than protein. Proteoglycans attract water to keep the ECM environment hydrated and also bind and store growth factors. Proteoglycans include chondroitin sulfate which provides tensile strength to cartilage, ligaments and aortic wall, heparan sulfate which regulates biological activities such as angiogenesis and blood coagulation, and keratan sulfate in cartilage and bone. Syndecan-1 is a proteoglycan and integral transmembrane protein that binds chemotactic cytokines and plays a role in the inflammatory process. Other components of ECM include laminin in the basal lamina of epithelia, and fibronectin which binds cells to ECM, modulates the cell cytoskeleton and facilitates cell movement. ECM also contains polysaccharides such as hyaluronic acid, and proteolytic enzymes which cause continuous turnover of ECM proteins (Teti, 1992; Bosman and Stamenkovic, 2003; Jacob, 2003).

Matrix metalloproteinases (MMPs) are endopeptidases first discovered in 1962 as a collagen proteolytic activity during the ECM protein degradation associated with resorption of the tadpole tail (Gross and Lapiere, 1962). Since then, the MMP family has grown to include at least 28 members. MMPs, also called matrixins, are multidomain zinc metalloproteinases that degrade various components of ECM and belong to the larger superfamily of proteases called metzincins, which also includes adamalysins, serralysins, and astacins. Sequence homology with the catalytic domain of MMP-1 (collagenase 1) is a common feature of all members of the MMP family. Several methods have been employed to classify MMPs. The most common method classifies MMPs based on domain organization and substrate preference into collagenases, gelatinases, stromelysins, matrilysins, membrane-type (MT)-MMPs and others (Visse and Nagase, 2003; Raffetto and Khalil, 2008) (Table 1).

MMPs degrade different components of ECM including collagen, casein and laminin. MMPs also modulate many bioactive molecules at the cell surface (Stefanidakis and Koivunen, 2006), and may regulate the cellular environment via interaction with G-protein coupled receptors (Eck et al., 2009). MMPs may play a role in cell proliferation, migration (adhesion/dispersion), differentiation and apoptosis, as well as physiological processes such as immune function, tissue healing, and angiogenesis (Egeblad and Werb, 2002). Changes in MMP expression/activity may also be involved in the vascular remodeling and placentation during pregnancy and in the hemodynamic and vascular changes associated with preeclampsia (Raffetto and Khalil, 2008).

The activity of MMPs in various tissues is tightly regulated by endogenous tissue inhibitors of MMPs (TIMPs) (Visse and Nagase, 2003). Alteration of the fine physiologic balance between MMPs and TIMPs may contribute to the pathophysiology of vascular diseases such as atherosclerosis, aneurysms, and varicose veins (Raffetto and Khalil, 2008). MMPs have been proposed as biomarkers of certain pathological conditions, and are often assessed by measuring their plasma levels, tissue gene expression and protein amount, as well as proteolytic activity using gel zymography.

Because there are no specific activators of MMPs, MMP inhibitors (MMPIs) have been used to investigate the role of MMPs in different physiologic processes and in the pathogenesis of specific diseases. Endogenous tissue inhibitors of MMP (TIMPs) include TIMP-1, -2, -3, and -4. Exogenous MMPIs include synthetic compounds that inhibit the activity of all MMPs (broad-spectrum) or specific members of the MMP family. Synthetic MMPIs include zinc binding globulins (ZBG), non-ZBG, and mechanism-based inhibitors. Loss of certain cellular function following treatment with MMPIs has supported a role of MMP in the

regulation of specific cellular functions. MMPIs have also been investigated as potential therapeutic tools for arthritis, cancer and vascular disease. While a large number of MMPIs have been developed, many of them lack specificity. Novel pharmacological tools and genetic engineering have improved the specificity of MMPIs and could be useful in targeting specific MMPs in vascular disease.

In this review, we utilized reports from the Pubmed database to highlight the structure and classification of different MMPs and their inhibitors, the vascular effects of MMPs and their role in pathophysiologic processes and vascular disease. Throughout the review, we will discuss the effects of MMPs in human, followed by data in animals, blood vessels and vascular cells, and then discuss how MMPIs could be used as investigative tools in determining the vascular effects of MMPs, and as novel therapeutic approaches in certain vascular diseases.

3. MMP Structure and Classification

The MMP family has 28 members that share a common core structure. Typically MMPs consist of a propeptide of about 80 amino acids, a catalytic metalloproteinase domain of about 170 amino acids, a linker peptide (hinge region) of variable lengths and a hemopexin domain of about 200 amino acids (Fig. 1). The catalytic domain contains the Zn^{2+} binding motif HEXXHXXGXXH and a conserved methionine, forming a 'Met-turn' 8-residues downstream, which supports the active site cleft structure around the catalytic Zn^{2+} (Bode et al., 1993). MMP-7, -23 and -26 are exceptions as they lack the linker peptide and the hemopexin domain. MMP-23 has a unique C-terminal cysteine-rich domain and an immunoglobulin-like domain immediately after the C-terminus of the catalytic domain (Ohuchi et al., 1997; Holmbeck et al., 1999; Nagase et al., 2006; Cauwe et al., 2007) (Table 1).

From the evolutionary point of view MMPs have been classified depending on their primary sequence into 6 subgroups (A–F): subgroup A (MMP-19, -26, -28), B (MMP -11, -21, -23), C (MMP-17, -25), D (MMP-1, -3, -8, -10, -12, -13, -27), E (MMP-14, -15, -16, -24), and F (MMP-2, -7, -9, -20) (Huxley-Jones et al., 2007). However, MMPs are more commonly classified on the basis of their structure, substrate and subcellular localization into collagenases, gelatinases, stromelysins, matrilysins, membrane-type (MT)-MMPs and others.

Collagenases include MMP-1, -2 (neutrophil collagenase), -13 and -18. These MMPs play an important role in cleaving fibrillar collagen type I, II and III into characteristic 3/4 and 1/4 fragments. They first unwind triple helical collagen then hydrolyze the peptide bonds (Fig. 2). The MMPs hemopexin domains are essential for cleaving native fibrillar collagen while the catalytic domains are needed for cleaving noncollagen substrates (Chung et al., 2004; Nagase and Fushimi, 2008). MMP-13 (collagenase 3) is overexpressed in cartilage tissues of osteoarthritis patients and is very efficient in degrading type II collagen (Dalvie et al., 2008).

Gelatinases include gelatinase A (MMP-2) and gelatinase B (MMP-9). MMP-2 cleaves collagen in two phases, the first resembling that of the interstitial collagenases, followed by gelatinolysis, which is promoted by the fibronectin-like domain (Aimes and Quigley, 1995; Patterson et al., 2001). The collagenolytic activity of MMP-2 is much weaker than collagenases. However, because proMMP-2 is recruited to the cell surface and activated by the membrane-bound MT-MMPs, it may accumulate pericellularly and express significant local collagenolytic activity (Nagase et al., 2006).

Stromelysins 1, 2 and 3, also known as MMP-3, -10, and -11, respectively, have the same domain arrangement as collagenases, but do not cleave interstitial collagen. MMP-3 and -10 are similar in structure and substrate specificity, while MMP-11 is distantly related. MMP-3 and MMP-10 digest a number of ECM molecules and participate in proMMP activation, but MMP-11 has very weak activity toward ECM molecules. Also, MMP-3 and -10 are secreted from the cells as inactive proMMP, but MMP-11 is activated intracellularly by furin and secreted from the cells as an active enzyme (Pei and Weiss, 1995).

Matrilysins include MMP-7 and -26, which lack the hemopexin domain. MMP-7 acts intracellularly in the intestine to process procryptidins to bactericidal forms. MMP-7 degrades ECM components, and also cleaves cell surface molecules such as Fas–ligand, pro-tumor necrosis factor-α, syndecan 1 and E-cadherin to generate soluble forms (Parks et al., 2004). MMP-26 is expressed in breast cancer cells (Marchenko et al., 2004).

Membrane-Type MMPs (MT-MMPs) include four transmembrane MMPs, MP-14, -15, -16 and -24, and two glycosyl-phosphatidylinositol-anchored MMPs, MMP-17 and -25 (Ohuchi et al., 1997; Holmbeck et al., 1999) (Table 1). MT-MMPs have a furin-like pro-protein convertase recognition sequence at the C-terminus of the propeptide. They are activated intracellularly and the active enzymes are expressed on the cell surface. All MT-MMPs except MT4-MMP (MMP-17) can activate proMMP-2 (English et al., 2001). MT1-MMP (MMP-14) activates proMMP-13 on the cell surface (Knauper et al., 1996).

Other MMPs include MMP-12, -20 and -27 which have a domain arrangement and chromosome location similar to stromelysins. MMP-12 (metalloelastase) is expressed in macrophages and is essential for macrophage migration (Shipley et al., 1996) and is also found in hypertrophic chondrocytes and osteoclasts (Kerkela et al., 2001; Hou et al., 2004). MMP-19 is a potent basement membrane-degrading enzyme that plays a role in tissue remodeling, wound healing and epithelial cell migration by cleaving laminin5γ2 chain (Stracke et al., 2000; Sadowski et al., 2003a; Sadowski et al., 2003b; Sadowski et al., 2005). MMP-19 deficient mice develop diet-induced obesity due to adipocyte hypertrophy, but are less susceptible to skin cancers induced by chemical carcinogens (Pendas et al., 2004).

Enamelysin (MMP-20) is a tooth-specific MMP expressed in newly formed tooth enamel and digests amelogenin (Ryu et al., 1999). Amelogenin imperfecta, a genetic disorder with defective enamel formation involves mutation at MMP-20 cleavage sites (Barron et al., 2001).

MMP-21 is an MMP with measurable gelatinolytic activity expressed in various fetal and adult tissues, macrophages of granulomatous skin lesions, fibroblasts in dermatofibromas, and also in basal and squamous cell carcinomas (Ahokas et al., 2003; Skoog et al., 2006).

MMP-23 is unique among the matrixins as it lacks the cysteine switch motif in the propeptide, and the hemopexin domain is substituted by cysteine-rich immunoglobulin-like domains (Velasco et al., 1999). MMP-23 is a type II membrane protein regulated by a single proteolytic cleavage for both its activation and secretion (Pei et al., 2000). It is expressed predominantly in ovary, testis and prostate, suggesting a specialized role in reproduction (Velasco et al., 1999). MMP-27 is expressed in B-lymphocytes and is overexpressed in cultured human lymphocytes treated with anti-(IgG/IgM) (Bar-Or et al., 2003).

Epilysin (MMP-28) was first cloned from the human keratinocyte and testis cDNA libraries, and is expressed in the lung, placenta, heart, gastrointestinal tract and testis (Lohi et al., 2001; Saarialho-Kere et al., 2002). MMP-28 is elevated in cartilage from patients with osteoarthritis and rheumatoid arthritis (Kevorkian et al., 2004; Momohara et al., 2004).

4. Catalytic Mechanisms of MMPs

MMPs may function through one of three catalytic mechanisms. The first mechanism called the base-catalysis mechanism is carried out by the conserved glutamate residue and Zn^{2+} (Browner et al., 1995). In the second mechanism, the catalytic action involves an interaction between a water molecule and Zn^{2+} during the acid-base catalysis (Kester and Matthews, 1977). In the third mechanism, a histidine from the HExxHxxGxxH-motif participates in catalysis by dissociation of Zn^{2+} from it, thus allowing the Zn^{2+} ion to assume a quasi-penta coordinated state. In this state, the Zn^{2+} ion is coordinated with the two oxygen atoms from the catalytic glutamic acid, the substrate's carbonyl oxygen atom, and the two histidine residues, and can polarize the glutamic acid's oxygen atom, proximate the scissile bond, and induce it to act as reversible electron donor. This forms an oxy-anion transition state. At this stage, a water molecule acts on the dissociated scissile bond and completes the hydrolysis of the substrate (Manzetti et al., 2003). Collectively, upon binding of the substrate, the zinc-bound water molecule attacks the substrate carbonyl carbon, and the transfer of protons through a conserved glutamine residue to the amide nitrogen of the scissile bond results in peptide cleavage (Lovejoy et al., 1994; Skiles et al., 2001).

5. Modulators of MMP Activity

MMPs are regulated at multiple levels including transcription, secretion, activation of the zymogen forms, extracellular inhibition and internalization by endocytosis. MMP activity is positively modulated by ions and reagents that induce MMP cleavage and activation. Zn^{2+} chelators suppress MMP activity by depriving MMPs from the Zn^{2+} critical for their activity (Newsome et al., 2007). Cu^{2+} ions may decrease MMP-2 secretion (Guo et al., 2005). MMPs are also inhibited by both endogenous and exogenous inhibitors.

5.1. MMP Cleavage and Activators

Matrixins are synthesized as pre-proenzymes and the signal peptide is removed during translation to generate proMMPs. ProMMPs have a 'cysteine switch' motif PRCGXPD in which the cysteine residue coordinates with the catalytic Zn^{2+} in the catalytic domain, keeping the proMMPs inactive (Van Wart and Birkedal-Hansen, 1990). Activation of proMMPs involves detaching of the hemopexin domain, which can be accomplished extracellularly by other MMPs or other classes of proteases. For example, MMP-3 activates a number of proMMPs including the processing of proMMP-1 into fully active MMP-1 (Suzuki et al., 1990). ProMMP-2 is not activated by general proteinases; instead its activation takes place on the cell surface by most MT-MMPs, but not MT4-MMP (Mulvany et al., 1996). MT1-MMP-mediated activation of proMMP-2 requires TIMP-2 (Butler et al., 1998; Wang et al., 2000). ProMMP-2 forms a complex with TIMP-2 through their C-terminal domains, thus permitting the N-terminal inhibitory domain of TIMP-2 to bind to MT1-MMP on the cell surface. The cell surface-bound proMMP-2 is then activated by an MT1-MMP that is free of TIMP-2. Alternatively, MT1-MMP inhibited by TIMP-2 can act as a "receptor" of proMMP-2. The MT1-MMP-TIMP-2-proMMP-2 complex is then presented to an adjacent free MT1-MMP for activation (Itoh et al., 2001). Thus, the TIMP-2 environment may determine the MT1-MMP choice between direct cleavage of its own substrates and activation of MMP-2 (Kudo et al., 2007). However, for a number of MMPs including membrane-bound MMP-11, -23, -28, activation occurs intracellularly via the endopeptidase furin, which selectively cleaves paired base residues (van de Ven et al., 1990; Pei and Weiss, 1995; Velasco et al., 1999; Marchenko and Strongin, 2001).

Oxidants generated by leukocytes or other cells can both activate (via oxidation of the prodomain thiol followed by autolytic cleavage) and inactivate MMPs (via modification of amino acids critical for catalytic activity), providing a mechanism to control bursts of

proteolytic activity. *In vitro*, a number of proMMPs are activated by reactive oxygen species (ROS) (Okamoto et al., 1997; Fu et al., 2001; Gu et al., 2002; Fu et al., 2004). Foam cell derived ROS can activate proMMP-2. Nitric oxide (NO) may also activate proMMP-9 during cerebral ischemia by reacting with the thiol group of the cysteine switch and forming an S-nitrosylated derivative (Gu et al., 2002). Also, hypoxia may increase MMP-2 and -9 mRNA levels (Oh et al., 2008). Other MMPs such as MMP-9 depend predominantly on plasmin for activation (Ogata et al., 1992). MMP-7 is activated both by MMP-3 and by hypochlorous acid, a product of myeloperoxidase found in plaque macrophages. MMP-7 can activate MMP-1 (Fu et al., 2001; Dollery and Libby, 2006). Also, serine proteinases such as neutrophil elastase, may favor matrix breakdown by inactivating TIMPs (Desrochers et al., 1992; Liu et al., 2000).

MMPs can be activated by thiol-modifying agents such as 4-aminophenylmercuric acetate, mercury chloride, and N-ethylmaleimide, oxidized glutathione, sodium dodecyl sulfate, and chaotropic agents by causing disturbance of the cysteine-Zn^{2+} interaction at the cysteine switch. MMPs can also be activated by heat treatment and low pH (Chen et al., 1993).

5.2. Endogenous MMP Inhibitors

TIMPs and α2-Macroglobulin are two major endogenous inhibitors of MMPs. TIMPs bind MMPs in a 1:1 stoichiometry (Fig. 3). There are 4 TIMPs in humans; TIMP 1–4. TIMP-1 and -3 are glycoproteins, while TIMP-2 and -4 do not contain carbohydrates. TIMPs have an N-terminal domain (125 aa) and C-terminal domain (65 aa); each containing 3 disulfide bonds. The N-terminal domain folds as a separate unit and is capable of inhibiting MMPs (Williamson et al., 1990; Murphy et al., 1991). The TIMP molecule wedges into the active-site cleft of MMP in a manner similar to that of the substrate. Cys1 is instrumental in chelating the active site Zn^{2+} with its N-terminal α-amino group and carbonyl group, thereby expelling the water molecule bound to the catalytic Zn^{2+} (Fig. 3). TIMPs inhibit all MMPs tested thus far, but TIMP-1 is a poor inhibitor of MT1-MMP, MT3-MMP, MT5-MMP and MMP-19 (Baker et al., 2002). TIMPs also inhibit a broader spectrum of metalloproteinases. TIMP-1 inhibits ADAM-10 while TIMP-2 inhibits ADAM12 (Amour, 2000), TIMP-3 has a much broader inhibition profile including ADAM-10, -12 (Jacobsen et al., 2008) and -17 (Amour et al., 2000) and ADAMTS-1, -2, -4 and -5 (Kashiwagi et al., 2001; Rodriguez-Manzaneque et al., 2002). Because of this broad inhibitory spectrum, TIMP-3 ablation in mice causes lung emphysema-like alveolar damage (Leco et al., 2001) and faster apoptosis of mammary epithelial cells after weaning (Fata et al., 2001), whereas TIMP-1-null mice and TIMP-2-null mice do not exhibit obvious abnormalities.

MMP activity is partly regulated by α2-macroglobulin and related proteins. Human α2-macroglobin, a glycoprotein consisting of four identical subunits and found in blood and tissue fluids, acts as a general proteinase inhibitor. Most endopepidases are inhibited by entrapping the enzyme within the macroglobulin. The complex is then rapidly cleared by endocytosis via a low density lipoprotein receptor-related protein-1 (Strickland et al., 1990).

Other proteins inhibit selected members of MMPs: a secreted form of β-amyloid precursor protein inhibits MMP-2 (Higashi and Miyazaki, 2003); a C terminal fragment of procollagen C-proteinase enhancer protein inhibits MMP-2 (Mott et al., 2000); tissue factor pathway inhibitor-2, a serine proteinase inhibitor, inhibits MMP-1 and -2 (Herman et al., 2001), and RECK, a GPI-anchored glycoprotein, inhibits MMP-2, -9 and -14. However, the mechanism of action of these inhibitors is not well-described (Murphy and Nagase, 2008).

5.3. Exogenous (Synthetic) MMP Inhibitors

Several MMP inhibitors (MMPIs) have been developed and some of them have been pursued as investigative or therapeutic tools (Jacobsen et al.),2010) (Table 2). Because the mechanism by which MMPs cleave their substrates requires catalytic Zn^{2+} ion, the design of MMPI has traditionally utilized zinc binding globulin (ZBG). ZBGs in MMPI displace the zinc-bound water molecule and inactivate the enzyme (Rao, 2005). ZBG also acts as an anchor to lock the MMPI in the active site and direct the backbone of the inhibitor into the target substrate-binding pockets (Table 2) (Jacobsen et al.),2010).

Early MMPIs typically included hydroxamic acids (ZBG1), carboxylates (ZBG2), thiols, and phosphonic acids (phosphorus-based ZBGs) (Skiles et al., 2001). Of these MMPIs, hydroxamic acids were preferred due to their relative ease of synthesis and potent binding (Brown et al., 2004; Elaut et al., 2007; Gupta et al., 2007; Moss et al., 2008). A contributing factor to the effectiveness of hydroxamates is the hydrogen bonding that results between the heteroatoms of the ZBG and neighboring amino acid residues that are conserved in all MMP active sites. Several hydroxamate- and carboxylate-based MMPIs show good selectivity among different MMPs (Cherney et al., 2004; Rossello et al., 2005; Nakatani et al., 2006; Whitlock et al., 2007; Subramaniam et al., 2008). Although hydroxamate MMPIs are potent inhibitors, many of them have shown adverse musculoskeletal side effects and poor oral bioavailability (Vihinen et al., 2005; Fingleton, 2008).

Research has been directed toward the development of MMPIs with increased selectivity toward a specific MMP. The development of highly specific synthetic active-site-directed MMPIs necessitates identifying the specific structural features of each individual MMP that can be exploited to obtain the desired selectivity. Site specific delivery is another approach that permits the use of MMPIs with low potency. With this goal in mind, a series of biphenyl sulfonamide carboxylate MMPIs with high selectivity for MMP-13 were designed for treatment of osteoarthritis (Li et al., 2005). The carboxylic acid scaffold of those MMPIs was also used to develop selective MMP-12 inhibitors for treatment of chronic obstructive pulmonary disease (Churg et al., 2003). Also, a series of MMPIs with improved selectivity towards MMP-12 over MMP-13 were generated by using a fused ring system. Selective hydroxamic acid inhibitors of MMP-2 have also been developed as potent anti-angiogenic agents. Inhibitor 7 is the most selective MMP-2 inhibitor of this series (Rossello et al., 2005). Another selective hydroxamate MMPI with specificity towards MMP-3 was designed for treatment of chronic non-healing wounds (Whitlock et al., 2007). Other ZBGs have been developed to improve selectivity, bioavailability, and pharmacokinetics, and include oxygen, nitrogen, and sulfur donor–atom ligands and monodentate, bidentate, and tridentate chelators.

5.4. Derivatives of Early ZBGs

Hydrazide (ZBG3) and sulfonylhydrazide (ZBG4) analogs of the hydroxamate MMPI illomastat have been developed (Table 2) (Auge et al., 2003). Sulfonylhydrazide 9 is a potent inhibitor of MMP-1, -2, and -9 with suboptimal potency (Ledour et al., 2008). Mercaptosulfide (ZBG8) inhibitors target MMP-14. MMPIs with phosphorus-based ZBGs have also demonstrated improved selectivity. Inhibitor 18 is a potent phosphonate inhibitor that exhibits selectivity for MMP-8 (Hurst et al., 2005). Other phosphorus-based ZBG for MMPI include the carbamoyl phosphonate ZBG (ZBG9) (Jacobsen et al.),2010).

The net negative charge on ZBGs prevents cell penetration and restricts these MMPIs to the extracellular space, and therefore contributes to their low toxicity (Hoffman et al., 2008). Several MMPIs based on these ZBGs are selective for MMP-2 and have been evaluated in both *in vitro* and *in vivo* models of tumor invasion and angiogenesis. Compound 20 shows

marked specificity towards MMP-2 with little inhibition of MMP-1, -3, -8, and -9. Administration of compound 20 intraperitoneally at 50 mg/kg/day for three weeks in a murine model of melanoma metastasis results in 55% inhibition of lung metastasis (Breuer et al., 2004).

Compound 21 was introduced as a carbamoyl phosphonate MMPI that targets MMP-2 and -9, but spares MMP-1, -3, -8, -12, and -13. Compound 21 dose-dependently inhibits cell invasion in a Matrigel assay and prevents tumor colonization in the murine melanoma model, and shows efficacy via both the oral and intraperitoneal routes. Compound 21 has shown promising results in reducing tumor growth and metastasis in the more aggressive murine model developed by implantation of human tumor prostate cells in immunodeficient mice. These ZBGs have the advantage of being water soluble at physiological pH and are not acutely toxic at the concentrations used in the murine models (Hoffman et al., 2008).

5.5. Nitrogen-Based ZBGs

Nitrogen-based ZBGs (ZBG10–16) have binding preference to late transition metals and improved selectivity towards Zn^{2+}-dependent enzymes (Cook et al., 2004; Jacobsen et al., 2006). An example of these ZBGs is compound 22, a modest inhibitor of MMP-9 that does not inhibit MMP-1, -2, or -12. The most extensively studied nitrogen-based ZBGs are the pyrimidine-2,4,6-trione and dionethione inhibitors. The pyrimidine-2,4,6-trione group is a known constituent of many FDA-approved drugs such as the barbiturates, and therefore its metabolic disposition and bioavailability have been well-studied (Grams et al., 2001). The pyrimidine-2,4,6-trione MMPIs were first optimized for gelatinase specificity and as anticancer drugs (Foley et al., 2001).

Compound 23 was evaluated for its anti-invasive, anti-tumorigenic, and anti-angiogenic activity. Compound 23 inhibits chemoinvasion by 85% at concentrations as low as 10 nM and shows anti-cancer efficacy in several *in vitro* and *in vivo* models (Maquoi et al., 2004). Pyrimidine-2,4,6-trione MMPIs have also been optimized to inhibit MMP-13 as part of the development of anti-osteoarthritis drugs (Blagg et al., 2005; Kim et al., 2005; Reiter et al., 2006; Freeman-Cook et al., 2007). Pyrimidinetrione-based inhibitors have demonstrated up to 100-fold selectivity for MMP-13 over MMP-2, -8, and -12 (Reiter et al., 2006).

5.6. Heterocyclic Bidentate ZBGs

A series of heterocyclic bidentate chelators ZBG20–30 was developed as alternative ZBGs and MMPIs (Puerta et al., 2004) . These ZBGs have some features in common with hydroxamic acids but with better biostability and tighter Zn^{2+} binding due to ligand rigidity and, in some cases, the incorporation of sulfur donor atoms (Puerta and Cohen, 2003; Jacobsen et al., 2007). *In vitro* assays showed that these ZBGs inhibited MMP-1, -2, and -3 with greater potency than acetohydroxamic acid (Puerta et al., 2004), and cell viability assays showed that these ZBGs have low toxicity (Puerta et al., 2006). Several of these ZBGs have been developed into complete MMPIs with good potency (Puerta et al., 2005; Agrawal et al., 2008). Compound 25 is a pyrone-based inhibitor with greater selectivity toward MMP-3 over MMP-1 and -2 (Puerta et al., 2005). Compound 26 is an inhibitor of MMP-12 at low concentrations, and a potent inhibitor of MMP-2, -3, and -8, but significantly less effective against MMP-1, -7, -9, and -13 (Agrawal et al., 2008). In an *ex vivo* rat heart model of ischemia and reperfusion, hearts treated with 5 μM of compound 26 were found to recover more than 80% of their original contractile function compared with 50% of untreated hearts (Agrawal et al., 2008).

Other ZBGs include 6-, 7-, and 8-membered heterocyclic chelators as 1-hydroxy-2-piperidinone, 1-hydroxyazepan-2-1, 1-hydroxyazocan-2-1, and 1-hydroxy-1,4-diazepan-2-1

(Zhang et al., 2008). Compound 27, which uses ZBG20, is selective to MMP-1 and moderately selective to MMP-3. Compound 27 exhibits a half-life of 47 h in rats when administered at 2 mg/kg intravenously, and causes reduction in brain edema following ischemia–reperfusion in a mouse model of transient mid-cerebral artery occlusion (Zhang et al., 2008).

Just as changes in the ZBG can generate differences in selectivity, changes in the connectivity and point of attachment of the ZBG to the backbone can also result in dramatic changes in potency and selectivity. For example, compound 30 has an IC50 of 240 nM against MMP-3 (Puerta et al., 2005; Agrawal et al., 2008), whereas the structural isomer compound 32 shows weaker inhibition (~30%) at concentrations as high as 100 μM (Yan and Cohen, 2007). This comparison shows that two MMPIs with similar chemical formula, ZBG and backbone, may have vastly different activities due to the relative positioning of the backbone on the ZBG.

5.7. Non-Zinc-Binding MMPIs

MMPIs that do not have a ZBG and hence do not bind the catalytic Zn^{2+} ion have been developed (Table 3) (Jacobsen et al.; Morales et al., 2004; Dublanchet et al., 2005; Engel et al., 2005; Gooljarsingh et al., 2008; Li et al., 2008; Pochetti et al., 2009). The rationale for this strategy is that eliminating or minimizing the interaction with the catalytic Zn^{2+} ion best achieves MMP selectivity, because the metal site is the most conserved feature in all MMPs. Nearly all Non-zinc-binding MMPIs show high MMP-13 selectivity and effectiveness in the treatment of osteoarthritis in animal models (Johnson et al., 2007; Li et al., 2008).

Several non-zinc-binding MMPIs show a noncompetitive mechanism of inhibition (Gooljarsingh et al., 2008) . Compound 37 inhibits MMP-13 but does not appreciably inhibit MMP-1, -2, -3, -7, -8, -9, -12, -13, -14, or -17. Binding of these inhibitors may rigidify the enzyme active site into a specific conformation that is less conducive for substrate binding. The flexibility of MMP-13, relative to other MMPs, may allow for this favorable conformation that is not accessible in other MMPs (Engel et al., 2005; Johnson et al., 2007).

As most of these non-zinc-binding MMPIs are potent and selective, derivatives aimed to improve their solubility and drug properties (Li et al., 2008). The hydrophobicity of these inhibitors is critical in maintaining significant protein–inhibitor interaction that result in high potency, but also results in poor water solubility. To improve the solubility with minimal effect on potency, derivatives were explored to specifically modify the solvent-exposed portions of the molecule while maintaining hydrophobic core structures (Dublanchet et al., 2005).

Preclinical studies with compound 37 have shown encouraging results in models of osteoarthritis. Compound 37 has an efficacy at doses as low as 0.1 mg/kg in MMP-13-induced rat model of cartilage knee joint damage. Also, oral administration of compound 37 twice daily at 30mg/kg resulted in a 68% reduction in the cartilage lesion area of tibial plateaus in rats with surgically induced cartilage knee damage. When the rat joints were subsequently examined for evidence of fibroplasias and expanded inner synovial lining, which are indicative of musculoskeletal syndrome, fibroplasias were absent in rats treated with compound 37, but present in rats treated with broad-spectrum MMPIs. MMPIs of this high degree of selectivity may minimize the toxic side effects associated with broad-spectrum MMPIs. However, it is not clear whether the selectivity of these inhibitors is due to their non-ZBG properties or other factor(s) (Engel et al., 2005; Johnson et al., 2007).

5.8. Mechanism-Based MMPIs

SB-3CT was introduced as the first mechanism-based inhibitor of MMPs. SB-3CT binds in the active site and forms a covalent bond with the substrate protein upon activation by Zn^{2+} coordination (Table 3) (Jacobsen et al.),2010). The formation of the covalent bond impedes inhibitor dissociation as compared to the traditional chelating competitive inhibitors. This reduces the rate of catalytic turnover, and decreases the amount of MMPI needed to saturate the enzyme active sites. Compound 40 is a selective inhibitor of MMP-2 and -9 that showed promise in pre-clinical studies as an inhibitor of bone metastasis in prostate cancer and in the prevention of damage caused by cerebral ischemia. The structure of 40 is relatively simple, as reflected by its low molecular weight. The mechanism of inhibition of 40 is similar to that of a "suicide substrate" in which a functional group is activated, leading to covalent modification of the enzyme active site (Bernardo et al., 2002). Compound 40 exhibits slow-binding kinetics with MMP-2, -3, and -9, with a time scale for establishing equilibrium between the enzyme and inhibitor and the enzyme–inhibitor complex in the order of seconds to minutes. Slow-binding inhibition is characterized by slow dissociation rates, though the binding rate can vary in speed (Morrison and Walsh, 1988). Progress curves, which display the enzyme activity of MMP-2, -9, and -3 with compound 40 over time, are non-linear (Bernardo et al., 2002). The curves show that the initial enzyme rate is not maintained and is instead reduced to a new "steady-state rate" of MMP activity. This indicates a slow-binding mechanism of inhibition, characteristic of an interaction between an enzyme and an inhibitor that resists dissociation. The binding of compound 40 with MMPs is nearly irreversible. Following 95% inhibition, MMP-2 regains 50% activity only after 3 days with dialysis, indicating some reversibility and distinguishing it from a true suicide inhibitor, which operates strictly by an irreversible mechanism (Morrison and Walsh, 1988; Bernardo et al., 2002). The selectivity of compound 40 stems from the difference in the binding kinetics for various MMPs. As demonstrated by the non-linear progress curves, inhibition increases over time, as slow-binding inhibitors do not dissociate readily from the active site (Lee et al., 2005). The selectivity of compound 40 might be related to its inhibition of MMP-2 and -9 via a slow-binding mechanism while inhibition of MMP-14 occurs through competitive inhibition (Toth et al., 2000).

In preclinical studies, compound 40 has produced anti-cancer effects in both a T-cell lymphoma model and a prostate cancer model (Kruger et al., 2005; Bonfil et al., 2006; Bonfil et al., 2007). Also, *in vitro* Matrigel tests showed that 1 μM of compound 40 reduces the invasion ability of human prostate cancer cells by 30% as compared to the vehicle control (Bonfil et al., 2006). In a mouse model of T-cell lymphoma, compound 40 administered at 5–50 mg/kg/d promotes a dose-dependent reduction in the number of liver metastases (Banke et al., 2005). At 50 mg/kg/d, compound 40 inhibits liver metastases by 73% and reduces the colony size of the metastases, while the broad-spectrum inhibitor Batimastat has led to increased metastasis in the same tumor model. Additionally, *in vitro* tests show that 40 does not affect cell growth or viability up to 12.5 μM. Compound 40 also showed promising results in a bone metastasis model of prostate cancer demonstrating reduced tumor growth and angiogenesis (Bonfil et al., 2006). Also, compound 40 provides neuronal protection in a murine stroke model (Gu et al., 2005). In mice treated with compound 40 either prior to or 2 h following ischemia induced by right middle cerebral artery occlusion, the infarct volume is decreased to 30% of the control. Administration of compound 40 is protective up to 6 h after the ischemic event in mice. Also, neurological behavioral scores evaluated 24 h after reperfusion show that compound 40-treated mice exhibit significant improvement as compared to the control mice, and the improvement is correlated with the observed infarct volume.

Although compound 40 has significant *in vivo* activity, it undergoes rapid metabolism in mice (Lee et al., 2007). This leads to low systemic exposure and suggests that a metabolite

of the parent compound may be responsible for the *in vivo* activity (Celenza et al., 2008). Compound 43 is a more potent inhibitor of MMP-2, -3, -7, -9, and -14 than compound 40. Also, compound 43 demonstrates slow-binding kinetics with MMP-2, -9, and -14 (Lee et al., 2009a). Analysis of the different MMPI metabolites led to the design of derivatives that have better *in vivo* stability and provide longer systemic effects (Lee et al., 2009a). Compound 45 is a slow-binding inhibitor of MMP-2 and -9, but a competitive inhibitor of other MMPs. Interestingly, the 45 inhibitor is more potent for MMP-9 than MMP-2. The metabolites of 45 are 75% more stable than those of 40, resulting in significantly longer systemic effects.

SB-3CT and its successors show great clinical promise, and the use of mechanism-based, slow-binding inhibitors may provide a new approach to gain selectivity in MMPI design. Other types of covalent modification in the active site may lead to new patterns of selectivity (Jacobsen et al.) 2010). However, even with the marked improvements in the design of MMPIs, therapeutic inhibition of MMPs is challenging as evidenced by the fact that the antibiotic doxycycline remains the only FDA-approved MMPI (Vihinen et al., 2005; Nuti et al., 2007; Fingleton, 2008; Georgiadis and Yiotakis, 2008). One limitation of many MMPIs is that their use triggers dose-limiting musculoskeletal syndrome as a side effect, characterized by joint stiffness, pain, inflammation, and tendinitis (Jacobsen et al.; Coussens et al., 2002; Renkiewicz et al., 2003; Fingleton, 2008).

6. Biological Effects of MMPs

MMPs play a role in many biological processes including tissue remodeling and growth and may also be involved in the tissues defense mechanisms and immune responses. Increased expression of MMPs has been documented during different stages of mammalian development, from embryonic implantation (Harvey et al., 1995) to the morphogenesis of different tissues including lung, bone and mammary gland (Vu and Werb, 2000; Page-McCaw et al., 2007). Other physiological processes such as growth and wound healing also involve increased expression of MMPs (Ravanti and Kahari, 2000).

MMPs are either secreted from the cell or anchored to the plasma membrane with heparin sulfate glycosaminoglycans. The collagenases MMP-1, -8, -13, and -14 efficiently degrade fibrillar collagens type I, II and III in their triple-helical domains (Lovejoy et al., 1999) (Fig. 2). Cleavage by these MMPs renders the collagen molecules thermally unstable so that they unwind to form gelatin, which is then degraded by other members of the MMP family including the major gelatinases MMP-2 and -9. MMP-2 localize at the cell surface by binding via its carboxyl terminus to integrin $\alpha_v\beta_3$ or the MMP-14-TIMP-2 complex (Park et al., 2000). When bound, the catalytic site of MMP-2 is exposed and can then be cleaved and activated. The α2 chains of collagen IV bind MMP-9 with a high affinity even when MMP-9 is inactive (Olson et al., 1998). This juxtaposition of enzyme and substrate makes a pool of the enzyme that is rapidly available upon activation for any remodeling events.

The ECM binds growth factors either directly or via growth-factor-binding proteins. Several MMPs stimulate the release of growth factors such as transforming growth factor β (TGF-β), fibroblast growth factor 1 (FGF-1), insulin-like growth factor 1 (IGF-1), TNFα, and heparin-binding epidermal growth factor (HB-EGF) by cleaving either the growth-factor binding protein or the matrix molecule to which these proteins attach. MMP-3 and -7 can cleave the adherens-junction protein E-cadherin (Imai et al., 1997; Manes et al., 1997; Suzuki et al., 1997; Noe et al., 2001; Steinhusen et al., 2001). MMP-3 can release a soluble form of the adhesion molecule L-selectin from leukocytes, and also sheds membrane-bound HB-EGF to exert signaling functions (Suzuki et al., 1997). MMP-7 releases soluble Fas ligand which induces apoptosis (Asamoto et al., 2001).

Some growth factors are proteolytically inactivated by MMPs, including the chemokine connective tissue activating peptide III (CTAP-III), monocyte chemoattractant protein and stromal cell-derived factor 1 (McQuibban et al., 2001; Fujiwara et al., 2002). Growth factors and cytokines are also negatively regulated when MMPs cause shedding of their receptors from the cell membrane, as in the case of surface FGF receptor 1 (Levi et al., 1996).

MMPs also affect the immune system. Defensins are a family of polar antimicrobial peptides that contribute to the innate immune system of some animals. Defensins are synthesized in an inactive form and are activated by the proteolytic removal of the pro-domain by MMP-7, which allows them to insert into the bacterial membrane and disrupt its integrity (Ganz, 1999; Wilson et al., 1999). MMP-3 and -7 can also cleave all IgG proteins, an important process that prevents the initiation of the complement cascade and helps in the removal of IgG from damaged or inflamed tissue (Gearing et al., 2002). Also, the receptor of the complement component C1q (C1qR) exists in both a membrane-bound form and a soluble form that inhibits the hemolytic activity of C1q. MT1-MMP releases the membrane bound C1qR, thus allows tumor cells to avoid targeted destruction by the complement system and thereby facilitates tumor-cell survival (Ruiz et al., 1999; Feng et al., 2002; Rozanov et al., 2002).

In addition to their known effects on ECM, experiments have demonstrated diverse effects of MMPs and TIMPs on ECs and VSMCs.

6.1. MMPs and the Vascular Endothelium

MMPs exert diverse effects on ECs. MMPs affect different receptors and pathways such that the overall effects of MMPs vary depending on the predominant receptors or pathways in the tissue examined. Also, individual MMPs vary in their proteolytic activity and tissue substrates, further contributing to the discrepancy in the effects of MMPs in different studies.

6.2. Effects of MMPs on EC Integrity and Vascular Permeability

MMPs may regulate EC integrity and vascular permeability. MMP-1 mediates the activation of HUVECs into prothrombotic, proinflammatory, and cell-adhesive state by supernatants from cultured melanoma and colon cancer cells (Goerge et al., 2006). In mouse aorta, MMP-13 mediates the endothelial protective effect of NO by cleaving the pro-inflammatory intercellular adhesion molecule-1 (ICAM-1) (Tarin et al., 2009). MMPs may also increase vascular permeability and cause vascular disruption. Upregulation of MMP-2 and -9 mediate the increase in membrane permeability and vascular disruption induced by human immunodeficiency virus-1 envelope gp120 in rat brain (Louboutin et al.),2010). Also, upregulation of MMP-2 and -9 decreases the integrity of the porcine blood brain barrier (Thanabalasundaram et al.),2010). In support of these findings, MMPIs such as GM6001 prevent degradation of the tight junction protein occludin and reduce the intercellular gap formation and permeability in porcine cerebral microcapillary ECs (Lischper et al.),2010).

6.3. MMPs and Endothelium-Dependent Vascular Relaxation

MMPs may have endothelium-dependent vasorelaxant effects. Upregulation of MMP-2 may mediate the bacterial LPS-induced vascular hyporeactivity to vasoconstrictors in rat aorta via an endothelium-dependent mechanism (Cena et al., 2008). Other studies demonstrated that upregulation of MMPs may be associated with impaired vasorelaxation. Upregulation of MMP-3 and downregulation of TIMP-1 mediate the impaired endothelium-dependent vasodilation, EC apoptosis and endothelial disruption exerted by FOXO3 in HUVECs (Lee et al., 2008). Also, upregulation of MMP-2 and -9 may be responsible for nicotine-induced endothelial disruption and unresponsiveness of blood vessels to the vasorelaxant

acetylcholine, and the MMPI doxycycline partially reversed this effect (Jacob-Ferreira et al.),2010). In renovascular rat model of hypertension (HTN), antioxidant treatment inhibited the decrease of endothelium-dependent vasorelaxation and attenuated the vascular dysfunction and remodeling by inhibiting oxidative stress-induced upregulation of MMP-2 (Castro et al., 2009). Further investigations are needed to determine the MMPs targets in ECs and explain their diverse effects in different tissues.

6.4. Effects of MMPs on VSM Contraction

Some studies suggested that MMPs, via PI_3K and ATP synthesis, may transactivate EGFR and mediate the α-adrenergic receptor-induced maintenance of vascular tone. Inhibition of the expression of MMP-2 or -7 blunted the phosphorylation of Akt by PI_3K and thus inhibited the response to phenylephrine (Phe) in rat mesenteric artery (Nagareddy et al., 2009). Other studies have shown that Phe-induced contraction of rat aorta is inhibited by MMP-2 (~50%) and MMP-9 (~70%) (Chew et al., 2004). The MMP-induced inhibition of aortic contraction is concentration- and time-dependent, and is reversible suggesting that the actions of MMPs are not solely due to irreversible degradation of ECM. Also, the inhibitory effects of MMPs on VSM contraction are not likely due to degradation of Phe or the α-adrenergic receptors because MMPs also inhibit prostaglandin F2α-induced contraction, suggesting that the effects of MMPs are not specific to a particular agonist/receptor, but likely involve direct effects on common VSM contraction pathway(s) downstream from receptor activation.

VSM contraction is triggered by increases in Ca^{2+} release from the intracellular stores and Ca^{2+} entry from the extracellular space. MMPs do not inhibit Phe-induced contraction in Ca^{2+}-free solution, suggesting that they do not inhibit the Ca^{2+} release mechanism. On the other hand, MMPs inhibit Phe-induced Ca^{2+} influx (Chew et al., 2004). The mechanism by which MMPs inhibit Ca^{2+} entry could involve direct effects on the Ca^{2+} channels. MMPs may also affect K^+ channels. MMP-2 causes relaxation of rat inferior vena cava (IVC) that is abolished by blockers of the large conductance Ca^{2+}-activated K^+ channels such as iberiotoxin, suggesting a role of VSM hyperpolarization (Raffetto et al., 2007). MMPs also induce collagen degradation and produce Arg-Gly-Asp (RGD)-containing peptides, which could bind to $\alpha_v\beta_3$ integrin receptors and inhibit Ca^{2+} entry into VSM (Waitkus-Edwards et al., 2002). MMPs may also stimulate protease-activated receptors (PARs) and activate signaling pathways that could lead to blockade of VSM Ca^{2+} channels (Macfarlane et al., 2001). This is supported by reports that proteases such as thrombin activate PARs and promote endothelium-dependent VSM relaxation by inhibiting Ca^{2+} influx (Hamilton et al., 1998). Thus while MMPs may affe ct VSM contraction and ion channels, further studies are needed to define the role of integrins and PARs as possible molecular mechanisms via which MMPs could inhibit VSM contraction.

6.5. MMPs and VSMC Migration

Evidence suggests that MMPs play a role in VSMC migration. In rat aortic smooth muscle cells (RASMCs) in culture using collagen I gel to mimic ECM, exposure to interstitial flow enhanced cell motility. Upregulation of MMP-1 enhanced flow-enhanced motility, while the MMPI GM-6001 attenuated flow-induced migration. ERK1/2 phosphorylation and increased expression of AP-1 transcription factors c-Jun and c-Fos appear to be involved in MMP-mediated enhancement of flow-induced cell motility (Shi et al.),2010). Young HASMCs produce active MMP-2 and possess a higher migratory capability than aged cells. The activation of pro-MMP-2 in young cells is likely related to an increase in MT1-MMP content. In contrast, aged cells produce only the inactive zymogen form of MMP-2, and upregulation of TIMPs in aged cells could prevent pro-MMP-2 activation. Interestingly, treatment of young cells with TIMP-1 and -2 promotes aged HASMCs migratory behavior

(Vigetti et al., 2008). MMP-2 activity could also influence chemokine-induced chemotaxis of human VSMC monolayers (Haque et al., 2004). Also, *in vivo* knockout of MMP-2 decreases VSMC migration and intima formation in the mouse carotid ligation model (Cheng et al., 2004; Johnson and Galis, 2004) (Table 4).

Studies have also suggested a role of MMP-9 in VSMC migration. Tanshinone IIA, a major constituent of Salvia miltiorrhiza bunge, inhibits TNF-α-induced HASMC migration, partly through inhibition of MMP-9 activity. Tanshinone IIA also inhibits TNF-α-induced ERK and c-jun phosphorylation, and NF-κB and AP-1 DNA-binding (Jin et al., 2008). Suppression of MMP-9 expression by down-regulation of NF-κB also mediates the inhibitory effect of curcumin on migration of HASMCs (Yu and Lin),2010). Also, knockout of MMP-9 is associated with reduced VSMC migration and intima formation observed after filament loop injury (Cho and Reidy, 2002) or carotid arterial occlusion in mice (Galis et al., 2002) (Table 4).

Disruption of the basement membrane is essential for VSMC migration (Aguilera et al., 2003). MMPs, by degrading the basement membrane, can facilitate a host of ECM integrin interactions leading to activation of focal adhesion kinases (FAK) and increased cell migration. MMPs also cause fragmentation of membrane components such as type I collagen, thus creating new integrin-binding sites. Growth factor receptors, cadherins and integrins mediate signaling pathways that play a role in reorganizing the cytoskeleton in preparation for migration (Carragher and Frame, 2004; Nelson and Nusse, 2004). MMPs cleave E-cadherin in epithelial cells, VE-cadherin in ECs and N-cadherin in VSMCs (Savani et al., 1995; Uglow et al., 2003), which in turn dissolve adherence junctions and frees the cells to move.

MMPs not only facilitate migration by promoting proteolysis of ECM, but may also directly enhance cell migration. MMP-1 promotes growth and invasion of cells by binding to and cleavage of PAR-1 which reveals a tethered ligand that initiates signaling via a G protein-coupled receptor and activates migration (Boire et al., 2005). This mechanism allows the cells to sense a proteolytic environment and actively move towards an area of degraded matrix.

MMPIs have been useful in demonstrating the effect of MMPs on VSMC migration. Gene transfer of TIMPs reduces VSMC migration *in vitro* and inhibits or delays intima thickening *in vivo*. TIMPs 1–4 delivered directly or by gene transfer inhibit migration of SMCs *in vitro* (Forough et al., 1996; Baker et al., 1998) and reduce neointima formation in organ cultures of human saphenous vein (George et al., 2000). TIMP gene transfer also preserves medial basement membrane and inhibits VSMC migration to the intima. Synthetic MMPIs inhibit migration of VSMC from baboon arterial explant cultures (Kenagy et al., 1996), and early VSMC migration in the rat carotid balloon injury model (Islam et al., 2003). Collectively, experimental evidence supports that MMPs enhance VSMC migration via both extracellular and intracellular effects, and MMPIs could reverse or prevent cell migration.

6.6. MMPs and VSMC Proliferation

VSMC proliferation at sites of endothelial injury and lipid deposition plays a role in atheroma formation. In addition to facilitating VSMC migration, MMPs may regulate VSMC proliferation. Pretreatment of human aortic VSMCs with ethanol extract of buddleja officinalis attenuates high-glucose-induced cell proliferation by suppressing MMP-9 activity (Lee et al.),2010). On the other hand, MMP-9 knockout is associated with inhibition of VSMC proliferation after filament loop injury (Cho and Reidy, 2002), but not after tying off the mouse carotid artery (Galis et al., 2002). A possible explanation for these inconsistent results is the compensatory activation of other proteases (Newby, 2005).

Several mechanisms have been postulated to explain the regulation of VSMC proliferation by MMPs. MMPs could promote permissive interactions between VSMC and components of the ECM. Integrin-mediated pathways may be essential for stimulation of VSMC proliferation (Morla and Mogford, 2000; Walker et al., 2003). MMPs may free growth factors from attachment to ECM components or cell surface so that they can act on their receptors. Heparin-binding growth factors, in particular FGF-1 and FGF-2, are potent mitogens for VSMCs and are released by the action of MMPs on proteoglycan core proteins (Visse and Nagase, 2003). Although ADAMs are often implicated, MMPs could also be responsible for releasing cell surface heparin-bound epidermal growth factor (HB-EGF), which stimulates VSMC proliferation (Hollenbeck et al., 2004; Lucchesi et al., 2004). MMPs also activate TGF-h by cleaving off the latency-associated peptide (Annes et al., 2003). MMPs can also liberate active insulin like growth factor 1 (IGF-1) by degrading its binding proteins. Together with signals from FAK, these processes upregulate and/or stabilize key regulators of the cell cycle. Also, MMP-induced cadherin shedding promotes dissolution of adherens junctions and translocation of h-catenin to the nucleus where it acts as a transcription factor to further promote cell proliferation (Uglow et al., 2003; Nelson and Nusse, 2004).

MMPIs have been used to study the role of MMPs in VSMC proliferation. Earlier studies have shown excess neointima proliferation in rat carotid arteries subjected to balloon injury after treatment with the MMPI GM-6001 (Bendeck et al., 1996; Zempo et al., 1996). However, recent studies demonstrated that synthetic MMPIs inhibit VSMC proliferation *in vitro* (Lovdahl et al., 2000; Uglow et al., 2003). Also, inhibition of MMPs is associated with decreased N-cadherin shedding, increased cell membrane N-cadherin levels, decreased h-catenin nuclear translocation and eventually decreased proliferation of cultured human VSMCs. Dismantling of cadherin:catenin complex also occurs in balloon-injured rat carotid arteries *in vivo* leading to increased expression of the cell cycle gene cyclin D1 which stimulates VSMC proliferation (Slater et al., 2004). Tetracycline-based MMPIs also reduce VSMC migration and neointima formation after balloon injury of rat carotid artery (Bendeck et al., 2002; Islam et al., 2003). Collectively, most of the experimental evidence points to a stimulatory effect of MMPs on VSMC proliferation, and inhibition of this effect by MMPIs.

6.7. MMPs and VSMC Apoptosis

Apoptosis is a form of cell death that involves activation of the intracellular cysteine proteases, caspases. Apoptosis of VSMCs plays a role in attenuating intimal thickening and destabilizing atherosclerotic plaques (Geng and Libby, 2002; Stoneman and Bennett, 2004). Several factors promote apoptosis including death signals originating from outside the cell and processes within the cell such as DNA damage, cell cycle status and levels of the tumor suppressor p53 (Stoneman and Bennett, 2004). MMP-7 is involved in the cleavage of N-cadherin and thus modulates VSMC apoptosis. In contrast, survival signals maintain VSMC viability even in the face of a pro-apoptotic environment. Survival pathways are closely linked to those triggering proliferation and therefore could be influenced by MMPs. Survival factors such as PDGF, HB-EGF and IGF-1 act via tyrosine kinase receptors to stimulate the PI_3-K/Akt pathway. MMP-2, -7 and -9 cleave cell surface pro-HB-EGF and liberate the soluble active growth factor which binds to EGFR and promotes growth (Hao et al., 2004; Lucchesi et al., 2004). Activation of PDGFR-β and ERK1/2 is involved in the production of MMP-1 in oxLDL-and 4-hydroxynonenal (4-HNE)-stimulated human coronary VSMCs (Akiba, Kumazawa, 2006). MMP-1, -2, -8 and -9 degrade members of the IGF binding protein family and thereby increase the bioavailability of IGF-1 and its anti-apoptotic effects (Visse and Nagase, 2003).

Cell–matrix contacts promote VSMC survival, and their disruption leads to apoptosis in a process originally termed anoikis (Frisch and Screaton, 2001). FAK activation triggered by

ECM–integrin interactions induces p53, a survival signaling pathway (Ilic et al., 1998; Almeida et al., 2000). Regulated MMP production appears to favor FAK activation and hence survival signaling. Conversely, excessive production of MMPs could degrade ECM proteins or integrins and promote anoikis (Levkau et al., 2002). MMPs may also modulate apoptosis by cleaving death ligands such as TNF-α and Fas ligand and their receptors. MMP-1, -2, - 9, -8 and -13 and the MT-MMPs MMPs 14–17 can cleave pro-TNF-α (Somerville et al., 2003; Visse and Nagase, 2003). Similarly, MMP-7 sheds Fas-L from the surface of several cell types (Bond et al., 2000; Mannello et al., 2005). Caspase-mediated cleavage of the DNA repair enzyme poly-ADP ribosepolymerase is an important step in apoptosis, and in isolated cardiac myocytes, nuclear-localized MMP-2 can carry out this cleavage (Kwan et al., 2004).

TIMP-3, but not TIMP-1 and -2, is an effective stimulator of apoptosis in many cells including VSMCs (Baker et al., 1998; Bond et al., 2000), suggesting that an ADAM rather than an MMP is the target. TIMP-4 also stimulates VSMC apoptosis (Guo et al., 2004). Thus, MMPs appear to regulate VSMC apoptosis via several pathways, and MMPIs could oppose the effects of MMPs on apoptosis.

7. MMPs and Angiogenesis

Angiogenesis is the process of forming new blood vessels and requires degradation of the vascular basement membrane and ECM remodeling in order to allow ECs to migrate into the surrounding tissue. Angiogenesis plays a role in several physiological and pathological processes including the progression of atherosclerotic plaques and cancer growth (Khatri et al., 2004; Folkman, 2006). MMPs mediate the effects of several pro- and anti-angiogenic substances by virtue of their proteolytic activity. Angiogenic growth factors such as FGF, TGF-α, TGF-β, TNF-α, VEGF and angiogenin are secreted by ECs and other cells, and act in an autocrine or paracrine fashion to accelerate angiogenesis. MMPs mediate the effects of these angiogenic substances. MMP-1, -3, -7, -8, -9, -10, -13, and -19 expression is up-regulated more than 1.5-fold in HUVECs treated with VEGF. VEGF also induces MMP-10 expression possibly via PI_3K and MAPK pathways (Heo et al.), 2010). MMPs take part in remodeling of the basement membrane and degradation of components of ECM necessary for angiogenesis. MMPs also enhance angiogenesis by detaching pericytes from the vessels, releasing ECM-bound angiogenic factors, exposing cryptic pro-angiogenic integrin binding sites in ECM, generating promigratory ECM component fragments, and cleaving EC-cell adhesions.

MT1-MMP plays a specific role in angiogenesis (Pepper, 2001; Mimura et al., 2009). Semaphorin 4D is overexpressed in cancers and promotes neovascularization upon stimulation of its receptor Plexin-B1 on ECs. MT1-MMP targets semaphorin 4D and releases it from its inactive membrane bound form to act in a paracrine manner on ECs (Basile et al., 2007). Also, MT1-MMP-dependent TGF-β signaling is required for PGE_2-induced endothelial cord formation in cultured HUVECs (Alfranca et al., 2008).

Upregulation of MMPs is positively linked to tumor size and the increased angiogenic and metastatic potential of tumors. Expression of MMP-2, -9 and VEGF is positively correlated to tumour size, depth of invasion, lymphatic and venous invasion, lymph node metastasis, and microvessel density of gastric carcinomas (Zheng et al., 2006). MMP-2 mediates the angiogenic effect of pituitary tumor transforming gene expression in HEK293 cells (Malik and Kakar, 2006). Downregulation of MMP-2 decreases tumor-induced angiogenesis in cultured human microvascular ECs (HMVECs). MMP-2 inhibition causes apoptotic cell death *in vitro*, and suppresses tumor growth of preestablished U-251 intracranial xenografts in nude mice (Kargiotis et al., 2008). Overexpression of MMP-9 in human breast cancer

MCF-7 cells results in increased tumor angiogenesis, tumor growth, and VEGF/VEGFR-2 complex formation (Rundhaug, 2005). MMP-9 may also be involved in FGF-2/FGFR-2 pathway in the mouse angiogenesis model (Ardi et al., 2009), and attenuation of MMP-9 expression inhibits tumor growth in nude mice (Ezhilarasan et al., 2009). MMP-3 may also play a role in the regulation of angiogenesis. MMP-3 mediates matriptase/MT-SP1-induced tumor growth and angiogenesis by enhancing ECM degradation in tumor cell microenvironments (Jin et al., 2006b).

While angiogenic factors can induce MMP expression in endothelial and stromal cells, MMPs can in turn enhance the availability/bioactivity of angiogenic factors. Degradation of ECM releases ECM/basement membrane-sequestered angiogenic factors such as VEGF, bFGF and TGF-β. MMP-1 and MMP-3 degrade perlecan in EC basement membranes to release bFGF. Connective tissue growth factor (CTGF) forms an inactive complex with VEGF165, and cleavage of CTGF by MMP-1, -3, -7, or -13 releases active VEGF165. MMP-2, -3, and -7 degrade the ECM proteoglycan decorin and release latent TGF-1, while MMP-2 and -9 cleave the latency-associated peptide to activate TGF-β1 (Chung and Kao, 2009).

In support of a role of MMPs in angiogenesis, dormant tumors may secrete TIMPs to prevent the tumor from switching to the angiogenic phenotype and thereby arrest the growth of tumors (Moller et al.; Handsley and Edwards, 2005). However, MMPs may exert anti-angiogenesic effects through the generation of endogenous angiogenesis inhibitors by proteolytic cleavage of certain collagen chains and plasminogen. MMP-9 mediates tamoxifen-induced increase in endostatin generation and thus decreases angiogenesis in hormone dependent ovarian cancer (Bendrik et al.)2010). MMP-7, -9 and -12 may block angiogenesis by converting plasminogen to angiostatin, a potent angiogenesis antagonist. MMP-14 cleaves endoglin, a TGF-β co-receptor, and thus inhibits its angiogenic effect (Hawinkels et al.) 2010). Thus MMPs are important regulators of angiogenesis with an overall tendency towards stimulation, and MMPIs reverse these angiogenic effects.

8. MMPs and Atherosclerosis

Atherosclerosis is a multifactorial vascular disease. Dysfunctional endothelium recruits different inflammatory pathways leading to intimal differentiation, VSMC proliferation, ox-LDL deposition, platelet activation and aggregation, and resulting in formation of an atheroma of fat, collagen and elastin with a thin fibrous cap. Dysregulated ECM metabolism may contribute to vascular remodeling during the development and complications of atherosclerotic lesions. Enhanced MMP expression has been detected in the atherosclerotic plaque, and activation of MMPs appears to facilitate atherogenesis, platelet aggregation and plaque destabilization (Beaudeux et al., 2004; Kadoglou et al., 2005). MMP-1, -2, -3, -7, -9 and -12 are produced by SMC and macrophages in the arterial wall, and have their highest expression in atherosclerotic lesions (Uzui et al., 2002; Johnson, 2007). Also, the plaques' shoulders and regions of foam cell accumulation display increased expression of MMP-1, -9 and stromelysin. Plaque extracts contain activated forms of gelatinases, and gelatinolytic and caseinolytic activities are detected in atherosclerotic areas, but not in uninvolved arterial tissues (Galis et al., 1994). Importantly, low-fat diet is associated with reduced plaque proteolysis and decline in MMP-1 levels and macrophage content (Aikawa et al., 1998). Patients on haemodialysis treatment develop atherosclerosis rapidly and show evidence of disordered fibrinolysis/proteolysis balance in their plasma, and MMP-2 may play a role in the development of atherosclerosis in these patients (Pawlak et al., 2008). Also, urine MMP-9 and TIMP-1 levels are elevated in patients with CAD and acute coronary syndrome (ACS) compared with healthy volunteers (Fitzsimmons et al., 2007). Plasma levels of MMP-1, -3, and -7 are higher among patients with high intima-media thickness compared

with those with low intima-media thickness. MMP-7 is positively associated with carotid calcification (Gaubatz et al.)2010), and an association between plasma levels of MMP-8 with occurrence of carotid plaques has been reported (Djuric et al.)2010). MMP-10 is induced by C-reactive protein in ECs, and is overexpressed in atherosclerotic lesions. Also, higher MMP-10 serum levels are associated with inflammatory markers, increased carotid intima-media thickness and atherosclerotic plaques (Rodriguez et al., 2008).

Certain genetic variants of MMPs have shown association with the progression and complications of atherosclerosis. In a 3-year atherosclerosis regression study, the 6A active variant of the MMP-3 promoter was found to correlate with progression of luminal narrowing (Ye et al., 1995) and acute MI (Terashima et al., 1999). In a study on 139 CAD patients and 119 healthy subjects, MMP-3 5A/6A genetic variant was associated with CAD, and the PON1 variant was associated with the number of diseased coronary vessels (Ozkok et al., 2008). In a subgroup of the Etude Cas-Temoin de l'Infarctus du Myocarde (ECTIM) study of acute MI, the more active T allele of an MMP-9 functional promoter polymorphism (C1562T) was more common in patients with 3-coronary vessel disease, but did not predict MI (Du et al., 1999). In a study of 1127 patients, higher MMP-9 serum levels were associated with the T allele, but did not predict cardiovascular death (Blankenberg et al., 2003). Another study showed associations of MMP-9 genotypes with different stages of carotid atherosclerosis (Rauch et al., 2008). Animal studies also showed an association between MMP levels and atherosclerosis. MMP-9 deficiency reduced atherosclerotic lesion size in ApoE$^{-/-}$ mice (Luttun et al., 2004), and in the carotid ligation mpdel, hypercholesterolaemic MMP-9$^{-/-}$ mice showed a reduced plaque burden as compared to wild-type mice (Choi et al., 2005).

MMPs contribute to the pathophysiology of atherosclerosis by interacting with several pathways that regulate the process. Vascular inflammation, an important factor in the atherogenic process, promotes the production of MMPs. In a study enrolling 18 patients with stable angina, 14 patients with unstable angina and non-ST-segment elevation MI, 14 patients with ST-elevation MI, and 16 healthy controls, the progression of CAD was mirrored by increased MMP-9/TIMP-1 ratio in circulating CD14+ monocytes and in serum. Circulating monocytes displayed similar imbalance in the expression of MMP-9 and TIMP-1 in monocyte-derived macrophages within atherosclerotic plaques (Brunner et al.)2010). Cholesterol lowering 3-HMGcoA reductase inhibitors decrease the tissue expression of various MMPs in atheromatous plaques by attenuating vascular inflammation (Cevik et al., 2008). For example, rosuvastatin inhibits the expression of MMP-2 and -9 (Guo et al.)2010).

VSMC migration and proliferation is essential for formation of atheromas. MMPs enhance VSMC migration to areas of atherogenesis where they proliferate and enlarge the size of the lesion. Downregulation of both MMP-9 and TNF-α mediate the inhibitory effect of the herb salvia miltorrhia extracts on VSMC migration in RASMCs (Jin et al., 2006a). An elegant study used mice with genetically modified collagen that resists digestion by MMP collagenases. In an atherogenic background, the lesion size of collagenase-resistant mice was similar in size to controls, but SMC number in the intimal lesions decreased and collagen was more abundant. These findings suggest a role for MMP-mediated collagenolysis in regulating collagen turnover and SMC accumulation in the atheromatous plaque (Fukumoto et al., 2004).

MMP-1 mediates the activation of the PDGFR-β and ERK1/2 atherogenic pathways by ox-LDL (Akiba et al., 2006). Ox-LDL also activates MMP-2 through upregulation of MT1-MMP and also through oxidative radicals generated by the xanthine/xanthine oxidase complex (Valentin et al., 2005). AngII plays a role in the pathogenesis of atherosclerosis.

AngII increases the expression of MMP-9 in VSMCs via AT1 receptor and NF-κB pathways (Guo et al., 2008). Thus studies have shown a clear association between MMPs levels, genetic variants of certain MMPs and the atherosclerotic process.

On the basis of the collective ability of MMPs to degrade ECM proteins and the detection of increased MMP protein and activity in vulnerable atherosclerotic plaques, it has been proposed that MMPs reduce the strength of the fibrous cap and contribute to plaque rupture. High-mobility group box 1 is an intracellular gene regulator protein produced by activated VSMCs and causes the progression and vulnerability of atherosclerotic lesions to rupture by stimulating the production of MMP-2, -3 and -9 (Inoue et al., 2007). Areas of atherosclerotic plaque rupture exhibit a paucity of VSMCs and increased macrophage-derived foam cells. One study compared brachiocephalic artery plaque instability in apoE/MMP-3, apoE/MMP-7, apoE/MMP-9, and apoE/MMP-12 double knockout mice with their age-, strain-, and sex-matched apoE knockout controls. The study concluded that MMP-12 supports lesion expansion and destabilization. MMP-7 had no effect on plaque growth or stability, although it is associated with reduced VSM content in plaques. On the other hand, MMP-3 and -9 appeared to play protective roles, limiting plaque growth and promoting a stable plaque phenotype (Johnson et al., 2005). MMP-1, -12 and -13 derived from intimal macrophages have been proposed to play a pivotal role in both plaque initiation and progression (Koike et al., 2008). However, mice with MMP-1-producing macrophages show smaller plaques than control mice and no evidence of plaque rupture (Lemaitre et al., 2001). These mice have altered MMP-1 from birth, which could reduce collagen accumulation, thus MMPs may be more critical in destabilization of established plaques than in atherogenesis (Newby, 2005). MMP-3 also appears to have a dual role. While mice lacking both MMP-3 and ApoE show reduced aneurysm formation, they have more extensive atheroma (Silence et al., 2001). Absence of MMP-3 causes increased collagen and fewer plaque macrophages, a characteristic associated with greater stability in human plaques. Adenoviral gene transfer of TIMP-1 into $ApoE^{-/-}$ mice 6 weeks after commencing a high-fat diet reduced both lesion size and macrophage content, supporting the prevailing concept that MMPs adversely influence established plaques (Rouis et al., 1999). Estrogen supplementation especially late after menopause may destabilize established plaques, and this could be explained at least in part by estrogen's ability to upregulate MT1-MMP without a corresponding increase in TIMP-2, thus activating MMP-2. Estrogen also up-regulates MMP-3 in the presence of IL1-β (Grandas et al., 2009). On the other hand, the ability of MMPs to promote migration and proliferation of VSMCs suggests that MMPs may promote atherosclerotic plaque cap growth and stability. MMPs such as MMP-2, -9, -13 and -14 MMPs release growth factors that are stored in ECM such as TGFh and VEGF. (Mott and Werb, 2004). MMP-9 releases VEGF bound to proteoglycans in ECM, enhancing its bioavailablity and thereby influencing plaque neovascularization. Collectively, evidence suggests a role for MMPs in regulating plaque stability although the specific roles of individual MMPs are not well established. Further investigation may allow targeting of individual MMPs with specific MMPIs to limit the growth of the atherosclerotic lesions yet promote their stability.

Atherosclerosis in the coronary arteries could lead to acute coronary syndromes (ACS) including unstable anginas and MI. Studies have shown an association between MMPs and the development of ACS (Jones et al., 2003a). Circulating MMP levels are elevated in patients with ACS. A case-control study on 261 patients who had suffered an MI and 194 healthy controls, all Spanish male smokers, showed that MMP-1 promoter polymorphisms are associated with the risk of early MI (Roman-Garcia et al., 2009). MMP-2 and -9 were elevated following acute MI in 91 patients compared to 172 control subjects with stable CAD. Higher early levels of MMP-9 were also associated with the extent of left ventricular remodeling and circulating white blood cell levels (Kelly et al., 2007). Increased MMP

expression is also observed after coronary angioplasty, suggesting that MMP expression may be involved in the formation of restenotic lesions (Ikeda and Shimada, 2003). Whether higher MMP levels induce ACSs or are merely an association is not yet established.

TIMPs also seem to have an association with atherosclerosis. TIMP4 is visible in cardiovascular tissue areas populated by inflammatory cells, mainly macrophages and CD3+ T cells. Human lymphocytes, monocytes, macrophages and mast cells produce TIMP-4. In advanced atherosclerotic lesions, TIMP-4 is detected around necrotic lipid cores, whereas TIMP-3 is detected within and around the core regions indicating different roles in inflammation-induced apoptosis and ECM turnover (Koskivirta et al., 2006). In a study on 238 men, TIMP-1 was positively associated with carotid intima-media thickness and carotid-femoral pulse-wave velocity using univariate analysis (Zureik et al., 2005). The mean fibrous cap thickness is greater in individuals with elevated TIMP-1 levels. Also, TIMP-1 is positively associated with measures of lipid core (Gaubatz et al.)2010). Experimental studies have shown that TIMP-1 deficiency produces macrophage-rich lesions with active proteinases and medial destruction in $ApoE^{-/-}$ mice (Lemaitre et al., 2003). In TIMP-1-deficient mice atherosclerotic lesions are 30% smaller than in control, but there is an enhanced aneurysm formation (Silence et al., 2002). However, studies using pharmacological MMPIs did not show any effect on lesion size in atheroma-prone mice (Prescott et al., 1999; Manning et al., 2003).

MMPs and TIMPs levels in early post-MI period may serve as estimates of post-MI cardiac damage and remodeling. MMP-9 and TIMP-1 correlate with echocardiographic parameters of left ventricular (LV) dysfunction after acute MI and may identify patients at risk of subsequent LV remodeling and adverse prognosis (Kelly et al., 2008). MMPIs have not been used extensively in cardiovascular clinical trials partly because cancer trials showed side effects such as tendonitis (possibly due to inhibition of ADAMs), lack of efficacy, and possible harmful effects (Coussens et al., 2002). In one clinical trial, 100 patients requiring carotid endarterectomy were randomized to receive 200 mg/d doxycycline or placebo for 2 to 8 weeks before surgery. Carotid plaques were retrieved by endarterectomy and showed that doxycycline penetrated atherosclerotic plaques with acceptable tissue levels resulting in reduction in MMP-1, but had no effect on atheroma progression (Axisa et al., 2002). However, most animal studies of post-angioplasty or in-stent stenosis have shown no effect of MMPIs or a catch-up phenomenon after short-term promise.

9. MMPs and Arterial Aneurysm

MMPs may play a role in the pathophysiology of thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA). Perhaps the most clinically-relevant association of MMPs has been with aneurysm growth and rupture. Also, there is an association between certain haplotypes of MMP-1, -3, -7, -12 and -13 and the risk of coronary artery aneurysms in patients with Kawazaki disease (Shimizu et al.)2010).

An imbalance between MMPs and TIMPs may represent a major mechanism of TAA formation (Barbour et al., 2007). High levels of MMP-2 and -9 have been demonstrated in patients with TAA, with MMP-9 predominantly expressed in the faster-growing anterior wall of the aneurysm while MMP-2 is higher in the slower-growing posterior wall (Sinha et al., 2006). Also, a study of 28 patients with degenerative TAA, 60 patients with thoracic aortic dissection, and 111 control subjects showed an association between a genetic variant of MMP-9 (8202A/G), TAA and dissection (Chen et al., 2006). Interestingly, different sets of MMPs/TIMPs imbalances were detected in bicuspid and triscuspid aorta patients with TAA (Ikonomidis et al., 2007). Experimental studies also suggested a role for MMPs in the pathophysiology of TAA. The expression of MT1-MMP, which is important for

macrophage-mediated elastolysis, increases progressively after induction of TAA in mice (Jones et al.; Xiong et al., 2008). Elevated levels of MMP-2, -8, -9 and -12 are detected at various stages of TAA development in mice (Barbour et al., 2006). Also, induction of TAA formation in rats is associated with increased levels of MMP-2 and -9, and ADAM-10 and -17 (Geng et al.). In the mouse model of Marfan syndrome, TAA was prevented in mice treated with the MMPI doxycycline, while mild aneurysm was evident in mice treated with the β-blocker atenolol. Doxycycline improved elastic fiber integrity, normalized aortic stiffness, and prevented vessel weakening. Also, the impaired vascular contraction and endothelium-dependent relaxation observed in the nontreated and atenolol mice was improved with doxycycline (Chung et al., 2008).

MMPs could also play a role in the pathophysiology of AAA. The histopathological changes of aneurysmatic aorta are mostly seen in tunica media and intima and include accumulation of lipids in foam cells, extracellular free cholesterol crystals, calcifications, thrombosis, ulcerations and rupture of the vascular layers. There is also an adventitial inflammatory infiltrate. Degradation of tunica media is a major pathophysiologic mechanism in AAA. Loss of elastin could be an initiating event in AAA formation, while loss of collagen is required for continued expansion. Medial neovascularization is characteristic of established AAA and involves proteolytic degradation of ECM by MMPs to facilitate EC proliferation and migration. Studies demonstrated upregulation of pro-angiogenic cytokines and increased medial neovascularization at the aneurysm rupture edge. Growth and rupture of AAA result from increased collagen turnover (Choke et al., 2006).

MMP-2 and -9 appear to play a role in AAA formation (Petersen et al., 2000; Goodall et al., 2001). In patients with AAA, plasma levels of MMP-2 and -9 are elevated in the range of 0.06–0.6 μg/ml (Hovsepian et al., 2000; Goodall et al., 2001; Nagashima et al., 2002). MMP-9 is the most abundantly expressed MMP in AAA and is produced mainly by the aneurysm-infiltrating macrophages (Sakalihasan et al., 1996). The plasma level and aortic wall expression of MMPs are especially elevated in patients with imminent aneurysm rupture. MMP-1 and -9 levels are elevated in the plasma of patients with ruptured AAA versus non-ruptured AAA. A 4-fold elevation in preoperative plasma MMP-9 were associated with non-survival at 30 days from rupture surgery compared with surviving patients for greater than 30 days (Wilson et al., 2008a). Elevation of MMP-9 was also associated with ruptured aneurysm related 30-day mortality. Secretion of MMP-2 and -9 by HASMC is enhanced in tissues of AAA in response to hypoxia (Erdozain et al.)2010). Also, MMP-2 and -9 are necessary to induce experimental AAA formation in mice (Longo et al., 2002), and targeted gene disruption of MMP-9 in mice suppresses the development of AAA (Pyo et al., 2000). MMP-8 may also have a role in AAA formation. High levels of MMP-8 were found in infrarenal aortic biopsies taken from AAA. Immunohistochemistry studies localized MMP-8 to mesenchymal cells within the adventitia of the aortic wall (Wilson et al., 2005). A localized increase in MMP-8 and -9, mediated by native mesenchymal cells, was shown in biopsies from aneurysm rupture sites compared with their paired anterior wall biopsies.

The identification of the potential role of MMPs in the pathogenesis of AAA has prompted the measurement of MMPs for estimation of aneurysmal area and matrilytic activity (Razavian et al.)2010). Plasma MMP-9 levels are associated with aneurysmal size and expansion (Hackmann et al., 2008). In another study, MMP-9 plasma levels were determined in peripheral venous blood from 25 patients with AAA, 15 patients with atherosclerotic occlusive disease, and 5 control subjects. MMP-9 levels were directly compared with the amount of MMP-9 produced in aortic tissue. Elevated MMP-9 levels were observed in one half of patients with AAA and less than 10% of those with atherosclerotic occlusive disease (positive predictive value, 92.3%). Plasma MMP-9 levels

in AAA patients appear to directly reflect the amount of MMP-9 produced within aneurysm tissue, and MMP-9 levels decrease substantially after aneurysm repair (Hovsepian et al., 2000). A meta-analysis of data on 580 AAA cases and 258 controls concluded that an elevated MMP-9 has 48% sensitivity and 95% specificity as a diagnostic screening test for the presence of AAA (Sangiorgi et al., 2001). However, normal MMP-9 levels may not exclude the presence of AAA (negative predictive value, 52%). Also, some studies demonstrated no significant correlation between MMP-9 serum levels and AAA diameter (Eugster et al., 2005; van Laake et al., 2005; Cui et al., 2006; Wilson et al., 2006) or between the plasma and aneurysm wall concentrations of any MMP or TIMP and AAA diameter (Wilson et al., 2008b). Further investigation is necessary to explore the validity and accuracy of MMP-9 and other MMPs as investigative tools of AAA.

Studies have investigated whether genetic variants of MMPs are associated with AAA risk. A study in 51 patients with AAA and 48 controls showed that variations in MMP-2 gene do not contribute to the development of AAA (Hinterseher et al., 2006). In contrast, a study enrolling 414 AAA patients and 203 control subjects showed an association between the T allele of the C-1562T functional promoter polymorphism of the MMP-9 gene and AAA formation (Jones et al., 2003b). Another study enrolling 146 AAA patients and 156 healthy individuals showed no association between MMP-9 and AAA (Armani et al., 2007). A meta-analysis of 6 gene polymorphisms (ACE I/D, MTHFR+677C>T, MMP9-1562C>T, IL-1β/3953C>T, eNOS 4a/4b and TIMP-1/+434C>T) reported in multiple case control studies, showed that 3 of these polymorphisms, ACE RR 1.33 [95% CI 1.20–1.48], MTHFR RR 1.14 [1.08–1.21] and MMP-9 RR 1.09 [1.01–1.18], were associated with a significant risk of AAA (Thompson et al., 2008). Further investigation of the MMP polymorphisms may offer prophylactic measures to individuals genetically prone to the development of AAA.

The mechanism of action of MMPs in aneurysm formation has largely been attributed to their proteolytic effects on ECM proteins and subsequent weakening of the aortic wall. MMP-2 has the greatest elastolytic activity and is produced mainly by VSMCs and fibroblasts (Wall et al., 2003). Additional inhibitory effects of MMP-2 and -9 on Ca^{2+}-dependent mechanism of aortic VSM contraction may play a role in the early development of aneurysm (Chew et al., 2004). MMP-9 is a more potent inhibitor of aortic contraction than MMP-2, consistent with the dominant MMP-9 expression in AAA wall (Sakalihasan et al., 1996). Aortic VSM contractile function may contribute to the structural integrity of the aortic wall and limit its tendency to dilate in response to pulsatile forces generated with each cardiac cycle. Atrophy of the tunica media and depletion of VSMCs are consistent histological findings in AAA (Lopez-Candales et al., 1997). Also, disruption of structural integrity of the tunica media e.g. in chronic aortic dissection, often leads to late aneurysm formation. MMP-induced inhibition of VSM contraction may function synergistically with their degradation of ECM, causing further weakening of the aortic wall and aneurysm formation.

Studies have investigated the effect of MMPIs on AAA growth and rupture. Small RCTs suggested favorable effects of doxycycline on retarding AAA expansion (Mosorin et al., 2001). One study demonstrated that two weeks doxycycline treatment in patients with advanced AAA resulted in selective reduction of aortic wall neutrophil and cytotoxic T-cell content, and suppression of inflammatory markers including cytokines IL-6 and IL-8 and transcription factors AP-1, C/EBP and STAT3 (Lindeman et al., 2009). In another study, patients undergoing endovascular AAA repair were randomized to doxycycline or placebo for 6 months following the procedure. Plasma MMP-9 decreased below baseline in doxycycline treated patients while there was a nonsignificant increase in the placebo group. In patients with endoleaks at 6 months, plasma MMP-9 increased in 83% of the placebo

group, but in only 14% of doxycycline-treated group. Among endoleak-free patients with AneuRx or Excluder endografts, doxycycline caused greater decreases in maximum aortic diameter and the aortic neck dilatation than placebo (Hackmann et al., 2008). The use of MMPIs as therapeutic tools in AAA is perhaps the most promising clinical application of MMPIs in vascular medicine.

10. MMPs and Varicose Veins

Varicose veins (VV) are a common venous disorder of the lower extremity that affects 25% of the adult population. Risk factors for VV include aging, female gender, pregnancy, obesity, and family history; however, the molecular mechanisms involved are not fully defined. Collagen and elastin are important for the integrity of the venous wall. Decreased elastin content has been implicated in the pathogenesis of VV (Venturi et al., 1996). In contrast, studies suggest increased (Gandhi et al., 1993), decreased (Haviarova et al., 1999), or unchanged (Kockx et al., 1998) collagen content in VV wall. The net collagen content represents a balance between its biosynthesis and its degradation by specific MMPs.

Several studies suggest increased MMPs in lower extremity venous blood of VV patients. The plasma and venous tissue levels of MMP-1, -2, -3, -9 and -13 are elevated in VV (Gillespie et al., 2002; Woodside et al., 2003; Kowalewski et al., 2004). A study in 8 patients with VV and 8 control subjects showed an increase in the elastic network, accumulation of collagen type I, fibrillin-1 and laminin, and overproduction of MMP-1, -2 and -3 in the veins and skin of patients with VV (Sansilvestri-Morel et al., 2007). Another study demonstrated that transcriptional MMP-1 or -13 mRNA was not different in VV vs. control veins or in proximal vs. distal varicose segments; however, protein expression of MMP-1 was elevated in VV compared with controls, and MMP-1 and -13 protein expressions were increased in proximal vs. distal varicose segments, suggesting that posttranscriptional modification of MMPs may explain the variation in their location in VV (Gillespie et al., 2002). Immunohistochemical studies in VV have demonstrated an increase in the distribution of MMP-1 in the intima, media and adventitia of the vein wall, while in normal veins MMP-1 is localized in the endothelium and adventitia. MMP-9 was found throughout the venous wall in both normal and VV, with VV expressing increased levels in the SMC layer. Interestingly, TIMPs were not present in any of the veins examined (Woodside et al., 2003). Other studies have shown MMP-9 immunostaining in SMC of VV, but not in control veins (Kosugi et al., 2003).

However, increased levels of MMPs in VV do not imply causation, and MMP expression/activity may even decrease in VV. In one study comparing segments from the sapheno-femoral junction in patients with VV and control sapheno-femoral vein specimens from patients undergoing bypass surgery, most MMPs were located in the adventitia, and MMP activity was not different in VV compared with control. Also, in a study on 7 VV patients, the MMP-2 content was decreased while TIMP-1 was increased (Parra et al., 1998). In another study, the TIMP-1/MMP-2 ratio was 3-fold greater in VV than normal veins, suggesting proteolytic inhibition and ECM accumulation in VV (Badier-Commander et al., 2000). A recent study showed greater expression of TIMP-2 and connective tissue accumulation in tunica media of VV compared with arm and neck veins of control subjects. TIMP-2 and -3 expression was greater in hypertrophic than atrophic segments, and in the thicker proximal VV segments compared to distal segments (Aravind et al.)2010).

The role of MMPs in VV has largely been attributed to their proteolytic effects on ECM, degradation of the valve leaflets and weakening of vein wall structure (Herouy et al., 1999; Pascarella et al., 2005). The localization of MMPs in the VV wall adventitia and fibroblasts is consistent with a role in ECM degradation (Woodside et al., 2003). In a study

investigating the effects of postural changes in patients with VV on the expression of MMPs, blood samples from the brachial vein and lower extremity VV were collected simultaneously from erect patients following 30 min of stasis. An increase in pro-MMP-9 was observed in VV compared to arm veins. Also, the proteolytic activity was associated with increased levels of endothelial ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), angiotensin converting enzyme and L-selectins, suggesting that EC and neutrophil activation and enzymatic granule release in VV occurs during periods of stasis (Jacob et al., 2002). MMP-2 also causes relaxation of Phe induced contraction in rat inferior vena cava via a mechanism involving hyperpolarization and activation of large conductance Ca^{2+} dependent K^+ channels (Raffetto et al., 2007). Excessive MMP-2 induced venous relaxation could lead to progressive wall dilatation and superimposed valve dysfunction, leading to VV formation (Raffetto and Khalil, 2008).

One of the complications of VV is thrombophlebitis characterized by endothelial, vein wall and valve inflammation, and leukocytes infiltration leading to disruption of vein function and venous thrombosis (Takase et al., 2000; Sayer and Smith, 2004; Bergan et al., 2006). Thrombophlebitic VV have an elevated content of MMPs in the vein wall, and increased activity of MMP-1, -2 and -9 (Kowalewski et al., 2004). Venous ulcer is another complication of VV. Lipodermatosclerotic skin, a precursor to venous ulcer, is characterized by excessive MMP activity and ECM turnover. Dermal biopsies from lipodermatosclerotic skin demonstrated increased mRNA and protein expression of MMP-1 and -2 and TIMP-1, and increased activity of MMP-2 as compared to healthy skin. MMP-1 and -2 were predominantly localized in the basal and suprabasal layers of the epidermis, perivascular region and reticular dermis, and reduced expression of TIMP-2 was observed in the basement membrane of the diseased skin (Herouy et al., 1998). In chronic venous ulcer wound fluid (VUWF), collagenase activity is elevated 116-fold over control acute wound fluid, while in healing venous ulcer collagenase activity is decreased. VUWF also causes inhibition of fibroblasts proliferation (Mendez et al., 1999; Raffetto et al., 2001). Chronic VUWF contains up to 10-fold higher levels and activity of MMP-2 and -9 as compared with acute wound fluid, suggesting elevated ECM turnover. The sources of high protease and collagenase activity are most probably fibroblasts, mononuclear cells, keratinocytes, and ECs (Weckroth et al., 1996). Fibroblasts in the ulcer bed demonstrate abundant amount of MMP-13. Also, MMP-1 is found in the migrating keratinocytes of the wound (Vaalamo et al., 1997). MMP-2, MT1-MMP, MT2-MMP, and EMMPRIN (MMP activator) are elevated in venous ulcer compared to control dermis (Norgauer et al., 2002). VUWF of healing ulcers have elevated levels of PDGF and TIMP-2 and low levels of MMP-2 as compared with non-healing ulcer, supporting that elevated proteinase activity favors a non-healing environment (Mwaura et al., 2006). The effects of MMPs in wound ulcer may also be related to their ability to affect angiogenesis and the microvasculature. In cultured ECs model of angiogenesis and tubule formation, the addition of inhibitor of MMP-2 and -9 to VUWF increases angiogenesis (Ulrich et al., 2005), suggesting that MMPs in VUWF may have anti-angiogenic effects that disrupt the microcirculation in the perivascular regions and thereby inhibit wound healing. MMP production in lipodermatosclerotic tissue and venous ulcers may involve MAPK which regulates MMP expression and proteolytic activity in dermal fibroblasts (Seah et al., 2005; Raffetto et al., 2006). Also, elevated iron deposits in the lower limb may cause activation of MMPs and ROS and lead to impaired ulcer healing (Zamboni et al., 2005). Whether MMPIs can minimize VV complications needs further investigation.

11. MMPs and Hypertension

Hypertension (HTN) is a multifactorial disorder involving alterations in renal, neuronal and vascular control mechanisms of blood pressure. HTN is often associated with vascular remodeling and rearrangement of various components of the vascular wall including ECM

proteins. The elevated plasma levels of some MMPs in HTN have suggested that the underlying pathophysiology may involve excessive elastolysis or accumulation of collagen degradation products in the vascular wall (Onal et al., 2009). Several MMPs and TIMPs may be involved in the vascular remodeling associated with HTN. Increased MMP activity could result in increased degradation of elastin relative to collagen leading to decreased elasticity, while decreased TIMP-1 activity could lead to accumulation of poorly cross-linked immature and unstable fibrin degradation products, which result in misdirected deposition of collagen (Onal et al., 2009). Some clinical studies have shown a correlation between MMP levels and HTN (Table 5). Other studies demonstrated lower MMPs and higher TIMP levels in HTN and suggested that decreased extracellular degradation of collagen type I could play a role in the development of HTN (Table 5). The effects of early and late chronic HTN on ECM remodeling were compared in Dahl rats: young salt-resistant (control), young salt-sensitive (early chronic HTN), middle-aged salt-resistant (aging), and middle-aged salt-sensitive (late chronic HTN). Total collagen increased, several MMPs decreased, and TIMP-1 increased in the early phase of HTN, consistent with fibrosis. The activity of MMP-8 decreased in young salt-sensitive rats. MMP-14 correlated positively with changes in left ventricular mass/body weight during the early phase. During the late phase, chronic HTN was associated with decreased total collagen levels and increased MMP-8 and -14. These findings suggest both upregulation and down-regulation of MMPs at different stages of HTN (Lin et al., 2008). We should also note that ECM remodeling in response to pressure overload is a dynamic process involving both ECM accumulation and degradation, and antihypertensive treatment may further modulate collagen metabolism.

MMPs could regulate the vascular remodeling associated with HTN via other cellular mechanisms. MMPs may mediate EGFR transactivation induced by excessive stimulation of GPCRs such as α_1-adrenergic receptors which in turn promote the synthesis of contractile proteins in VSMCs and thereby contribute to the development of HTN. Also, in fructose hypertensive rat (FHRs) model of acquired systolic HTN and insulin resistance, the insulin-resistant VSMCs demonstrated increased expression and activity of MMP-2 and -7, EGFR, contractile proteins such as myosin light chain (MLC) kinase and MLC-II and their transcriptional activators possibly via activation of ERK1/2. Disruption of MMP-EGFR signaling normalized the increased expression and activity of contractile proteins and their transcriptional activators in insulin-resistant VSMCs and arteries and prevented the development of HTN in FHRs (Nagareddy et al.)2010). Also, in a study on wild-type and MMP-9 knockout mice treated with AngII for 10 days, the onset of AngII-induced HTN was associated with increased MMP-9 activity in conductance vessels, and MMP-9 deficiency was associated with vessel stiffness and increased pulse pressure (Flamant et al., 2007).

Unbalanced increase in MMPs without a corresponding increase in TIMPs in blood vessels, particularly in the intima and media, may account for the increased proteolytic activity observed in HTN-induced maladaptive vascular remodeling. Increased amount of MMP-2, -9, and -14 and enhanced gelatinolytic activity were found in the aortas of 2K-1C rat model of HTN. Doxycycline treatment for 8 weeks attenuated 2K-1C HTN, prevented the increase in the aortic intima and media thicknesses, attenuated the increases in MMP-2, -9, and -14 in the intima and media, but did not change the amount of TIMPs 1–4 (Castro et al.)2010). In SHR-derived VSMCs, MMP-9 expression and cell migration are increased in response to TNF-α and upregulation of MMP-9 is transcriptionally regulated at the AP-1 and NF-κB sites in the MMP-9 promoter, suggesting a role for increased VSMC proliferative capacity, G1 to S-phase cell-cycle progress, and MMP-9 expression in the vascular remodeling in HTN (Lee et al., 2009b). Also, induction of acute HTN by AngII in SHR was associated with post-transcriptional activation of vascular MMP-7, transcription of myocardiac ADAM-12, a major metalloproteinase implicated in cardiac hypertrophy, and overexpression of downstream hypertrophy marker genes. Knockdown of MMP-7

attenuated HTN, inhibited ADAM-12 overexpression, and prevented cardiac hypertrophy (Wang et al., 2009). MMPs may also play a role in hypertensive complications such as intracranial hemorrhage (Wakisaka et al.)2010) and cardiac hypertrophy (Castro et al.; Franz et al., 2009)

12. MMPs in Pregnancy and Preeclampsia

Embryo implantation and trophoblast invasion are tightly regulated processes involving interaction between maternal decidual cells and fetal trophoblast cells. Decidualization is a prerequisite for successful implantation and is promoted by many factors including MMPs. Decidual cells secrete the highest levels of MMPs and their invasive potential increases in the presence of cytotrophoblast (Cohen et al.)2010). Studies have shown that the endometrium produces proMMP-2, -3, -7, -9, and active MMP-2 (Jones et al., 2006). MMPs may also be involved in placental remodeling throughout pregnancy. MMP-9 levels are higher in normal pregnant than non-pregnant women, with positive correlation with the gestational period (Montagnana et al., 2009). In first trimester human placenta, MMP-2 expression/activity is observed in extravillous trophoblasts and MMP-9 mainly in villous cytotrophoblasts. The invasive ability of early cytotrophoblasts is inhibited by TIMP-2 and anti-MMP-2 antibody, suggesting a role of gelatinases, especially MMP-2. This is supported by reports of polarized release of MMP-2 and -9 from cultured human placental syncytiotrophoblasts. In full-term placental tissue, MMP-2 expression in the extravillous trophoblasts is similar to that in first trimester, but the gelatinase activity is decreased or completely lost (Sawicki et al., 2000). MMP-2 also seems to mediate the protease activity of uterine natural killer cells which regulate trophoblast invasion and spiral artery remodeling in early placentation (Naruse et al., 2009). PKC-α may be responsible for the regulation of MMP-2 expression during decidualization (Tsai et al., 2009). EMMPRIN relase from the luminal epithelium may regulate the expression of stromal MMP-2 and -14, and thereby affect the adhesion and fusion of embryo to luminal epithelium (Mishra et al.)2010). Increased plasma levels of MMPs are also detected during normal pregnancy, suggesting a role for MMPs in the pregnancy-associated changes in vascular function (Merchant and Davidge, 2004).

Experimental studies supported a role of MMPs during pregnancy. The serum activity of MMP-2 and -9 is higher in pregnant than non-pregnant bitches, and is correlated with the serum levels of estrogen (Schafer-Somi et al., 2005). Furin is highly expressed in placental villi of rhesus monkeys and humans during early pregnancy. In HTR8/SVneo cells, knocking-down furin expression inhibits cell invasion and migration, and decreases MMP-9 activity. In contrast, overexpression of furin is associated with increased cell invasion and migration, and MMP-9 activity (Zhou et al., 2009). MMP-26 mRNA is expressed in the mouse uterus during the estrous cycle and early pregnancy (Liu et al., 2005), while TIMP-2 mRNA is upregulated in the endometrium during the luteal phase of the estrous cycle and during early pregnancy in cows (Ledgard et al., 2009).

MMPs could also play a role in the uterine artery remodeling during pregnancy. MMP-2, MT1-MMP, MMP-3 and TIMP-1 transcripts are elevated in the uterine artery of early pregnant rats (day 7). In late pregnant rats (day 21), the mRNA expression of MMP-2, -3, -7, -9, -12, -13, MT1-MMP, and TIMP-1 and -2 are increased. TIMP-1 and MMP-3 mRNA expression return to virgin control levels in the post-partum period, whereas MMP-9 and -13 remain elevated or increase further. Maximum elevation of MMP-2 is observed at day 21 of gestation, suggesting a role in maintaining uterine blood flow in late pregnancy. Continued elevatation of the levels of some MMPs post-partum may contribute to vessel regression and return to a non-pregnant state (Kelly et al., 2003). Increased mRNA and protein expression of pro- and active MMP-2 was also observed in renal and mesenteric arteries from pregnant

compared with virgin rats (Jeyabalan et al., 2006). It has also been suggested that vascular gelatinase activity may function upstream of the endothelial endothelin B (ET_B) receptor and the NO pathway in the renal vasodilatory response during pregnancy (Jeyabalan et al., 2007).

Modification of the fine balance between MMPs and MMPIs may play a role in the vascular changes associated with complications of pregnancy such as preeclampsia (PE). PE is characterized by HTN and proteinuria and may lead to eclampsia, convulsions, cerebral hemorrhage, HELLP syndrome, and placental abruption. The pathogenesis of PE is unclear, but inadequate blood supply to the placenta may stimulate the release of mediators such as cytokines and growth factor inhibitors leading to endothelial cell damage and vascular inflammation. Abnormalities in the maternal immune system and inadequate gestational immune tolerance may also contribute to the development of PE. Placental hypoxia may increase the release of fetal mediators into the maternal circulation leading to an immune response, endothelial damage and ultimately PE (Maynard et al., 2003).

MMP-mediated vascular remodeling may play a role in the pathogenesis of PE (Merchant and Davidge, 2004). Higher levels of MMPs such as MMP-2 and lower levels of TIMPs have been shown in women with PE (Narumiya et al., 2001; Montagnana et al., 2009; Shokry et al., 2009) or who subsequently develop PE (Myers et al., 2005; Lavee et al., 2009). Increased MMP-2 activity may contribute to the endothelial dysfunction in PE (Myers et al., 2005). However, the proteases intrinsic to syncytiotrophoblast microvillous membranes (STBM) are unlikely to be the cause of the endothelial changes (de Jager et al., 2003). A recent study investigating 128 cases of PE and 569 control pregnancies showed higher serum levels of MMP-9 in PE than controls, and an association between serum MMP-9 and TNF-receptor levels, suggesting an underlying inflammatory process (Poon et al., 2009). MMP-7 and -26 may contribute to ECM remodeling in the umbilical cord of PE pregnancies by activating MMP-9. The high MMP-9 activity may enhance the proteolytic release of growth factors from their complexes with ECM components, thus facilitating their interaction with membrane receptors, and stimulation of cell division and ECM synthesis (Galewska et al.; Galewska et al., 2008). These findings have suggested MMP-9 as one of the biomarkers of PE (Poon et al.) 2010).

MMPIs have been used to study the role of MMPs in PE. In a study on hypertensive and control pregnant rats, doxycycline treatment from gestational day 12 to day 18 resulted in intrauterine growth retardation and lighter placentas in both groups. Hypertensive pregnant rats exhibited a deeper endovascular trophoblast invasion. Doxycycline treatment in PE rats was associated with reduction in trophoblast invasion, spiral artery remodeling as assessed by the deposition of fibrinoid and α-actin in the spiral artery contour, and the vascularity index as assessed by measurement of placental perfusion (Geusens et al.)2010).

Some studies suggest different role of MMPs in gestational HTN as compared to PE. Higher plasma pro-MMP-9 levels and pro-MMP-9/TIMP-1 ratios were demonstrated in women with gestational HTN, but not in PE (Palei et al.)2010). Also, the C(-1562)T polymorphism in MMP-9 gene showed an association with gestational HTN, but not PE (Palei et al.)2010). Other studies demonstrated reduced levels of MMPs and elevated TIMPs in PE and suggested that reduced degradation of ECM components results in intimal thickening, tissue hypoxia and eventual PE cascade. Decreased amount and activity of MMP-1 and elevated amounts of TIMP-1 were detected in PE umbilical cord arteries (Galewska et al., 2006). Also, in cultured human decidual ECs, basal and stimulated secretion of MMP-1 was higher in normal compared with PE ECs. The lower MMP-1 expression of decidual ECs from PE women may inhibit endovascular invasion by cytotrophoblasts. These findings may partly explain the relative failure of trophoblasts to invade maternal decidual blood vessels in PE

pregnancy (Gallery et al., 1999). Lower levels of MMP-1, -9 and -3 were also detected in extracts of human umbilical cord artery. MMP-2 is the main collagenolytic enzyme in umbilical cord artery (UCA) wall. PE was associated with a distinct reduction in those MMPs content and activity, which may reduce the breakdown of collagen in the arterial wall. The accumulation of collagen with simultaneous reduction in elastin content of UCA may reduce the elasticity of arterial wall and decreases the blood flow to the fetus (Galewska et al., 2003). MMP-3 expression levels are also reduced in the placental invasive trophoblasts of patients with severe PE (Husslein et al., 2009).

A maternal immune cell network accumulating in the placental bed may alter the cytokine environment, resulting in disturbed trophoblast cell function, impaired MMP expression and reduced invasiveness. Expression of MMP-3 and -7 by extravillous trophoblasts is reduced in PE patients, especially close to spiral arteries. In contrast to healthy pregnancies, in PE extravillous trophoblasts strongly express the receptor for leukemia inhibitory factor (LIF). LIF suppresses MMP-expression and is produced by uterine natural killer cells which accumulate alongside the spiral arteries in the placental bed of PE patients (Reister et al., 2006). MMP-9 expression is also low in PE pregnancies (Shokry et al., 2009).

TIMP-1 is elevated in PE (Tayebjee et al., 2005; Montagnana et al., 2009). Also, mean amniotic TIMP-2 levels are higher in women who developed a hypertensive disorder compared to normotensive women (Lavee et al., 2009; Montagnana et al., 2009). A decrease in ECM remodeling could play a role in HELLP syndrome. The mRNA expression of MMP-2 and TIMP-2 are decreased, whereas TIMP-1 and -3 levels are unchanged in 11 females with HELLP syndrome and 8 controls matched for gestational age (von Steinburg et al., 2009).

Some studies showed no association between MMP levels and HTN in pregnancy. A study enrolling 133 women showed no statistical difference in MMP-2 levels between patients with gestational HTN and normotensive controls (Lavee et al., 2009) or between PE and normotensive women (Galewska et al., 2008). Another study enrolling 83 pregnant women showed no difference in pro-MMP-2 levels (Palei et al., 2008). Also, some studies showed no statistical difference in TIMP-1 and -2 between PE and control samples (Galewska et al., 2008). Collectively, studies showed an imbalance between MMPs and TIMPs in HTN in pregnancy, but the mechanisms via which these imbalances contribute to the pathogenesis of the disease need to be further examined.

13. Conclusions and Perspectives

MMPs play an important role in ECM metabolism and other physiological processes, and increased MMP expression/activity has been associated with connective tissue remodeling in autoimmune and vascular disease. The role of MMPs is often examined by measuring their plasma levels, and tissue expression and activity. Molecular imaging of MMP function *in vivo* is an emerging area of research. In murine tumors a near infrared fluorescent MMP substrate detects the activity of MMPs *in vivo*, and the activity decreases after intervention with an MMPI (Bremer et al., 2001). Similar approaches have identified active cathepsin B in atherosclerotic mice and increased MMP-2 and -9 activities after murine MI (Chen et al., 2002). Although this technology presents challenges, such as limited tissue penetration and autofluorescence of elastin in arteries, initial results have provided proof of principle for proteinase imaging *in vivo*.

Several MMPIs have been used as investigative tools of the role of MMPs in physiological and pathological processes. MMPIs have also been proposed as potential therapeutic tools in the management of cancer, arthritis and vascular disease. However, many of these MMPIs lack specificity. Also, the majority of clinical trials using synthetic MMPIs were conducted

in cancer patients and proved unsuccessful, mainly due to the lack of efficacy and untoward side effects including musculoskeletal pain and tendonitis (Milner and Cawston, 2005). In animal models, MMPIs have been effective in preventing the development and progression of early disease, but have had little effect in advanced disease. Also, many of the studies used MMPIs as single agent therapies for patients with advanced disease, which may explain the poor performance of MMPIs in the clinical trials undertaken to date (Coussens et al., 2002).

Several approaches were suggested as potential solutions to the drawbacks of classic MMPIs. The production of specific antibody fragments developed from phage library screens could be promising. Such antibodies could target the MMP active site in a more specific way than chemical inhibitors and could identify sites on the MMP molecule that determine their substrate specificity and extracellular location. For instance, the hemopexin domain of the collagenase MMP-1 is essential for the specificity of the catalytic domain cleavage of collagen. Also, MMP-2 is localized to specific extracellular collagenous sites by its fibronectin domains and MT1-MMP (MMP-14) requires the hemopexin domain for cell surface clustering as part of its collagenolytic capacity and ability to mediate proMMP-2 activation. The hemopexin domain also determines its binding to CD44 (Suenaga et al., 2005). Further understanding of the nature of these interactions will allow the development of specific inhibitors of MMP-substrate binding or fragment antibodies that target these interactions.

Several other strategies may potentially downregulate MMPs. Both the intracellular signaling pathways and the downstream transcription factors which induce gene expression are being studied. Blockade of MAPK pathways, NF-Kb or activator protein (AP)-1 have shown some efficacy *in vitro* or in animal models of arthritis (Mix et al., 2004). The use of biological reagents to block inflammatory cytokines also reduces MMP expression in many tissues. Tetracyclines are rather weak inhibitors of MMP activity, but they could also influence MMP synthesis and have been tested successfully in rheumatoid arthritis (Voils et al., 2005). Gene therapy has been successful in animal models and overexpression of TIMPs may have future applications after overcoming the problems of safe and efficient delivery of genes into target cells and tissues (van der Laan et al., 2003).

Acknowledgments

This work was supported by grants from National Heart, Lung, and Blood Institute (HL-65998, HL-98724) and The Eunice Kennedy Shriver National Institute of Child Health and Human Development (HD-60702).

List of abbreviations

AAA	abdominal aortic aneurysm
ADAM	a disintegrin and metalloproteinase
BP	blood pressure
EC	endothelial cell
ECM	extracellular matrix
FGF	fibroblast growth factor
GPCR	G-protein coupled receptor
HUVECs	human umbilical vein endothelial cells
IGF	insulin-like growth factor

MAPK	mitogen-activated protein kinase
MMP	matrix metalloproteinase
MI	myocardial infarction
NO	nitric oxide
Phe	phenylephrine
PKC	protein kinase C
TGF	transforming growth factor
TIMP	tissue inhibitor of matrix metalloproteinase
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
VSM	vascular smooth muscle

References

Agrawal A, Romero-Perez D, Jacobsen JA, Villarreal FJ, Cohen SM. Zinc-binding groups modulate selective inhibition of MMPs. ChemMedChem. 2008; 3:812–820. [PubMed: 18181119]

Aguilera CM, George SJ, Johnson JL, Newby AC. Relationship between type IV collagen degradation, metalloproteinase activity and smooth muscle cell migration and proliferation in cultured human saphenous vein. Cardiovasc Res. 2003; 58:679–688. [PubMed: 12798442]

Ahokas K, Lohi J, Illman SA, Llano E, Elomaa O, Impola U, Karjalainen-Lindsberg ML, Saarialho-Kere U. Matrix metalloproteinase-21 is expressed epithelially during development and in cancer and is up-regulated by transforming growth factor-beta1 in keratinocytes. Lab Invest. 2003; 83:1887–1899. [PubMed: 14691307]

Aikawa M, Rabkin E, Voglic SJ, Shing H, Nagai R, Schoen FJ, Libby P. Lipid lowering promotes accumulation of mature smooth muscle cells expressing smooth muscle myosin heavy chain isoforms in rabbit atheroma. Circ Res. 1998; 83:1015–1026. [PubMed: 9815149]

Aimes RT, Quigley JP. Matrix metalloproteinase-2 is an interstitial collagenase. Inhibitor-free enzyme catalyzes the cleavage of collagen fibrils and soluble native type I collagen generating the specific 3/4- and 1/4-length fragments. J Biol Chem. 1995; 270:5872–5876. [PubMed: 7890717]

Akiba S, Kumazawa S, Yamaguchi H, Hontani N, Matsumoto T, Ikeda T, Oka M, Sato T. Acceleration of matrix metalloproteinase-1 production and activation of platelet-derived growth factor receptor beta in human coronary smooth muscle cells by oxidized LDL and 4-hydroxynonenal. Biochim Biophys Acta. 2006; 1763:797–804. [PubMed: 16876267]

Alfranca A, Lopez-Oliva JM, Genis L, Lopez-Maderuelo D, Mirones I, Salvado D, Quesada AJ, Arroyo AG, Redondo JM. PGE2 induces angiogenesis via MT1-MMP-mediated activation of the TGFbeta/Alk5 signaling pathway. Blood. 2008; 112:1120–1128. [PubMed: 18541723]

Almeida EA, Ilic D, Han Q, Hauck CR, Jin F, Kawakatsu H, Schlaepfer DD, Damsky CH. Matrix survival signaling: from fibronectin via focal adhesion kinase to c-Jun NH(2)-terminal kinase. J Cell Biol. 2000; 149:741–754. [PubMed: 10791986]

Amour A, Knight CG, Webster A, Slocombe PM, Stephens PE, Knauper V, Docherty AJ, Murphy G. The in vitro activity of ADAM-10 is inhibited by TIMP-1 and TIMP-3. FEBS Lett. 2000; 473:275–279. [PubMed: 10818225]

Annes JP, Munger JS, Rifkin DB. Making sense of latent TGFbeta activation. J Cell Sci. 2003; 116:217–224. [PubMed: 12482908]

Aravind B, Saunders B, Navin T, Sandison A, Monaco C, Paleolog EM, Davies AH. Inhibitory effect of TIMP influences the morphology of varicose veins. Eur J Vasc Endovasc Surg. 40:754–765. [PubMed: 20598922]

Ardi VC, Van den Steen PE, Opdenakker G, Schweighofer B, Deryugina EI, Quigley JP. Neutrophil MMP-9 proenzyme, unencumbered by TIMP-1, undergoes efficient activation in vivo and catalytically induces angiogenesis via a basic fibroblast growth factor (FGF-2)/FGFR-2 pathway. J Biol Chem. 2009; 284:25854–25866. [PubMed: 19608737]

Armani C, Curcio M, Barsotti MC, Santoni T, Di Stefano R, Dell'omodarme M, Brandi ML, Ferrari M, Scatena F, Carpi A, Balbarini A. Polymorphic analysis of the matrix metalloproteinase-9 gene and susceptibility to sporadic abdominal aortic aneurysm. Biomed Pharmacother. 2007; 61:268–271. [PubMed: 17223007]

Asamoto M, Hokaiwado N, Cho YM, Takahashi S, Ikeda Y, Imaida K, Shirai T. Prostate carcinomas developing in transgenic rats with SV40 T antigen expression under probasin promoter control are strictly androgen dependent. Cancer Res. 2001; 61:4693–4700. [PubMed: 11406539]

Auge F, Hornebeck W, Decarme M, Laronze JY. Improved gelatinase a selectivity by novel zinc binding groups containing galardin derivatives. Bioorg Med Chem Lett. 2003; 13:1783–1786. [PubMed: 12729664]

Axisa B, Loftus IM, Naylor AR, Goodall S, Jones L, Bell PR, Thompson MM. Prospective, randomized, double-blind trial investigating the effect of doxycycline on matrix metalloproteinase expression within atherosclerotic carotid plaques. Stroke. 2002; 33:2858–2864. [PubMed: 12468782]

Badier-Commander C, Verbeuren T, Lebard C, Michel JB, Jacob MP. Increased TIMP/MMP ratio in varicose veins: a possible explanation for extracellular matrix accumulation. J Pathol. 2000; 192:105–112. [PubMed: 10951407]

Baker AH, Edwards DR, Murphy G. Metalloproteinase inhibitors: biological actions and therapeutic opportunities. J Cell Sci. 2002; 115:3719–3727. [PubMed: 12235282]

Baker AH, Zaltsman AB, George SJ, Newby AC. Divergent effects of tissue inhibitor of metalloproteinase-1, -2, or -3 overexpression on rat vascular smooth muscle cell invasion, proliferation, and death in vitro. TIMP-3 promotes apoptosis. J Clin Invest. 1998; 101:1478–1487. [PubMed: 9502791]

Banke IJ, Arlt MJ, Mueller MM, Sperl S, Stemberger A, Sturzebecher J, Amirkhosravi A, Moroder L, Kruger A. Effective inhibition of experimental metastasis and prolongation of survival in mice by a potent factor Xa-specific synthetic serine protease inhibitor with weak anticoagulant activity. Thromb Haemost. 2005; 94:1084–1093. [PubMed: 16363253]

Bar-Or A, Nuttall RK, Duddy M, Alter A, Kim HJ, Ifergan I, Pennington CJ, Bourgoin P, Edwards DR, Yong VW. Analyses of all matrix metalloproteinase members in leukocytes emphasize monocytes as major inflammatory mediators in multiple sclerosis. Brain. 2003; 126:2738–2749. [PubMed: 14506071]

Barbour JR, Spinale FG, Ikonomidis JS. Proteinase systems and thoracic aortic aneurysm progression. J Surg Res. 2007; 139:292–307. [PubMed: 17292415]

Barbour JR, Stroud RE, Lowry AS, Clark LL, Leone AM, Jones JA, Spinale FG, Ikonomidis JS. Temporal disparity in the induction of matrix metalloproteinases and tissue inhibitors of metalloproteinases after thoracic aortic aneurysm formation. J Thorac Cardiovasc Surg. 2006; 132:788–795. [PubMed: 17000289]

Barron LA, Giardina JB, Granger JP, Khalil RA. High-salt diet enhances vascular reactivity in pregnant rats with normal and reduced uterine perfusion pressure. Hypertension. 2001; 38:730–735. [PubMed: 11566966]

Basile JR, Holmbeck K, Bugge TH, Gutkind JS. MT1-MMP controls tumor-induced angiogenesis through the release of semaphorin 4D. J Biol Chem. 2007; 282:6899–6905. [PubMed: 17204469]

Beaudeux JL, Giral P, Bruckert E, Foglietti MJ, Chapman MJ. Matrix metalloproteinases, inflammation and atherosclerosis: therapeutic perspectives. Clin Chem Lab Med. 2004; 42:121–131. [PubMed: 15061349]

Bendeck MP, Conte M, Zhang M, Nili N, Strauss BH, Farwell SM. Doxycycline modulates smooth muscle cell growth, migration, and matrix remodeling after arterial injury. Am J Pathol. 2002; 160:1089–1095. [PubMed: 11891205]

Bendeck MP, Irvin C, Reidy MA. Inhibition of matrix metalloproteinase activity inhibits smooth muscle cell migration but not neointimal thickening after arterial injury. Circ Res. 1996; 78:38–43. [PubMed: 8603503]

Bendrik C, Karlsson L, Dabrosin C. Increased endostatin generation and decreased angiogenesis via MMP-9 by tamoxifen in hormone dependent ovarian cancer. Cancer Lett. 292:32–40. [PubMed: 19944523]

Bergan JJ, Schmid-Schonbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. N Engl J Med. 2006; 355:488–498. [PubMed: 16885552]

Bernardo MM, Brown S, Li ZH, Fridman R, Mobashery S. Design, synthesis, and characterization of potent, slow-binding inhibitors that are selective for gelatinases. J Biol Chem. 2002; 277:11201–11207. [PubMed: 11790786]

Biasone A, Tortorella P, Campestre C, Agamennone M, Preziuso S, Chiappini M, Nuti E, Carelli P, Rossello A, Mazza F, Gallina C. alpha-Biphenylsulfonylamino 2-methylpropyl phosphonates: enantioselective synthesis and selective inhibition of MMPs. Bioorg Med Chem. 2007; 15:791–799. [PubMed: 17088065]

Blagg JA, Noe MC, Wolf-Gouveia LA, Reiter LA, Laird ER, Chang SP, Danley DE, Downs JT, Elliott NC, Eskra JD, Griffiths RJ, Hardink JR, Haugeto AI, Jones CS, Liras JL, Lopresti-Morrow LL, Mitchell PG, Pandit J, Robinson RP, Subramanyam C, Vaughn-Bowser ML, Yocum SA. Potent pyrimidinetrione-based inhibitors of MMP-13 with enhanced selectivity over MMP-14. Bioorg Med Chem Lett. 2005; 15:1807–1810. [PubMed: 15780611]

Blankenberg S, Rupprecht HJ, Poirier O, Bickel C, Smieja M, Hafner G, Meyer J, Cambien F, Tiret L. Plasma concentrations and genetic variation of matrix metalloproteinase 9 and prognosis of patients with cardiovascular disease. Circulation. 2003; 107:1579–1585. [PubMed: 12668489]

Bode W, Gomis-Ruth FX, Stockler W. Astacins, serralysins, snake venom and matrix metalloproteinases exhibit identical zinc-binding environments (HEXXHXXGXXH and Met-turn) and topologies and should be grouped into a common family, the 'metzincins'. FEBS Lett. 1993; 331:134–140. [PubMed: 8405391]

Boire A, Covic L, Agarwal A, Jacques S, Sherifi S, Kuliopulos A. PAR1 is a matrix metalloprotease-1 receptor that promotes invasion and tumorigenesis of breast cancer cells. Cell. 2005; 120:303–313. [PubMed: 15707890]

Bond M, Murphy G, Bennett MR, Amour A, Knauper V, Newby AC, Baker AH. Localization of the death domain of tissue inhibitor of metalloproteinase-3 to the N terminus. Metalloproteinase inhibition is associated with proapoptotic activity. J Biol Chem. 2000; 275:41358–41363. [PubMed: 11007798]

Bonfil RD, Dong Z, Trindade Filho JC, Sabbota A, Osenkowski P, Nabha S, Yamamoto H, Chinni SR, Zhao H, Mobashery S, Vessella RL, Fridman R, Cher ML. Prostate cancer-associated membrane type 1-matrix metalloproteinase: a pivotal role in bone response and intraosseous tumor growth. Am J Pathol. 2007; 170:2100–2111. [PubMed: 17525276]

Bonfil RD, Sabbota A, Nabha S, Bernardo MM, Dong Z, Meng H, Yamamoto H, Chinni SR, Lim IT, Chang M, Filetti LC, Mobashery S, Cher ML, Fridman R. Inhibition of human prostate cancer growth, osteolysis and angiogenesis in a bone metastasis model by a novel mechanism-based selective gelatinase inhibitor. Int J Cancer. 2006; 118:2721–2726. [PubMed: 16381009]

Borkakoti N, Winkler FK, Williams DH, D'Arcy A, Broadhurst MJ, Brown PA, Johnson WH, Murray EJ. Structure of the catalytic domain of human fibroblast collagenase complexed with an inhibitor. Nat Struct Biol. 1994; 1:106–110. [PubMed: 7656013]

Bosman FT, Stamenkovic I. Functional structure and composition of the extracellular matrix. J Pathol. 2003; 200:423–428. [PubMed: 12845610]

Bremer C, Tung CH, Weissleder R. In vivo molecular target assessment of matrix metalloproteinase inhibition. Nat Med. 2001; 7:743–748. [PubMed: 11385514]

Breuer E, Salomon CJ, Katz Y, Chen W, Lu S, Roschenthaler GV, Hadar R, Reich R. Carbamoylphosphonates, a new class of in vivo active matrix metalloproteinase inhibitors. 1. Alkyl- and cycloalkylcarbamoylphosphonic acids. J Med Chem. 2004; 47:2826–2832. [PubMed: 15139760]

Brown S, Meroueh SO, Fridman R, Mobashery S. Quest for selectivity in inhibition of matrix metalloproteinases. Curr Top Med Chem. 2004; 4:1227–1238. [PubMed: 15320723]

Browner MF, Smith WW, Castelhano AL. Matrilysin-inhibitor complexes: common themes among metalloproteases. Biochemistry. 1995; 34:6602–6610. [PubMed: 7756291]

Brunner S, Kim JO, Methe H. Relation of matrix metalloproteinase-9/tissue inhibitor of metalloproteinase-1 ratio in peripheral circulating CD14+ monocytes to progression of coronary artery disease. Am J Cardiol. 105:429–434. [PubMed: 20152234]

Butler GS, Butler MJ, Atkinson SJ, Will H, Tamura T, Schade van Westrum S, Crabbe T, Clements J, d'Ortho MP, Murphy G. The TIMP2 membrane type 1 metalloproteinase "receptor" regulates the concentration and efficient activation of progelatinase A. A kinetic study. J Biol Chem. 1998; 273:871–880. [PubMed: 9422744]

Campestre C, Agamennone M, Tortorella P, Preziuso S, Biasone A, Gavuzzo E, Pochetti G, Mazza F, Hiller O, Tschesche H, Consalvi V, Gallina C. N-Hydroxyurea as zinc binding group in matrix metalloproteinase inhibition: mode of binding in a complex with MMP-8. Bioorg Med Chem Lett. 2006; 16:20–24. [PubMed: 16242329]

Carragher NO, Frame MC. Focal adhesion and actin dynamics: a place where kinases and proteases meet to promote invasion. Trends Cell Biol. 2004; 14:241–249. [PubMed: 15130580]

Castro MM, Rizzi E, Prado CM, Rossi MA, Tanus-Santos JE, Gerlach RF. Imbalance between matrix metalloproteinases and tissue inhibitor of metalloproteinases in hypertensive vascular remodeling. Matrix Biol. 29:194–201. [PubMed: 19969080]

Castro MM, Rizzi E, Rodrigues GJ, Ceron CS, Bendhack LM, Gerlach RF, Tanus-Santos JE. Antioxidant treatment reduces matrix metalloproteinase-2-induced vascular changes in renovascular hypertension. Free Radic Biol Med. 2009; 46:1298–1307. [PubMed: 19248829]

Cauwe B, Van den Steen PE, Opdenakker G. The biochemical, biological, and pathological kaleidoscope of cell surface substrates processed by matrix metalloproteinases. Crit Rev Biochem Mol Biol. 2007; 42:113–185. [PubMed: 17562450]

Celenza G, Villegas-Estrada A, Lee M, Boggess B, Forbes C, Wolter WR, Suckow MA, Mobashery S, Chang M. Metabolism of (4-phenoxyphenylsulfonyl) methylthiirane, a selective gelatinase inhibitor. Chem Biol Drug Des. 2008; 71:187–196. [PubMed: 18221479]

Cena J, Lalu MM, Rosenfelt C, Schulz R. Endothelial dependence of matrix metalloproteinase-mediated vascular hyporeactivity caused by lipopolysaccharide. Eur J Pharmacol. 2008; 582:116–122. [PubMed: 18242597]

Cevik C, Otahbachi M, Nugent K, Warangkana C, Meyerrose G. Effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition on serum matrix metalloproteinase-13 and tissue inhibitor matrix metalloproteinase-1 levels as a sign of plaque stabilization. J Cardiovasc Med (Hagerstown). 2008; 9:1274–1278. [PubMed: 19001938]

Chen J, Tung CH, Mahmood U, Ntziachristos V, Gyurko R, Fishman MC, Huang PL, Weissleder R. In vivo imaging of proteolytic activity in atherosclerosis. Circulation. 2002; 105:2766–2771. [PubMed: 12057992]

Chen L, Wang X, Carter SA, Shen YH, Bartsch HR, Thompson RW, Coselli JS, Wilcken DL, Wang XL, LeMaire SA. A single nucleotide polymorphism in the matrix metalloproteinase 9 gene (-8202A/G) is associated with thoracic aortic aneurysms and thoracic aortic dissection. J Thorac Cardiovasc Surg. 2006; 131:1045–1052. [PubMed: 16678588]

Chen LC, Noelken ME, Nagase H. Disruption of the cysteine-75 and zinc ion coordination is not sufficient to activate the precursor of human matrix metalloproteinase 3 (stromelysin 1). Biochemistry. 1993; 32:10289–10295. [PubMed: 8399171]

Cheng XW, Kuzuya M, Sasaki T, Arakawa K, Kanda S, Sumi D, Koike T, Maeda K, Tamaya-Mori N, Shi GP, Saito N, Iguchi A. Increased expression of elastolytic cysteine proteases, cathepsins S and K, in the neointima of balloon-injured rat carotid arteries. Am J Pathol. 2004; 164:243–251. [PubMed: 14695337]

Cherney RJ, Mo R, Meyer DT, Hardman KD, Liu RQ, Covington MB, Qian M, Wasserman ZR, Christ DD, Trzaskos JM, Newton RC, Decicco CP. Sultam hydroxamates as novel matrix metalloproteinase inhibitors. J Med Chem. 2004; 47:2981–2983. [PubMed: 15163180]

Chew DK, Conte MS, Khalil RA. Matrix metalloproteinase-specific inhibition of Ca2+ entry mechanisms of vascular contraction. J Vasc Surg. 2004; 40:1001–1010. [PubMed: 15557917]

Cho A, Reidy MA. Matrix metalloproteinase-9 is necessary for the regulation of smooth muscle cell replication and migration after arterial injury. Circ Res. 2002; 91:845–851. [PubMed: 12411400]

Choi ET, Collins ET, Marine LA, Uberti MG, Uchida H, Leidenfrost JE, Khan MF, Boc KP, Abendschein DR, Parks WC. Matrix metalloproteinase-9 modulation by resident arterial cells is responsible for injury-induced accelerated atherosclerotic plaque development in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol. 2005; 25:1020–1025. [PubMed: 15746435]

Choke E, Cockerill GW, Dawson J, Wilson RW, Jones A, Loftus IM, Thompson MM. Increased angiogenesis at the site of abdominal aortic aneurysm rupture. Ann N Y Acad Sci. 2006; 1085:315–319. [PubMed: 17182949]

Chung AS, Kao WJ. Fibroblasts regulate monocyte response to ECM-derived matrix: the effects on monocyte adhesion and the production of inflammatory, matrix remodeling, and growth factor proteins. J Biomed Mater Res A. 2009; 89:841–853. [PubMed: 19437738]

Chung AW, Yang HH, Radomski MW, van Breemen C. Long-term doxycycline is more effective than atenolol to prevent thoracic aortic aneurysm in marfan syndrome through the inhibition of matrix metalloproteinase-2 and -9. Circ Res. 2008; 102:e73–85. [PubMed: 18388324]

Chung L, Dinakarpandian D, Yoshida N, Lauer-Fields JL, Fields GB, Visse R, Nagase H. Collagenase unwinds triple-helical collagen prior to peptide bond hydrolysis. EMBO J. 2004; 23:3020–3030. [PubMed: 15257288]

Churg A, Wang RD, Tai H, Wang X, Xie C, Dai J, Shapiro SD, Wright JL. Macrophage metalloelastase mediates acute cigarette smoke-induced inflammation via tumor necrosis factor-alpha release. Am J Respir Crit Care Med. 2003; 167:1083–1089. [PubMed: 12522030]

Cohen M, Wuillemin C, Irion O, Bischof P. Role of decidua in trophoblastic invasion. Neuro Endocrinol Lett. 31:193–197. [PubMed: 20424580]

Cook GR, Manivannan E, Underdahl T, Lukacova V, Zhang Y, Balaz S. Synthesis and evaluation of novel oxazoline MMP inhibitors. Bioorg Med Chem Lett. 2004; 14:4935–4939. [PubMed: 15341955]

Coussens LM, Fingleton B, Matrisian LM. Matrix metalloproteinase inhibitors and cancer: trials and tribulations. Science. 2002; 295:2387–2392. [PubMed: 11923519]

Creemers EE, Davis JN, Parkhurst AM, Leenders P, Dowdy KB, Hapke E, Hauet AM, Escobar PG, Cleutjens JP, Smits JF, Daemen MJ, Zile MR, Spinale FG. Deficiency of TIMP-1 exacerbates LV remodeling after myocardial infarction in mice. Am J Physiol Heart Circ Physiol. 2003; 284:H364–371. [PubMed: 12388239]

Cui Y, Takamatsu H, Kakiuchi T, Ohba H, Kataoka Y, Yokoyama C, Onoe H, Watanabe Y, Hosoya T, Suzuki M, Noyori R, Tsukada H. Neuroprotection by a central nervous system-type prostacyclin receptor ligand demonstrated in monkeys subjected to middle cerebral artery occlusion and reperfusion: a positron emission tomography study. Stroke. 2006; 37:2830–2836. [PubMed: 17008612]

Dalvie D, Cosker T, Boyden T, Zhou S, Schroeder C, Potchoiba MJ. Metabolism distribution and excretion of a matrix metalloproteinase-13 inhibitor, 4-[4-(4-fluorophenoxy)-benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide (CP-544439), in rats and dogs: assessment of the metabolic profile of CP-544439 in plasma and urine of humans. Drug Metab Dispos. 2008; 36:1869–1883. [PubMed: 18566038]

de Jager CA, Linton EA, Spyropoulou I, Sargent IL, Redman CW. Matrix metalloprotease-9, placental syncytiotrophoblast and the endothelial dysfunction of pre-eclampsia. Placenta. 2003; 24:84–91. [PubMed: 12495663]

Derosa G, D'Angelo A, Ciccarelli L, Piccinni MN, Pricolo F, Salvadeo S, Montagna L, Gravina A, Ferrari I, Galli S, Paniga S, Tinelli C, Cicero AF. Matrix metalloproteinase-2, -9, and tissue inhibitor of metalloproteinase-1 in patients with hypertension. Endothelium. 2006; 13:227–231. [PubMed: 16840178]

Desrochers PE, Mookhtiar K, Van Wart HE, Hasty KA, Weiss SJ. Proteolytic inactivation of alpha 1-proteinase inhibitor and alpha 1-antichymotrypsin by oxidatively activated human neutrophil metalloproteinases. J Biol Chem. 1992; 267:5005–5012. [PubMed: 1311327]

Dhingra R, Pencina MJ, Schrader P, Wang TJ, Levy D, Pencina K, Siwik DA, Colucci WS, Benjamin EJ, Vasan RS. Relations of matrix remodeling biomarkers to blood pressure progression and incidence of hypertension in the community. Circulation. 2009; 119:1101–1107. [PubMed: 19221217]

Djuric T, Zivkovic M, Stankovic A, Kolakovic A, Jekic D, Selakovic V, Alavantic D. Plasma levels of matrix metalloproteinase-8 in patients with carotid atherosclerosis. J Clin Lab Anal. 24:246–251. [PubMed: 20626027]

Dollery CM, Libby P. Atherosclerosis and proteinase activation. Cardiovasc Res. 2006; 69:625–635. [PubMed: 16376322]

Du WD, Zhang YE, Zhai WR, Zhou XM. Dynamic changes of type I,III and IV collagen synthesis and distribution of collagen-producing cells in carbon tetrachloride-induced rat liver fibrosis. World J Gastroenterol. 1999; 5:397–403. [PubMed: 11819476]

Dublanchet AC, Ducrot P, Andrianjara C, O'Gara M, Morales R, Compere D, Denis A, Blais S, Cluzeau P, Courte K, Hamon J, Moreau F, Prunet ML, Tertre A. Structure-based design and synthesis of novel non-zinc chelating MMP-12 inhibitors. Bioorg Med Chem Lett. 2005; 15:3787–3790. [PubMed: 16002291]

Ducharme A, Frantz S, Aikawa M, Rabkin E, Lindsey M, Rohde LE, Schoen FJ, Kelly RA, Werb Z, Libby P, Lee RT. Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction. J Clin Invest. 2000; 106:55–62. [PubMed: 10880048]

Eck SM, Blackburn JS, Schmucker AC, Burrage PS, Brinckerhoff CE. Matrix metalloproteinase and G protein coupled receptors: co-conspirators in the pathogenesis of autoimmune disease and cancer. J Autoimmun. 2009; 33:214–221. [PubMed: 19800199]

Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. Nat Rev Cancer. 2002; 2:161–174. [PubMed: 11990853]

El-Bradey MH, Cheng L, Bartsch DU, Niessman M, El-Musharaf A, Freeman WR. The effect of prinomastat (AG3340), a potent inhibitor of matrix metalloproteinase, on a new animal model of epiretinal membrane. Retina. 2004; 24:783–789. [PubMed: 15492635]

Elaut G, Rogiers V, Vanhaecke T. The pharmaceutical potential of histone deacetylase inhibitors. Curr Pharm Des. 2007; 13:2584–2620. [PubMed: 17897003]

Engel CK, Pirard B, Schimanski S, Kirsch R, Habermann J, Klingler O, Schlotte V, Weithmann KU, Wendt KU. Structural basis for the highly selective inhibition of MMP-13. Chem Biol. 2005; 12:181–189. [PubMed: 15734645]

English WR, Holtz B, Vogt G, Knauper V, Murphy G. Characterization of the role of the "MT-loop": an eight-amino acid insertion specific to progelatinase A (MMP2) activating membrane-type matrix metalloproteinases. J Biol Chem. 2001; 276:42018–42026. [PubMed: 11555661]

Erdozain OJ, Pegrum S, Winrow VR, Horrocks M, Stevens CR. Hypoxia in abdominal aortic aneurysm supports a role for HIF-1alpha and Ets-1 as drivers of matrix metalloproteinase upregulation in human aortic smooth muscle cells. J Vasc Res. 48:163–170. [PubMed: 20938207]

Eugster T, Huber A, Obeid T, Schwegler I, Gurke L, Stierli P. Aminoterminal propeptide of type III procollagen and matrix metalloproteinases-2 and -9 failed to serve as serum markers for abdominal aortic aneurysm. Eur J Vasc Endovasc Surg. 2005; 29:378–382. [PubMed: 15749038]

Ezhilarasan R, Jadhav U, Mohanam I, Rao JS, Gujrati M, Mohanam S. The hemopexin domain of MMP-9 inhibits angiogenesis and retards the growth of intracranial glioblastoma xenograft in nude mice. Int J Cancer. 2009; 124:306–315. [PubMed: 18942717]

Fata JE, Leco KJ, Voura EB, Yu HY, Waterhouse P, Murphy G, Moorehead RA, Khokha R. Accelerated apoptosis in the Timp-3-deficient mammary gland. J Clin Invest. 2001; 108:831–841. [PubMed: 11560952]

Fedak PW, Smookler DS, Kassiri Z, Ohno N, Leco KJ, Verma S, Mickle DA, Watson KL, Hojilla CV, Cruz W, Weisel RD, Li RK, Khokha R. TIMP-3 deficiency leads to dilated cardiomyopathy. Circulation. 2004; 110:2401–2409. [PubMed: 15262835]

Feng X, Tonnesen MG, Peerschke EI, Ghebrehiwet B. Cooperation of C1q receptors and integrins in C1q-mediated endothelial cell adhesion and spreading. J Immunol. 2002; 168:2441–2448. [PubMed: 11859136]

Fingleton B. MMPs as therapeutic targets--still a viable option? Semin Cell Dev Biol. 2008; 19:61–68. [PubMed: 17693104]

Fitzsimmons PJ, Forough R, Lawrence ME, Gantt DS, Rajab MH, Kim H, Weylie B, Spiekerman AM, Dehmer GJ. Urinary levels of matrix metalloproteinase 9 and 2 and tissue inhibitor of matrix metalloproteinase in patients with coronary artery disease. Atherosclerosis. 2007; 194:196–203. [PubMed: 16942771]

Flamant M, Placier S, Dubroca C, Esposito B, Lopes I, Chatziantoniou C, Tedgui A, Dussaule JC, Lehoux S. Role of matrix metalloproteinases in early hypertensive vascular remodeling. Hypertension. 2007; 50:212–218. [PubMed: 17515450]

Foda HD, Rollo EE, Drews M, Conner C, Appelt K, Shalinsky DR, Zucker S. Ventilator-induced lung injury upregulates and activates gelatinases and EMMPRIN: attenuation by the synthetic matrix metalloproteinase inhibitor, Prinomastat (AG3340). Am J Respir Cell Mol Biol. 2001; 25:717–724. [PubMed: 11726397]

Foley LH, Palermo R, Dunten P, Wang P. Novel 5,5-disubstitutedpyrimidine-2,4,6-triones as selective MMP inhibitors. Bioorg Med Chem Lett. 2001; 11:969–972. [PubMed: 11327602]

Folgueras AR, Fueyo A, Garcia-Suarez O, Cox J, Astudillo A, Tortorella P, Campestre C, Gutierrez-Fernandez A, Fanjul-Fernandez M, Pennington CJ, Edwards DR, Overall CM, Lopez-Otin C. Collagenase-2 deficiency or inhibition impairs experimental autoimmune encephalomyelitis in mice. J Biol Chem. 2008; 283:9465–9474. [PubMed: 18245084]

Folkman J. Antiangiogenesis in cancer therapy--endostatin and its mechanisms of action. Exp Cell Res. 2006; 312:594–607. [PubMed: 16376330]

Forough R, Koyama N, Hasenstab D, Lea H, Clowes M, Nikkari ST, Clowes AW. Overexpression of tissue inhibitor of matrix metalloproteinase-1 inhibits vascular smooth muscle cell functions in vitro and in vivo. Circ Res. 1996; 79:812–820. [PubMed: 8831505]

Franz M, Berndt A, Altendorf-Hofmann A, Fiedler N, Richter P, Schumm J, Fritzenwanger M, Figulla HR, Brehm BR. Serum levels of large tenascin-C variants, matrix metalloproteinase-9, and tissue inhibitors of matrix metalloproteinases in concentric versus eccentric left ventricular hypertrophy. Eur J Heart Fail. 2009; 11:1057–1062. [PubMed: 19815660]

Freeman-Cook KD, Reiter LA, Noe MC, Antipas AS, Danley DE, Datta K, Downs JT, Eisenbeis S, Eskra JD, Garmene DJ, Greer EM, Griffiths RJ, Guzman R, Hardink JR, Janat F, Jones CS, Martinelli GJ, Mitchell PG, Laird ER, Liras JL, Lopresti-Morrow LL, Pandit J, Reilly UD, Robertson D, Vaughn-Bowser ML, Wolf-Gouviea LA, Yocum SA. Potent, selective spiropyrrolidine pyrimidinetrione inhibitors of MMP-13. Bioorg Med Chem Lett. 2007; 17:6529–6534. [PubMed: 17935984]

Frisch SM, Screaton RA. Anoikis mechanisms. Curr Opin Cell Biol. 2001; 13:555–562. [PubMed: 11544023]

Fu X, Kao JL, Bergt C, Kassim SY, Huq NP, d'Avignon A, Parks WC, Mecham RP, Heinecke JW. Oxidative cross-linking of tryptophan to glycine restrains matrix metalloproteinase activity: specific structural motifs control protein oxidation. J Biol Chem. 2004; 279:6209–6212. [PubMed: 14670964]

Fu X, Kassim SY, Parks WC, Heinecke JW. Hypochlorous acid oxygenates the cysteine switch domain of pro-matrilysin (MMP-7). A mechanism for matrix metalloproteinase activation and atherosclerotic plaque rupture by myeloperoxidase. J Biol Chem. 2001; 276:41279–41287. [PubMed: 11533038]

Fujiwara K, Matsukawa A, Ohkawara S, Takagi K, Yoshinaga M. Functional distinction between CXC chemokines, interleukin-8 (IL-8), and growth related oncogene (GRO)alpha in neutrophil infiltration. Lab Invest. 2002; 82:15–23. [PubMed: 11796822]

Fukumoto Y, Deguchi JO, Libby P, Rabkin-Aikawa E, Sakata Y, Chin MT, Hill CC, Lawler PR, Varo N, Schoen FJ, Krane SM, Aikawa M. Genetically determined resistance to collagenase action augments interstitial collagen accumulation in atherosclerotic plaques. Circulation. 2004; 110:1953–1959. [PubMed: 15451791]

Galewska Z, Bankowski E, Romanowicz L, Jaworski S. Pre-eclampsia (EPH-gestosis)-induced decrease of MMP-s content in the umbilical cord artery. Clin Chim Acta. 2003; 335:109–115. [PubMed: 12927692]

Galewska Z, Romanowicz L, Gogiel T, Jaworski S, Bankowski E. The inhibitory effect of preeclamptic umbilical cord blood serum on matrix metalloproteinase-1 in arterial slices incubated in vitro. Pathobiology. 2006; 73:310–316. [PubMed: 17374969]

Galewska Z, Romanowicz L, Jaworski S, Bankowski E. Matrix metalloproteinases, MMP-7 and MMP-26, in plasma and serum of control and preeclamptic umbilical cord blood. Eur J Obstet Gynecol Reprod Biol. 150:152–156. [PubMed: 20371146]

Galewska Z, Romanowicz L, Jaworski S, Bankowski E. Gelatinase matrix metalloproteinase (MMP)-2 and MMP-9 of the umbilical cord blood in preeclampsia. Clin Chem Lab Med. 2008; 46:517–522. [PubMed: 18298353]

Galis ZS, Johnson C, Godin D, Magid R, Shipley JM, Senior RM, Ivan E. Targeted disruption of the matrix metalloproteinase-9 gene impairs smooth muscle cell migration and geometrical arterial remodeling. Circ Res. 2002; 91:852–859. [PubMed: 12411401]

Galis ZS, Sukhova GK, Lark MW, Libby P. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. J Clin Invest. 1994; 94:2493–2503. [PubMed: 7989608]

Gallery ED, Campbell S, Arkell J, Nguyen M, Jackson CJ. Preeclamptic decidual microvascular endothelial cells express lower levels of matrix metalloproteinase-1 than normals. Microvasc Res. 1999; 57:340–346. [PubMed: 10329260]

Gandhi RH, Irizarry E, Nackman GB, Halpern VJ, Mulcare RJ, Tilson MD. Analysis of the connective tissue matrix and proteolytic activity of primary varicose veins. J Vasc Surg. 1993; 18:814–820. [PubMed: 8230568]

Ganz T. Defensins and host defense. Science. 1999; 286:420–421. [PubMed: 10577203]

Garcia C, Bartsch DU, Rivero ME, Hagedorn M, McDermott CD, Bergeron-Lynn G, Cheng L, Appelt K, Freeman WR. Efficacy of Prinomastat) (AG3340), a matrix metalloprotease inhibitor, in treatment of retinal neovascularization. Curr Eye Res. 2002; 24:33–38. [PubMed: 12187492]

Gaubatz JW, Ballantyne CM, Wasserman BA, He M, Chambless LE, Boerwinkle E, Hoogeveen RC. Association of circulating matrix metalloproteinases with carotid artery characteristics: the Atherosclerosis Risk in Communities Carotid MRI Study. Arterioscler Thromb Vasc Biol. 30:1034–1042. [PubMed: 20167662]

Gearing AJ, Thorpe SJ, Miller K, Mangan M, Varley PG, Dudgeon T, Ward G, Turner C, Thorpe R. Selective cleavage of human IgG by the matrix metalloproteinases, matrilysin and stromelysin. Immunol Lett. 2002; 81:41–48. [PubMed: 11841844]

Geng L, Wang W, Chen Y, Cao J, Lu L, Chen Q, He R, Shen W. Elevation of ADAM10, ADAM17, MMP-2 and MMP-9 expression with media degeneration features CaCl2-induced thoracic aortic aneurysm in a rat model. Exp Mol Pathol. 89:72–81. [PubMed: 20621845]

Geng YJ, Libby P. Progression of atheroma: a struggle between death and procreation. Arterioscler Thromb Vasc Biol. 2002; 22:1370–1380. [PubMed: 12231554]

George SJ, Lloyd CT, Angelini GD, Newby AC, Baker AH. Inhibition of late vein graft neointima formation in human and porcine models by adenovirus-mediated overexpression of tissue inhibitor of metalloproteinase-3. Circulation. 2000; 101:296–304. [PubMed: 10645926]

Georgiadis D, Yiotakis A. Specific targeting of metzincin family members with small-molecule inhibitors: progress toward a multifarious challenge. Bioorg Med Chem. 2008; 16:8781–8794. [PubMed: 18790648]

Geusens N, Hering L, Verlohren S, Luyten C, Drijkoningen K, Taube M, Vercruysse L, Hanssens M, Dechend R, Pijnenborg R. Changes in endovascular trophoblast invasion and spiral artery remodelling at term in a transgenic preeclamptic rat model. Placenta. 31:320–326. [PubMed: 20144482]

Gillespie DL, Patel A, Fileta B, Chang A, Barnes S, Flagg A, Kidwell M, Villavicencio JL, Rich NM. Varicose veins possess greater quantities of MMP-1 than normal veins and demonstrate regional variation in MMP-1 and MMP-13. J Surg Res. 2002; 106:233–238. [PubMed: 12175972]

Goerge T, Barg A, Schnaeker EM, Poppelmann B, Shpacovitch V, Rattenholl A, Maaser C, Luger TA, Steinhoff M, Schneider SW. Tumor-derived matrix metalloproteinase-1 targets endothelial proteinase-activated receptor 1 promoting endothelial cell activation. Cancer Res. 2006; 66:7766–7774. [PubMed: 16885380]

Goodall S, Crowther M, Hemingway DM, Bell PR, Thompson MM. Ubiquitous elevation of matrix metalloproteinase-2 expression in the vasculature of patients with abdominal aneurysms. Circulation. 2001; 104:304–309. [PubMed: 11457749]

Gooljarsingh LT, Lakdawala A, Coppo F, Luo L, Fields GB, Tummino PJ, Gontarek RR. Characterization of an exosite binding inhibitor of matrix metalloproteinase 13. Protein Sci. 2008; 17:66–71. [PubMed: 18042679]

Grams F, Brandstetter H, D'Alo S, Geppert D, Krell HW, Leinert H, Livi V, Menta E, Oliva A, Zimmermann G, Gram F, Livi VE. Pyrimidine-2,4,6-Triones: a new effective and selective class of matrix metalloproteinase inhibitors. Biol Chem. 2001; 382:1277–1285. [PubMed: 11592410]

Grandas OH, Mountain DH, Kirkpatrick SS, Cassada DC, Stevens SL, Freeman MB, Goldman MH. Regulation of vascular smooth muscle cell expression and function of matrix metalloproteinases is mediated by estrogen and progesterone exposure. J Vasc Surg. 2009; 49:185–191. [PubMed: 18829229]

Gross J, Lapiere CM. Collagenolytic activity in amphibian tissues: a tissue culture assay. Proc Natl Acad Sci U S A. 1962; 48:1014–1022. [PubMed: 13902219]

Gu Z, Cui J, Brown S, Fridman R, Mobashery S, Strongin AY, Lipton SA. A highly specific inhibitor of matrix metalloproteinase-9 rescues laminin from proteolysis and neurons from apoptosis in transient focal cerebral ischemia. J Neurosci. 2005; 25:6401–6408. [PubMed: 16000631]

Gu Z, Kaul M, Yan B, Kridel SJ, Cui J, Strongin A, Smith JW, Liddington RC, Lipton SA. S-nitrosylation of matrix metalloproteinases: signaling pathway to neuronal cell death. Science. 2002; 297:1186–1190. [PubMed: 12183632]

Guo H, Lee JD, Uzui H, Toyoda K, Geshi T, Yue H, Ueda T. Effects of copper and zinc on the production of homocysteine-induced extracellular matrix metalloproteinase-2 in cultured rat vascular smooth muscle cells. Acta Cardiol. 2005; 60:353–359. [PubMed: 16128366]

Guo RW, Yang LX, Wang H, Liu B, Wang L. Angiotensin II induces matrix metalloproteinase-9 expression via a nuclear factor-kappaB-dependent pathway in vascular smooth muscle cells. Regul Pept. 2008; 147:37–44. [PubMed: 18252266]

Guo YH, Gao W, Li Q, Li PF, Yao PY, Chen K. Tissue inhibitor of metalloproteinases-4 suppresses vascular smooth muscle cell migration and induces cell apoptosis. Life Sci. 2004; 75:2483–2493. [PubMed: 15350823]

Guo Z, Sun X, He Z, Jiang Y, Zhang X. Role of matrix metalloproteinase-9 in apoptosis of hippocampal neurons in rats during early brain injury after subarachnoid hemorrhage. Neurol Sci. 31:143–149. [PubMed: 20033829]

Gupta K, Shukla M, Cowland JB, Malemud CJ, Haqqi TM. Neutrophil gelatinase-associated lipocalin is expressed in osteoarthritis and forms a complex with matrix metalloproteinase 9. Arthritis Rheum. 2007; 56:3326–3335. [PubMed: 17907186]

Hackmann AE, Rubin BG, Sanchez LA, Geraghty PA, Thompson RW, Curci JA. A randomized, placebo-controlled trial of doxycycline after endoluminal aneurysm repair. J Vasc Surg. 2008; 48:519–526. discussion 526. [PubMed: 18632241]

Hamilton JR, Nguyen PB, Cocks TM. Atypical protease-activated receptor mediates endothelium-dependent relaxation of human coronary arteries. Circ Res. 1998; 82:1306–1311. [PubMed: 9648727]

Handsley MM, Edwards DR. Metalloproteinases and their inhibitors in tumor angiogenesis. Int J Cancer. 2005; 115:849–860. [PubMed: 15729716]

Hao L, Du M, Lopez-Campistrous A, Fernandez-Patron C. Agonist-induced activation of matrix metalloproteinase-7 promotes vasoconstriction through the epidermal growth factor-receptor pathway. Circ Res. 2004; 94:68–76. [PubMed: 14656925]

Haque NS, Fallon JT, Pan JJ, Taubman MB, Harpel PC. Chemokine receptor-8 (CCR8) mediates human vascular smooth muscle cell chemotaxis and metalloproteinase-2 secretion. Blood. 2004; 103:1296–1304. [PubMed: 14576057]

Harvey MB, Leco KJ, Arcellana-Panlilio MY, Zhang X, Edwards DR, Schultz GA. Proteinase expression in early mouse embryos is regulated by leukaemia inhibitory factor and epidermal growth factor. Development. 1995; 121:1005–1014. [PubMed: 7743917]

Haviarova Z, Weismann P, Stvrtinova V, Benuska J. The determination of the collagen and elastin amount in the human varicose vein by the computer morphometric method. Gen Physiol Biophys. 1999; 18(Suppl 1):30–33. [PubMed: 10707829]

Hawinkels LJ, Kuiper P, Wiercinska E, Verspaget HW, Liu Z, Pardali E, Sier CF, ten Dijke P. Matrix metalloproteinase-14 (MT1-MMP)-mediated endoglin shedding inhibits tumor angiogenesis. Cancer Res. 70:4141–4150. [PubMed: 20424116]

Heo SH, Choi YJ, Ryoo HM, Cho JY. Expression profiling of ETS and MMP factors in VEGF-activated endothelial cells: role of MMP-10 in VEGF-induced angiogenesis. J Cell Physiol. 224:734–742. [PubMed: 20432469]

Herman MP, Sukhova GK, Kisiel W, Foster D, Kehry MR, Libby P, Schonbeck U. Tissue factor pathway inhibitor-2 is a novel inhibitor of matrix metalloproteinases with implications for atherosclerosis. J Clin Invest. 2001; 107:1117–1126. [PubMed: 11342575]

Herouy Y, May AE, Pornschlegel G, Stetter C, Grenz H, Preissner KT, Schopf E, Norgauer J, Vanscheidt W. Lipodermatosclerosis is characterized by elevated expression and activation of matrix metalloproteinases: implications for venous ulcer formation. J Invest Dermatol. 1998; 111:822–827. [PubMed: 9804345]

Herouy Y, Nockowski P, Schopf E, Norgauer J. Lipodermatosclerosis and the significance of proteolytic remodeling in the pathogenesis of venous ulceration (Review). Int J Mol Med. 1999; 3:511–515. [PubMed: 10202183]

Higashi S, Miyazaki K. Novel processing of beta-amyloid precursor protein catalyzed by membrane type 1 matrix metalloproteinase releases a fragment lacking the inhibitor domain against gelatinase A. Biochemistry. 2003; 42:6514–6526. [PubMed: 12767235]

Hinterseher I, Bergert H, Kuhlisch E, Bloomenthal A, Pilarsky C, Ockert D, Schellong S, Saeger HD, Krex D. Matrix metalloproteinase 2 polymorphisms in a caucasian population with abdominal aortic aneurysm. J Surg Res. 2006; 133:121–128. [PubMed: 16458924]

Hoffman A, Qadri B, Frant J, Katz Y, Bhusare SR, Breuer E, Hadar R, Reich R. Carbamoylphosphonate matrix metalloproteinase inhibitors 6: cis-2-aminocyclohexylcarbamoylphosphonic acid, a novel orally active antimetastatic matrix metalloproteinase-2 selective inhibitor--synthesis and pharmacodynamic and pharmacokinetic analysis. J Med Chem. 2008; 51:1406–1414. [PubMed: 18257543]

Hollenbeck ST, Sakakibara K, Faries PL, Workhu B, Liu B, Kent KC. Stem cell factor and c-kit are expressed by and may affect vascular SMCs through an autocrine pathway. J Surg Res. 2004; 120:288–294. [PubMed: 15234225]

Holmbeck K, Bianco P, Caterina J, Yamada S, Kromer M, Kuznetsov SA, Mankani M, Robey PG, Poole AR, Pidoux I, Ward JM, Birkedal-Hansen H. MT1-MMP-deficient mice develop dwarfism, osteopenia, arthritis, and connective tissue disease due to inadequate collagen turnover. Cell. 1999; 99:81–92. [PubMed: 10520996]

Hou P, Troen T, Ovejero MC, Kirkegaard T, Andersen TL, Byrjalsen I, Ferreras M, Sato T, Shapiro SD, Foged NT, Delaisse JM. Matrix metalloproteinase-12 (MMP-12) in osteoclasts: new lesson on the involvement of MMPs in bone resorption. Bone. 2004; 34:37–47. [PubMed: 14751561]

Hovsepian DM, Ziporin SJ, Sakurai MK, Lee JK, Curci JA, Thompson RW. Elevated plasma levels of matrix metalloproteinase-9 in patients with abdominal aortic aneurysms: a circulating marker of degenerative aneurysm disease. J Vasc Interv Radiol. 2000; 11:1345–1352. [PubMed: 11099248]

Hu Y, Xiang JS, DiGrandi MJ, Du X, Ipek M, Laakso LM, Li J, Li W, Rush TS, Schmid J, Skotnicki JS, Tam S, Thomason JR, Wang Q, Levin JI. Potent, selective, and orally bioavailable matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis. Bioorg Med Chem. 2005; 13:6629–6644. [PubMed: 16216515]

Hurst DR, Schwartz MA, Jin Y, Ghaffari MA, Kozarekar P, Cao J, Sang QX. Inhibition of enzyme activity of and cell-mediated substrate cleavage by membrane type 1 matrix metalloproteinase by newly developed mercaptosulphide inhibitors. Biochem J. 2005; 392:527–536. [PubMed: 16026329]

Husslein H, Haider S, Meinhardt G, Prast J, Sonderegger S, Knofler M. Expression, regulation and functional characterization of matrix metalloproteinase-3 of human trophoblast. Placenta. 2009; 30:284–291. [PubMed: 19155066]

Huxley-Jones J, Clarke TK, Beck C, Toubaris G, Robertson DL, Boot-Handford RP. The evolution of the vertebrate metzincins; insights from Ciona intestinalis and Danio rerio. BMC Evol Biol. 2007; 7:63. [PubMed: 17439641]

Ikeda U, Shimada K. Matrix metalloproteinases and coronary artery diseases. Clin Cardiol. 2003; 26:55–59. [PubMed: 12625594]

Ikonomidis JS, Jones JA, Barbour JR, Stroud RE, Clark LL, Kaplan BS, Zeeshan A, Bavaria JE, Gorman JH 3rd, Spinale FG, Gorman RC. Expression of matrix metalloproteinases and endogenous inhibitors within ascending aortic aneurysms of patients with bicuspid or tricuspid aortic valves. J Thorac Cardiovasc Surg. 2007; 133:1028–1036. [PubMed: 17382648]

Ilic D, Almeida EA, Schlaepfer DD, Dazin P, Aizawa S, Damsky CH. Extracellular matrix survival signals transduced by focal adhesion kinase suppress p53-mediated apoptosis. J Cell Biol. 1998; 143:547–560. [PubMed: 9786962]

Imai K, Hiramatsu A, Fukushima D, Pierschbacher MD, Okada Y. Degradation of decorin by matrix metalloproteinases: identification of the cleavage sites, kinetic analyses and transforming growth factor-beta1 release. Biochem J. 1997; 322 (Pt 3):809–814. [PubMed: 9148753]

Inoue S, Nakazawa T, Cho A, Dastvan F, Shilling D, Daum G, Reidy M. Regulation of arterial lesions in mice depends on differential smooth muscle cell migration: a role for sphingosine-1-phosphate receptors. J Vasc Surg. 2007; 46:756–763. [PubMed: 17903653]

Islam MM, Franco CD, Courtman DW, Bendeck MP. A nonantibiotic chemically modified tetracycline (CMT-3) inhibits intimal thickening. Am J Pathol. 2003; 163:1557–1566. [PubMed: 14507662]

Itoh Y, Takamura A, Ito N, Maru Y, Sato H, Suenaga N, Aoki T, Seiki M. Homophilic complex formation of MT1-MMP facilitates proMMP-2 activation on the cell surface and promotes tumor cell invasion. EMBO J. 2001; 20:4782–4793. [PubMed: 11532942]

Jacob-Ferreira AL, Palei AC, Cau SB, Moreno H Jr, Martinez ML, Izidoro-Toledo TC, Gerlach RF, Tanus-Santos JE. Evidence for the involvement of matrix metalloproteinases in the cardiovascular effects produced by nicotine. Eur J Pharmacol. 627:216–222. [PubMed: 19879865]

Jacob MP. Extracellular matrix remodeling and matrix metalloproteinases in the vascular wall during aging and in pathological conditions. Biomed Pharmacother. 2003; 57:195–202. [PubMed: 12888254]

Jacob MP, Cazaubon M, Scemama A, Prie D, Blanchet F, Guillin MC, Michel JB. Plasma matrix metalloproteinase-9 as a marker of blood stasis in varicose veins. Circulation. 2002; 106:535–538. [PubMed: 12147532]

Jacobsen FE, Lewis JA, Cohen SM. A new role for old ligands: discerning chelators for zinc metalloproteinases. J Am Chem Soc. 2006; 128:3156–3157. [PubMed: 16522091]

Jacobsen FE, Lewis JA, Cohen SM. The design of inhibitors for medicinally relevant metalloproteins. ChemMedChem. 2007; 2:152–171. [PubMed: 17163561]

Jacobsen J, Visse R, Sorensen HP, Enghild JJ, Brew K, Wewer UM, Nagase H. Catalytic properties of ADAM12 and its domain deletion mutants. Biochemistry. 2008; 47:537–547. [PubMed: 18081311]

Jacobsen JA, Major Jourden JL, Miller MT, Cohen SM. To bind zinc or not to bind zinc: an examination of innovative approaches to improved metalloproteinase inhibition. Biochim Biophys Acta. 1803:72–94. [PubMed: 19712708]

Jadhav V, Yamaguchi M, Obenaus A, Zhang JH. Matrix metalloproteinase inhibition attenuates brain edema after surgical brain injury. Acta Neurochir Suppl. 2008; 102:357–361. [PubMed: 19388345]

Jeyabalan A, Kerchner LJ, Fisher MC, McGuane JT, Doty KD, Conrad KP. Matrix metalloproteinase-2 activity, protein, mRNA, and tissue inhibitors in small arteries from pregnant and relaxin-treated nonpregnant rats. J Appl Physiol. 2006; 100:1955–1963. [PubMed: 16484357]

Jeyabalan A, Novak J, Doty KD, Matthews J, Fisher MC, Kerchner LJ, Conrad KP. Vascular matrix metalloproteinase-9 mediates the inhibition of myogenic reactivity in small arteries isolated from

rats after short-term administration of relaxin. Endocrinology. 2007; 148:189–197. [PubMed: 17053025]

Jin UH, Kang SK, Suh SJ, Hong SY, Park SD, Kim DW, Chang HW, Son JK, Lee SH, Son KH, Kim CH. Inhibitory effect of Salvia miltiorrhia BGE on matrix metalloproteinase-9 activity and migration of TNF-alpha-induced human aortic smooth muscle cells. Vascul Pharmacol. 2006a; 44:345–353. [PubMed: 16540379]

Jin UH, Suh SJ, Chang HW, Son JK, Lee SH, Son KH, Chang YC, Kim CH. Tanshinone IIA from Salvia miltiorrhiza BUNGE inhibits human aortic smooth muscle cell migration and MMP-9 activity through AKT signaling pathway. J Cell Biochem. 2008; 104:15–26. [PubMed: 17979138]

Jin X, Yagi M, Akiyama N, Hirosaki T, Higashi S, Lin CY, Dickson RB, Kitamura H, Miyazaki K. Matriptase activates stromelysin (MMP-3) and promotes tumor growth and angiogenesis. Cancer Sci. 2006b; 97:1327–1334. [PubMed: 16999819]

Johnson AR, Pavlovsky AG, Ortwine DF, Prior F, Man CF, Bornemeier DA, Banotai CA, Mueller WT, McConnell P, Yan C, Baragi V, Lesch C, Roark WH, Wilson M, Datta K, Guzman R, Han HK, Dyer RD. Discovery and characterization of a novel inhibitor of matrix metalloprotease-13 that reduces cartilage damage in vivo without joint fibroplasia side effects. J Biol Chem. 2007; 282:27781–27791. [PubMed: 17623656]

Johnson C, Galis ZS. Matrix metalloproteinase-2 and -9 differentially regulate smooth muscle cell migration and cell-mediated collagen organization. Arterioscler Thromb Vasc Biol. 2004; 24:54–60. [PubMed: 14551157]

Johnson JL. Matrix metalloproteinases: influence on smooth muscle cells and atherosclerotic plaque stability. Expert Rev Cardiovasc Ther. 2007; 5:265–282. [PubMed: 17338671]

Johnson JL, George SJ, Newby AC, Jackson CL. Divergent effects of matrix metalloproteinases 3, 7, 9, and 12 on atherosclerotic plaque stability in mouse brachiocephalic arteries. Proc Natl Acad Sci U S A. 2005; 102:15575–15580. [PubMed: 16221765]

Jones CB, Sane DC, Herrington DM. Matrix metalloproteinases: a review of their structure and role in acute coronary syndrome. Cardiovasc Res. 2003a; 59:812–823. [PubMed: 14553821]

Jones GT, Phillips VL, Harris EL, Rossaak JI, van Rij AM. Functional matrix metalloproteinase-9 polymorphism (C-1562T) associated with abdominal aortic aneurysm. J Vasc Surg. 2003b; 38:1363–1367. [PubMed: 14681642]

Jones JA, Ruddy JM, Bouges S, Zavadzkas JA, Brinsa TA, Stroud RE, Mukherjee R, Spinale FG, Ikonomidis JS. Alterations in membrane type-1 matrix metalloproteinase abundance after the induction of thoracic aortic aneurysm in a murine model. Am J Physiol Heart Circ Physiol. 299:H114–124. [PubMed: 20418476]

Jones RL, Findlay JK, Salamonsen LA. The role of activins during decidualisation of human endometrium. Aust N Z J Obstet Gynaecol. 2006; 46:245–249. [PubMed: 16704482]

Kadoglou NP, Daskalopoulou SS, Perrea D, Liapis CD. Matrix metalloproteinases and diabetic vascular complications. Angiology. 2005; 56:173–189. [PubMed: 15793607]

Kargiotis O, Chetty C, Gondi CS, Tsung AJ, Dinh DH, Gujrati M, Lakka SS, Kyritsis AP, Rao JS. Adenovirus-mediated transfer of siRNA against MMP-2 mRNA results in impaired invasion and tumor-induced angiogenesis, induces apoptosis in vitro and inhibits tumor growth in vivo in glioblastoma. Oncogene. 2008; 27:4830–4840. [PubMed: 18438431]

Kashiwagi M, Tortorella M, Nagase H, Brew K. TIMP-3 is a potent inhibitor of aggrecanase 1 (ADAM-TS4) and aggrecanase 2 (ADAM-TS5). J Biol Chem. 2001; 276:12501–12504. [PubMed: 11278243]

Kelly BA, Bond BC, Poston L. Gestational profile of matrix metalloproteinases in rat uterine artery. Mol Hum Reprod. 2003; 9:351–358. [PubMed: 12771236]

Kelly D, Cockerill G, Ng LL, Thompson M, Khan S, Samani NJ, Squire IB. Plasma matrix metalloproteinase-9 and left ventricular remodelling after acute myocardial infarction in man: a prospective cohort study. Eur Heart J. 2007; 28:711–718. [PubMed: 17339265]

Kelly D, Khan SQ, Thompson M, Cockerill G, Ng LL, Samani N, Squire IB. Plasma tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9: novel indicators of left ventricular

remodelling and prognosis after acute myocardial infarction. Eur Heart J. 2008; 29:2116–2124. [PubMed: 18614523]

Kenagy RD, Vergel S, Mattsson E, Bendeck M, Reidy MA, Clowes AW. The role of plasminogen, plasminogen activators, and matrix metalloproteinases in primate arterial smooth muscle cell migration. Arterioscler Thromb Vasc Biol. 1996; 16:1373–1382. [PubMed: 8911276]

Kerkela E, Bohling T, Herva R, Uria JA, Saarialho-Kere U. Human macrophage metalloelastase (MMP-12) expression is induced in chondrocytes during fetal development and malignant transformation. Bone. 2001; 29:487–493. [PubMed: 11704502]

Kester WR, Matthews BW. Crystallographic study of the binding of dipeptide inhibitors to thermolysin: implications for the mechanism of catalysis. Biochemistry. 1977; 16:2506–2516. [PubMed: 861218]

Kevorkian L, Young DA, Darrah C, Donell ST, Shepstone L, Porter S, Brockbank SM, Edwards DR, Parker AE, Clark IM. Expression profiling of metalloproteinases and their inhibitors in cartilage. Arthritis Rheum. 2004; 50:131–141. [PubMed: 14730609]

Khatri JJ, Johnson C, Magid R, Lessner SM, Laude KM, Dikalov SI, Harrison DG, Sung HJ, Rong Y, Galis ZS. Vascular oxidant stress enhances progression and angiogenesis of experimental atheroma. Circulation. 2004; 109:520–525. [PubMed: 14744973]

Kim SH, Pudzianowski AT, Leavitt KJ, Barbosa J, McDonnell PA, Metzler WJ, Rankin BM, Liu R, Vaccaro W, Pitts W. Structure-based design of potent and selective inhibitors of collagenase-3 (MMP-13). Bioorg Med Chem Lett. 2005; 15:1101–1106. [PubMed: 15686921]

Knauper V, Will H, Lopez-Otin C, Smith B, Atkinson SJ, Stanton H, Hembry RM, Murphy G. Cellular mechanisms for human procollagenase-3 (MMP-13) activation. Evidence that MT1-MMP (MMP-14) and gelatinase a (MMP-2) are able to generate active enzyme. J Biol Chem. 1996; 271:17124–17131. [PubMed: 8663255]

Kockx MM, Knaapen MW, Bortier HE, Cromheeke KM, Boutherin-Falson O, Finet M. Vascular remodeling in varicose veins. Angiology. 1998; 49:871–877. [PubMed: 9822042]

Koike Y, Shima F, Nakamizo A, Miyagi Y. Direct localization of subthalamic nucleus supplemented by single-track electrophysiological guidance in deep brain stimulation lead implantation: techniques and clinical results. Stereotact Funct Neurosurg. 2008; 86:173–178. [PubMed: 18334860]

Koskivirta I, Rahkonen O, Mayranpaa M, Pakkanen S, Husheem M, Sainio A, Hakovirta H, Laine J, Jokinen E, Vuorio E, Kovanen P, Jarvelainen H. Tissue inhibitor of metalloproteinases 4 (TIMP4) is involved in inflammatory processes of human cardiovascular pathology. Histochem Cell Biol. 2006; 126:335–342. [PubMed: 16521002]

Kosugi I, Urayama H, Kasashima F, Ohtake H, Watanabe Y. Matrix metalloproteinase-9 and urokinase-type plasminogen activator in varicose veins. Ann Vasc Surg. 2003; 17:234–238. [PubMed: 12704537]

Kowalewski R, Sobolewski K, Wolanska M, Gacko M. Matrix metalloproteinases in the vein wall. Int Angiol. 2004; 23:164–169. [PubMed: 15507895]

Kruger A, Arlt MJ, Gerg M, Kopitz C, Bernardo MM, Chang M, Mobashery S, Fridman R. Antimetastatic activity of a novel mechanism-based gelatinase inhibitor. Cancer Res. 2005; 65:3523–3526. [PubMed: 15867341]

Kudo T, Takino T, Miyamori H, Thompson EW, Sato H. Substrate choice of membrane-type 1 matrix metalloproteinase is dictated by tissue inhibitor of metalloproteinase-2 levels. Cancer Sci. 2007; 98:563–568. [PubMed: 17425593]

Kwan JA, Schulze CJ, Wang W, Leon H, Sariahmetoglu M, Sung M, Sawicka J, Sims DE, Sawicki G, Schulz R. Matrix metalloproteinase-2 (MMP-2) is present in the nucleus of cardiac myocytes and is capable of cleaving poly (ADP-ribose) polymerase (PARP) in vitro. FASEB J. 2004; 18:690–692. [PubMed: 14766804]

Lavee M, Goldman S, Daniel-Spiegel E, Shalev E. Matrix metalloproteinase-2 is elevated in midtrimester amniotic fluid prior to the development of preeclampsia. Reprod Biol Endocrinol. 2009; 7:85. [PubMed: 19698156]

Laviades C, Varo N, Fernandez J, Mayor G, Gil MJ, Monreal I, Diez J. Abnormalities of the extracellular degradation of collagen type I in essential hypertension. Circulation. 1998; 98:535–540. [PubMed: 9714110]

Leco KJ, Waterhouse P, Sanchez OH, Gowing KL, Poole AR, Wakeham A, Mak TW, Khokha R. Spontaneous air space enlargement in the lungs of mice lacking tissue inhibitor of metalloproteinases-3 (TIMP-3). J Clin Invest. 2001; 108:817–829. [PubMed: 11560951]

Ledgard AM, Lee RS, Peterson AJ. Bovine endometrial legumain and TIMP-2 regulation in response to presence of a conceptus. Mol Reprod Dev. 2009; 76:65–74. [PubMed: 18449874]

Ledour G, Moroy G, Rouffet M, Bourguet E, Guillaume D, Decarme M, Elmourabit H, Auge F, Alix AJ, Laronze JY, Bellon G, Hornebeck W, Sapi J. Introduction of the 4-(4-bromophenyl)benzenesulfonyl group to hydrazide analogs of Ilomastat leads to potent gelatinase B (MMP-9) inhibitors with improved selectivity. Bioorg Med Chem. 2008; 16:8745–8759. [PubMed: 18782669]

Lee HY, You HJ, Won JY, Youn SW, Cho HJ, Park KW, Park WY, Seo JS, Park YB, Walsh K, Oh BH, Kim HS. Forkhead factor, FOXO3a, induces apoptosis of endothelial cells through activation of matrix metalloproteinases. Arterioscler Thromb Vasc Biol. 2008; 28:302–308. [PubMed: 18063811]

Lee M, Bernardo MM, Meroueh SO, Brown S, Fridman R, Mobashery S. Synthesis of chiral 2-(4-phenoxyphenylsulfonylmethyl)thiiranes as selective gelatinase inhibitors. Org Lett. 2005; 7:4463–4465. [PubMed: 16178559]

Lee M, Celenza G, Boggess B, Blase J, Shi Q, Toth M, Bernardo MM, Wolter WR, Suckow MA, Hesek D, Noll BC, Fridman R, Mobashery S, Chang M. A potent gelatinase inhibitor with anti-tumor-invasive activity and its metabolic disposition. Chem Biol Drug Des. 2009a; 73:189–202. [PubMed: 19207421]

Lee M, Villegas-Estrada A, Celenza G, Boggess B, Toth M, Kreitinger G, Forbes C, Fridman R, Mobashery S, Chang M. Metabolism of a highly selective gelatinase inhibitor generates active metabolite. Chem Biol Drug Des. 2007; 70:371–382. [PubMed: 17927722]

Lee YH, Kim TY, Hong YM. Metalloproteinase-3 genotype as a predictor of cardiovascular risk in hypertensive adolescents. Korean Circ J. 2009b; 39:328–334. [PubMed: 19949639]

Lee YJ, Kim JS, Kang DG, Lee HS. Buddleja officinalis suppresses high glucose-induced vascular smooth muscle cell proliferation: role of mitogen-activated protein kinases, nuclear factor-kappaB and matrix metalloproteinases. Exp Biol Med (Maywood). 235:247–255. [PubMed: 20404041]

Lemaitre V, O'Byrne TK, Borczuk AC, Okada Y, Tall AR, D'Armiento J. ApoE knockout mice expressing human matrix metalloproteinase-1 in macrophages have less advanced atherosclerosis. J Clin Invest. 2001; 107:1227–1234. [PubMed: 11375412]

Lemaitre V, Soloway PD, D'Armiento J. Increased medial degradation with pseudo-aneurysm formation in apolipoprotein E-knockout mice deficient in tissue inhibitor of metalloproteinases-1. Circulation. 2003; 107:333–338. [PubMed: 12538437]

Levi E, Fridman R, Miao HQ, Ma YS, Yayon A, Vlodavsky I. Matrix metalloproteinase 2 releases active soluble ectodomain of fibroblast growth factor receptor 1. Proc Natl Acad Sci U S A. 1996; 93:7069–7074. [PubMed: 8692946]

Levkau B, Kenagy RD, Karsan A, Weitkamp B, Clowes AW, Ross R, Raines EW. Activation of metalloproteinases and their association with integrins: an auxiliary apoptotic pathway in human endothelial cells. Cell Death Differ. 2002; 9:1360–1367. [PubMed: 12478473]

Li J, Rush TS 3rd, Li W, DeVincentis D, Du X, Hu Y, Thomason JR, Xiang JS, Skotnicki JS, Tam S, Cunningham KM, Chockalingam PS, Morris EA, Levin JI. Synthesis and SAR of highly selective MMP-13 inhibitors. Bioorg Med Chem Lett. 2005; 15:4961–4966. [PubMed: 16153831]

Li JJ, Nahra J, Johnson AR, Bunker A, O'Brien P, Yue WS, Ortwine DF, Man CF, Baragi V, Kilgore K, Dyer RD, Han HK. Quinazolinones and pyrido[3,4-d]pyrimidin-4-ones as orally active and specific matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis. J Med Chem. 2008; 51:835–841. [PubMed: 18251495]

Li W, Li J, Wu Y, Wu J, Hotchandani R, Cunningham K, McFadyen I, Bard J, Morgan P, Schlerman F, Xu X, Tam S, Goldman SJ, Williams C, Sypek J, Mansour TS. A selective matrix metalloprotease 12 inhibitor for potential treatment of chronic obstructive pulmonary disease (COPD): discovery of (S)-2-(8-(methoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbu tanoic acid (MMP408). J Med Chem. 2009; 52:1799–1802. [PubMed: 19278250]

Lijnen HR, Van Hoef B, Vanlinthout I, Verstreken M, Rio MC, Collen D. Accelerated neointima formation after vascular injury in mice with stromelysin-3 (MMP-11) gene inactivation. Arterioscler Thromb Vasc Biol. 1999; 19:2863–2870. [PubMed: 10591662]

Lin J, Davis HB, Dai Q, Chou YM, Craig T, Hinojosa-Laborde C, Lindsey ML. Effects of early and late chronic pressure overload on extracellular matrix remodeling. Hypertens Res. 2008; 31:1225–1231. [PubMed: 18716372]

Lindeman JH, Abdul-Hussien H, van Bockel JH, Wolterbeek R, Kleemann R. Clinical trial of doxycycline for matrix metalloproteinase-9 inhibition in patients with an abdominal aneurysm: doxycycline selectively depletes aortic wall neutrophils and cytotoxic T cells. Circulation. 2009; 119:2209–2216. [PubMed: 19364980]

Lischper M, Beuck S, Thanabalasundaram G, Pieper C, Galla HJ. Metalloproteinase mediated occludin cleavage in the cerebral microcapillary endothelium under pathological conditions. Brain Res. 1326:114–127. [PubMed: 20197061]

Liu G, Zhang X, Lin H, Li Q, Wang H, Ni J, Amy Sang QX, Zhu C. Expression of matrix metalloproteinase-26 (MMP-26) mRNA in mouse uterus during the estrous cycle and early pregnancy. Life Sci. 2005; 77:3355–3365. [PubMed: 15987643]

Liu Z, Zhou X, Shapiro SD, Shipley JM, Twining SS, Diaz LA, Senior RM, Werb Z. The serpin alpha1-proteinase inhibitor is a critical substrate for gelatinase B/MMP-9 in vivo. Cell. 2000; 102:647–655. [PubMed: 11007483]

Lohi J, Wilson CL, Roby JD, Parks WC. Epilysin, a novel human matrix metalloproteinase (MMP-28) expressed in testis and keratinocytes and in response to injury. J Biol Chem. 2001; 276:10134–10144. [PubMed: 11121398]

Longo GM, Xiong W, Greiner TC, Zhao Y, Fiotti N, Baxter BT. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. J Clin Invest. 2002; 110:625–632. [PubMed: 12208863]

Lopez-Candales A, Holmes DR, Liao S, Scott MJ, Wickline SA, Thompson RW. Decreased vascular smooth muscle cell density in medial degeneration of human abdominal aortic aneurysms. Am J Pathol. 1997; 150:993–1007. [PubMed: 9060837]

Louboutin JP, Agrawal L, Reyes BA, Van Bockstaele EJ, Strayer DS. HIV-1 gp120-induced injury to the blood-brain barrier: role of metalloproteinases 2 and 9 and relationship to oxidative stress. J Neuropathol Exp Neurol. 69:801–816. [PubMed: 20613638]

Lovdahl C, Thyberg J, Hultgardh-Nilsson A. The synthetic metalloproteinase inhibitor batimastat suppresses injury-induced phosphorylation of MAP kinase ERK1/ERK2 and phenotypic modification of arterial smooth muscle cells in vitro. J Vasc Res. 2000; 37:345–354. [PubMed: 11025397]

Lovejoy B, Hassell AM, Luther MA, Weigl D, Jordan SR. Crystal structures of recombinant 19-kDa human fibroblast collagenase complexed to itself. Biochemistry. 1994; 33:8207–8217. [PubMed: 8031754]

Lovejoy B, Welch AR, Carr S, Luong C, Broka C, Hendricks RT, Campbell JA, Walker KA, Martin R, Van Wart H, Browner MF. Crystal structures of MMP-1 and -13 reveal the structural basis for selectivity of collagenase inhibitors. Nat Struct Biol. 1999; 6:217–221. [PubMed: 10074939]

Lucchesi PA, Sabri A, Belmadani S, Matrougui K. Involvement of metalloproteinases 2/9 in epidermal growth factor receptor transactivation in pressure-induced myogenic tone in mouse mesenteric resistance arteries. Circulation. 2004; 110:3587–3593. [PubMed: 15557365]

Luttun A, Lutgens E, Manderveld A, Maris K, Collen D, Carmeliet P, Moons L. Loss of matrix metalloproteinase-9 or matrix metalloproteinase-12 protects apolipoprotein E-deficient mice against atherosclerotic media destruction but differentially affects plaque growth. Circulation. 2004; 109:1408–1414. [PubMed: 14993123]

Macfarlane SR, Seatter MJ, Kanke T, Hunter GD, Plevin R. Proteinase-activated receptors. Pharmacol Rev. 2001; 53:245–282. [PubMed: 11356985]

Malik MT, Kakar SS. Regulation of angiogenesis and invasion by human Pituitary tumor transforming gene (PTTG) through increased expression and secretion of matrix metalloproteinase-2 (MMP-2). Mol Cancer. 2006; 5:61. [PubMed: 17096843]

Manes S, Mira E, Barbacid MM, Cipres A, Fernandez-Resa P, Buesa JM, Merida I, Aracil M, Marquez G, Martinez AC. Identification of insulin-like growth factor-binding protein-1 as a potential physiological substrate for human stromelysin-3. J Biol Chem. 1997; 272:25706–25712. [PubMed: 9325295]

Mannello F, Luchetti F, Falcieri E, Papa S. Multiple roles of matrix metalloproteinases during apoptosis. Apoptosis. 2005; 10:19–24. [PubMed: 15711919]

Manning MW, Cassis LA, Daugherty A. Differential effects of doxycycline, a broad-spectrum matrix metalloproteinase inhibitor, on angiotensin II-induced atherosclerosis and abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol. 2003; 23:483–488. [PubMed: 12615694]

Manzetti S, McCulloch DR, Herington AC, van der Spoel D. Modeling of enzyme-substrate complexes for the metalloproteases MMP-3, ADAM-9 and ADAM-10. J Comput Aided Mol Des. 2003; 17:551–565. [PubMed: 14713188]

Maquoi E, Sounni NE, Devy L, Olivier F, Frankenne F, Krell HW, Grams F, Foidart JM, Noel A. Anti-invasive, antitumoral, and antiangiogenic efficacy of a pyrimidine-2,4,6-trione derivative, an orally active and selective matrix metalloproteinases inhibitor. Clin Cancer Res. 2004; 10:4038–4047. [PubMed: 15217936]

Marchenko GN, Strongin AY. MMP-28, a new human matrix metalloproteinase with an unusual cysteine-switch sequence is widely expressed in tumors. Gene. 2001; 265:87–93. [PubMed: 11255011]

Marchenko ND, Marchenko GN, Weinreb RN, Lindsey JD, Kyshtoobayeva A, Crawford HC, Strongin AY. Beta-catenin regulates the gene of MMP-26, a novel metalloproteinase expressed both in carcinomas and normal epithelial cells. Int J Biochem Cell Biol. 2004; 36:942–956. [PubMed: 15006646]

Matsumura S, Iwanaga S, Mochizuki S, Okamoto H, Ogawa S, Okada Y. Targeted deletion or pharmacological inhibition of MMP-2 prevents cardiac rupture after myocardial infarction in mice. J Clin Invest. 2005; 115:599–609. [PubMed: 15711638]

Matziari M, Beau F, Cuniasse P, Dive V, Yiotakis A. Evaluation of P1'-diversified phosphinic peptides leads to the development of highly selective inhibitors of MMP-11. J Med Chem. 2004; 47:325–336. [PubMed: 14711305]

Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003; 111:649–658. [PubMed: 12618519]

McQuibban GA, Butler GS, Gong JH, Bendall L, Power C, Clark-Lewis I, Overall CM. Matrix metalloproteinase activity inactivates the CXC chemokine stromal cell-derived factor-1. J Biol Chem. 2001; 276:43503–43508. [PubMed: 11571304]

Mendez MV, Raffetto JD, Phillips T, Menzoian JO, Park HY. The proliferative capacity of neonatal skin fibroblasts is reduced after exposure to venous ulcer wound fluid: A potential mechanism for senescence in venous ulcers. J Vasc Surg. 1999; 30:734–743. [PubMed: 10514213]

Merchant SJ, Davidge ST. The role of matrix metalloproteinases in vascular function: implications for normal pregnancy and pre-eclampsia. BJOG. 2004; 111:931–939. [PubMed: 15327607]

Michaelides MR, Dellaria JF, Gong J, Holms JH, Bouska JJ, Stacey J, Wada CK, Heyman HR, Curtin ML, Guo Y, Goodfellow CL, Elmore IB, Albert DH, Magoc TJ, Marcotte PA, Morgan DW, Davidsen SK. Biaryl ether retrohydroxamates as potent, long-lived, orally bioavailable MMP inhibitors. Bioorg Med Chem Lett. 2001; 11:1553–1556. [PubMed: 11412979]

Milner JM, Cawston TE. Matrix metalloproteinase knockout studies and the potential use of matrix metalloproteinase inhibitors in the rheumatic diseases. Curr Drug Targets Inflamm Allergy. 2005; 4:363–375. [PubMed: 16101546]

Mimura T, Han KY, Onguchi T, Chang JH, Kim TI, Kojima T, Zhou Z, Azar DT. MT1-MMP-mediated cleavage of decorin in corneal angiogenesis. J Vasc Res. 2009; 46:541–550. [PubMed: 19571574]

Mishra B, Kizaki K, Koshi K, Ushizawa K, Takahashi T, Hosoe M, Sato T, Ito A, Hashizume K. Expression of extracellular matrix metalloproteinase inducer (EMMPRIN) and its related extracellular matrix degrading enzymes in the endometrium during estrous cycle and early gestation in cattle. Reprod Biol Endocrinol. 8:60. [PubMed: 20540754]

Mix KS, Coon CI, Rosen ED, Suh N, Sporn MB, Brinckerhoff CE. Peroxisome proliferator-activated receptor-gamma-independent repression of collagenase gene expression by 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid and prostaglandin 15-deoxy-delta(12,14) J2: a role for Smad signaling. Mol Pharmacol. 2004; 65:309–318. [PubMed: 14742672]

Moller MN, Werther K, Nalla A, Stangerup SE, Thomsen J, Bog-Hansen TC, Nielsen HJ, Caye-Thomasen P. Angiogenesis in vestibular schwannomas: expression of extracellular matrix factors MMP-2, MMP-9, and TIMP-1. Laryngoscope. 120:657–662. [PubMed: 20205165]

Momohara S, Okamoto H, Komiya K, Ikari K, Takeuchi M, Tomatsu T, Kamatani N. Matrix metalloproteinase 28/epilysin expression in cartilage from patients with rheumatoid arthritis and osteoarthritis: comment on the article by Kevorkian et al. Arthritis Rheum. 2004; 50:4074–4075. author reply 4075. [PubMed: 15593191]

Montagnana M, Lippi G, Albiero A, Scevarolli S, Salvagno GL, Franchi M, Guidi GC. Evaluation of metalloproteinases 2 and 9 and their inhibitors in physiologic and pre-eclamptic pregnancy. J Clin Lab Anal. 2009; 23:88–92. [PubMed: 19288452]

Morales R, Perrier S, Florent JM, Beltra J, Dufour S, De Mendez I, Manceau P, Tertre A, Moreau F, Compere D, Dublanchet AC, O'Gara M. Crystal structures of novel non-peptidic, non-zinc chelating inhibitors bound to MMP-12. J Mol Biol. 2004; 341:1063–1076. [PubMed: 15289103]

Morla AO, Mogford JE. Control of smooth muscle cell proliferation and phenotype by integrin signaling through focal adhesion kinase. Biochem Biophys Res Commun. 2000; 272:298–302. [PubMed: 10872843]

Morrison JF, Walsh CT. The behavior and significance of slow-binding enzyme inhibitors. Adv Enzymol Relat Areas Mol Biol. 1988; 61:201–301. [PubMed: 3281418]

Mosorin M, Juvonen J, Biancari F, Satta J, Surcel HM, Leinonen M, Saikku P, Juvonen T. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. J Vasc Surg. 2001; 34:606–610. [PubMed: 11668312]

Moss ML, Sklair-Tavron L, Nudelman R. Drug insight: tumor necrosis factor-converting enzyme as a pharmaceutical target for rheumatoid arthritis. Nat Clin Pract Rheumatol. 2008; 4:300–309. [PubMed: 18414459]

Mott JD, Thomas CL, Rosenbach MT, Takahara K, Greenspan DS, Banda MJ. Post-translational proteolytic processing of procollagen C-terminal proteinase enhancer releases a metalloproteinase inhibitor. J Biol Chem. 2000; 275:1384–1390. [PubMed: 10625689]

Mott JD, Werb Z. Regulation of matrix biology by matrix metalloproteinases. Curr Opin Cell Biol. 2004; 16:558–564. [PubMed: 15363807]

Mulvany MJ, Baumbach GL, Aalkjaer C, Heagerty AM, Korsgaard N, Schiffrin EL, Heistad DD. Vascular remodeling. Hypertension. 1996; 28:505–506. [PubMed: 8794840]

Murphy G, Houbrechts A, Cockett MI, Williamson RA, O'Shea M, Docherty AJ. The N-terminal domain of tissue inhibitor of metalloproteinases retains metalloproteinase inhibitory activity. Biochemistry. 1991; 30:8097–8102. [PubMed: 1868085]

Murphy G, Nagase H. Progress in matrix metalloproteinase research. Mol Aspects Med. 2008; 29:290–308. [PubMed: 18619669]

Mwaura B, Mahendran B, Hynes N, Defreitas D, Avalos G, Adegbola T, Adham M, Connolly CE, Sultan S. The impact of differential expression of extracellular matrix metalloproteinase inducer, matrix metalloproteinase-2, tissue inhibitor of matrix metalloproteinase-2 and PDGF-AA on the chronicity of venous leg ulcers. Eur J Vasc Endovasc Surg. 2006; 31:306–310. [PubMed: 16169261]

Myers JE, Merchant SJ, Macleod M, Mires GJ, Baker PN, Davidge ST. MMP-2 levels are elevated in the plasma of women who subsequently develop preeclampsia. Hypertens Pregnancy. 2005; 24:103–115. [PubMed: 16036395]

Nagareddy PR, Chow FL, Hao L, Wang X, Nishimura T, MacLeod KM, McNeill JH, Fernandez-Patron C. Maintenance of adrenergic vascular tone by MMP transactivation of the EGFR requires PI3K and mitochondrial ATP synthesis. Cardiovasc Res. 2009; 84:368–377. [PubMed: 19578070]

Nagareddy PR, MacLeod KM, McNeill JH. GPCR agonist-induced transactivation of the EGFR upregulates MLC II expression and promotes hypertension in insulin-resistant rats. Cardiovasc Res. 87:177–186. [PubMed: 20110336]

Nagase H, Fushimi K. Elucidating the function of non catalytic domains of collagenases and aggrecanases. Connect Tissue Res. 2008; 49:169–174. [PubMed: 18661336]

Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res. 2006; 69:562–573. [PubMed: 16405877]

Nagashima H, Aoka Y, Sakomura Y, Sakuta A, Aomi S, Ishizuka N, Hagiwara N, Kawana M, Kasanuki H. A 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, cerivastatin, suppresses production of matrix metalloproteinase-9 in human abdominal aortic aneurysm wall. J Vasc Surg. 2002; 36:158–163. [PubMed: 12096274]

Nakatani S, Ikura M, Yamamoto S, Nishita Y, Itadani S, Habashita H, Sugiura T, Ogawa K, Ohno H, Takahashi K, Nakai H, Toda M. Design and synthesis of novel metalloproteinase inhibitors. Bioorg Med Chem. 2006; 14:5402–5422. [PubMed: 16621578]

Narumiya H, Zhang Y, Fernandez-Patron C, Guilbert LJ, Davidge ST. Matrix metalloproteinase-2 is elevated in the plasma of women with preeclampsia. Hypertens Pregnancy. 2001; 20:185–194. [PubMed: 12044329]

Naruse K, Lash GE, Innes BA, Otun HA, Searle RF, Robson SC, Bulmer JN. Localization of matrix metalloproteinase (MMP)-2, MMP-9 and tissue inhibitors for MMPs (TIMPs) in uterine natural killer cells in early human pregnancy. Hum Reprod. 2009; 24:553–561. [PubMed: 19088110]

Nelson WJ, Nusse R. Convergence of Wnt, beta-catenin, and cadherin pathways. Science. 2004; 303:1483–1487. [PubMed: 15001769]

Newby AC. Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture. Physiol Rev. 2005; 85:1–31. [PubMed: 15618476]

Newsome AL, Johnson JP, Seipelt RL, Thompson MW. Apolactoferrin inhibits the catalytic domain of matrix metalloproteinase-2 by zinc chelation. Biochem Cell Biol. 2007; 85:563–572. [PubMed: 17901898]

Noe V, Fingleton B, Jacobs K, Crawford HC, Vermeulen S, Steelant W, Bruyneel E, Matrisian LM, Mareel M. Release of an invasion promoter E-cadherin fragment by matrilysin and stromelysin-1. J Cell Sci. 2001; 114:111–118. [PubMed: 11112695]

Norgauer J, Hildenbrand T, Idzko M, Panther E, Bandemir E, Hartmann M, Vanscheidt W, Herouy Y. Elevated expression of extracellular matrix metalloproteinase inducer (CD147) and membrane-type matrix metalloproteinases in venous leg ulcers. Br J Dermatol. 2002; 147:1180–1186. [PubMed: 12452868]

Nuti E, Tuccinardi T, Rossello A. Matrix metalloproteinase inhibitors: new challenges in the era of post broad-spectrum inhibitors. Curr Pharm Des. 2007; 13:2087–2100. [PubMed: 17627541]

Ogata Y, Enghild JJ, Nagase H. Matrix metalloproteinase 3 (stromelysin) activates the precursor for the human matrix metalloproteinase 9. J Biol Chem. 1992; 267:3581–3584. [PubMed: 1371271]

Oh C, Dong Y, Liu H, Thompson LP. Intrauterine hypoxia upregulates proinflammatory cytokines and matrix metalloproteinases in fetal guinea pig hearts. Am J Obstet Gynecol. 2008; 199:78 e71–76. [PubMed: 18279828]

Ohuchi E, Imai K, Fujii Y, Sato H, Seiki M, Okada Y. Membrane type 1 matrix metalloproteinase digests interstitial collagens and other extracellular matrix macromolecules. J Biol Chem. 1997; 272:2446–2451. [PubMed: 8999957]

Okamoto T, Akaike T, Nagano T, Miyajima S, Suga M, Ando M, Ichimori K, Maeda H. Activation of human neutrophil procollagenase by nitrogen dioxide and peroxynitrite: a novel mechanism for

procollagenase activation involving nitric oxide. Arch Biochem Biophys. 1997; 342:261–274. [PubMed: 9186487]

Olson MW, Toth M, Gervasi DC, Sado Y, Ninomiya Y, Fridman R. High affinity binding of latent matrix metalloproteinase-9 to the alpha2(IV) chain of collagen IV. J Biol Chem. 1998; 273:10672–10681. [PubMed: 9553130]

Onal IK, Altun B, Onal ED, Kirkpantur A, Gul Oz S, Turgan C. Serum levels of MMP-9 and TIMP-1 in primary hypertension and effect of antihypertensive treatment. Eur J Intern Med. 2009; 20:369–372. [PubMed: 19524176]

Onaran MB, Comeau AB, Seto CT. Squaric acid-based peptidic inhibitors of matrix metalloprotease-1. J Org Chem. 2005; 70:10792–10802. [PubMed: 16356002]

Ozerdem U, Mach-Hofacre B, Varki N, Folberg R, Mueller AJ, Ochabski R, Pham T, Appelt K, Freeman WR. The effect of prinomastat (AG3340), a synthetic inhibitor of matrix metalloproteinases, on uveal melanoma rabbit model. Curr Eye Res. 2002; 24:86–91. [PubMed: 12187478]

Ozkok E, Aydin M, Babalik E, Ozbek Z, Ince N, Kara I. Combined impact of matrix metalloproteinase-3 and paraoxonase 1 55/192 gene variants on coronary artery disease in Turkish patients. Med Sci Monit. 2008; 14:CR536–542. [PubMed: 18830194]

Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol. 2007; 8:221–233. [PubMed: 17318226]

Palei AC, Sandrim VC, Cavalli RC, Tanus-Santos JE. Comparative assessment of matrix metalloproteinase (MMP)-2 and MMP-9, and their inhibitors, tissue inhibitors of metalloproteinase (TIMP)-1 and TIMP-2 in preeclampsia and gestational hypertension. Clin Biochem. 2008; 41:875–880. [PubMed: 18477480]

Palei AC, Sandrim VC, Duarte G, Cavalli RC, Gerlach RF, Tanus-Santos JE. Matrix metalloproteinase (MMP)-9 genotypes and haplotypes in preeclampsia and gestational hypertension. Clin Chim Acta. 411:874–877. [PubMed: 20211160]

Park HI, Ni J, Gerkema FE, Liu D, Belozerov VE, Sang QX. Identification and characterization of human endometase (Matrix metalloproteinase-26) from endometrial tumor. J Biol Chem. 2000; 275:20540–20544. [PubMed: 10801841]

Parks WC, Wilson CL, Lopez-Boado YS. Matrix metalloproteinases as modulators of inflammation and innate immunity. Nat Rev Immunol. 2004; 4:617–629. [PubMed: 15286728]

Parra JR, Cambria RA, Hower CD, Dassow MS, Freischlag JA, Seabrook GR, Towne JB. Tissue inhibitor of metalloproteinase-1 is increased in the saphenofemoral junction of patients with varices in the leg. J Vasc Surg. 1998; 28:669–675. [PubMed: 9786263]

Pascarella L, Penn A, Schmid-Schonbein GW. Venous hypertension and the inflammatory cascade: major manifestations and trigger mechanisms. Angiology. 2005; 56(Suppl 1):S3–10. [PubMed: 16193224]

Patterson ML, Atkinson SJ, Knauper V, Murphy G. Specific collagenolysis by gelatinase A, MMP-2, is determined by the hemopexin domain and not the fibronectin-like domain. FEBS Lett. 2001; 503:158–162. [PubMed: 11513874]

Pawlak K, Pawlak D, Mysliwiec M. Urokinase-type plasminogen activator and metalloproteinase-2 are independently related to the carotid atherosclerosis in haemodialysis patients. Thromb Res. 2008; 121:543–548. [PubMed: 17706748]

Pei D, Kang T, Qi H. Cysteine array matrix metalloproteinase (CA-MMP)/MMP-23 is a type II transmembrane matrix metalloproteinase regulated by a single cleavage for both secretion and activation. J Biol Chem. 2000; 275:33988–33997. [PubMed: 10945999]

Pei D, Weiss SJ. Furin-dependent intracellular activation of the human stromelysin-3 zymogen. Nature. 1995; 375:244–247. [PubMed: 7746327]

Pendas AM, Folgueras AR, Llano E, Caterina J, Frerard F, Rodriguez F, Astudillo A, Noel A, Birkedal-Hansen H, Lopez-Otin C. Diet-induced obesity and reduced skin cancer susceptibility in matrix metalloproteinase 19-deficient mice. Mol Cell Biol. 2004; 24:5304–5313. [PubMed: 15169894]

Pepper MS. Role of the matrix metalloproteinase and plasminogen activator-plasmin systems in angiogenesis. Arterioscler Thromb Vasc Biol. 2001; 21:1104–1117. [PubMed: 11451738]

Petersen E, Gineitis A, Wagberg F, Angquist KA. Activity of matrix metalloproteinase-2 and -9 in abdominal aortic aneurysms. Relation to size and rupture. Eur J Vasc Endovasc Surg. 2000; 20:457–461. [PubMed: 11112465]

Pochetti G, Gavuzzo E, Campestre C, Agamennone M, Tortorella P, Consalvi V, Gallina C, Hiller O, Tschesche H, Tucker PA, Mazza F. Structural insight into the stereoselective inhibition of MMP-8 by enantiomeric sulfonamide phosphonates. J Med Chem. 2006; 49:923–931. [PubMed: 16451058]

Pochetti G, Montanari R, Gege C, Chevrier C, Taveras AG, Mazza F. Extra binding region induced by non-zinc chelating inhibitors into the S1' subsite of matrix metalloproteinase 8 (MMP-8). J Med Chem. 2009; 52:1040–1049. [PubMed: 19173605]

Poon LC, Akolekar R, Lachmann R, Beta J, Nicolaides KH. Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11–13 weeks. Ultrasound Obstet Gynecol. 35:662–670. [PubMed: 20232288]

Poon LC, Nekrasova E, Anastassopoulos P, Livanos P, Nicolaides KH. First-trimester maternal serum matrix metalloproteinase-9 (MMP-9) and adverse pregnancy outcome. Prenat Diagn. 2009; 29:553–559. [PubMed: 19242924]

Prescott MF, Sawyer WK, Von Linden-Reed J, Jeune M, Chou M, Caplan SL, Jeng AY. Effect of matrix metalloproteinase inhibition on progression of atherosclerosis and aneurysm in LDL receptor-deficient mice overexpressing MMP-3, MMP-12, and MMP-13 and on restenosis in rats after balloon injury. Ann N Y Acad Sci. 1999; 878:179–190. [PubMed: 10415729]

Price A, Shi Q, Morris D, Wilcox ME, Brasher PM, Rewcastle NB, Shalinsky D, Zou H, Appelt K, Johnston RN, Yong VW, Edwards D, Forsyth P. Marked inhibition of tumor growth in a malignant glioma tumor model by a novel synthetic matrix metalloproteinase inhibitor AG3340. Clin Cancer Res. 1999; 5:845–854. [PubMed: 10213221]

Puerta DT, Cohen SM. Examination of novel zinc-binding groups for use in matrix metalloproteinase inhibitors. Inorg Chem. 2003; 42:3423–3430. [PubMed: 12767177]

Puerta DT, Griffin MO, Lewis JA, Romero-Perez D, Garcia R, Villarreal FJ, Cohen SM. Heterocyclic zinc-binding groups for use in next-generation matrix metalloproteinase inhibitors: potency, toxicity, and reactivity. J Biol Inorg Chem. 2006; 11:131–138. [PubMed: 16391944]

Puerta DT, Lewis JA, Cohen SM. New beginnings for matrix metalloproteinase inhibitors: identification of high-affinity zinc-binding groups. J Am Chem Soc. 2004; 126:8388–8389. [PubMed: 15237990]

Puerta DT, Mongan J, Tran BL, McCammon JA, Cohen SM. Potent, selective pyrone-based inhibitors of stromelysin-1. J Am Chem Soc. 2005; 127:14148–14149. [PubMed: 16218585]

Pyo R, Lee JK, Shipley JM, Curci JA, Mao D, Ziporin SJ, Ennis TL, Shapiro SD, Senior RM, Thompson RW. Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms. J Clin Invest. 2000; 105:1641–1649. [PubMed: 10841523]

Raffetto JD, Khalil RA. Matrix metalloproteinases and their inhibitors in vascular remodeling and vascular disease. Biochem Pharmacol. 2008; 75:346–359. [PubMed: 17678629]

Raffetto JD, Mendez MV, Marien BJ, Byers HR, Phillips TJ, Park HY, Menzoian JO. Changes in cellular motility and cytoskeletal actin in fibroblasts from patients with chronic venous insufficiency and in neonatal fibroblasts in the presence of chronic wound fluid. J Vasc Surg. 2001; 33:1233–1241. [PubMed: 11389423]

Raffetto JD, Ross RL, Khalil RA. Matrix metalloproteinase 2-induced venous dilation via hyperpolarization and activation of K+ channels: relevance to varicose vein formation. J Vasc Surg. 2007; 45:373–380. [PubMed: 17264019]

Raffetto JD, Vasquez R, Goodwin DG, Menzoian JO. Mitogen-activated protein kinase pathway regulates cell proliferation in venous ulcer fibroblasts. Vasc Endovascular Surg. 2006; 40:59–66. [PubMed: 16456607]

Rao BG. Recent developments in the design of specific Matrix Metalloproteinase inhibitors aided by structural and computational studies. Curr Pharm Des. 2005; 11:295–322. [PubMed: 15723627]

Rauch I, Iglseder B, Paulweber B, Ladurner G, Strasser P. MMP-9 haplotypes and carotid artery atherosclerosis: an association study introducing a novel multicolour multiplex RealTime PCR protocol. Eur J Clin Invest. 2008; 38:24–33. [PubMed: 18173548]

Ravanti L, Kahari VM. Matrix metalloproteinases in wound repair (review). Int J Mol Med. 2000; 6:391–407. [PubMed: 10998429]

Razavian M, Zhang J, Nie L, Tavakoli S, Razavian N, Dobrucki LW, Sinusas AJ, Edwards DS, Azure M, Sadeghi MM. Molecular imaging of matrix metalloproteinase activation to predict murine aneurysm expansion in vivo. J Nucl Med. 51:1107–1115. [PubMed: 20554725]

Reister F, Kingdom JC, Ruck P, Marzusch K, Heyl W, Pauer U, Kaufmann P, Rath W, Huppertz B. Altered protease expression by periarterial trophoblast cells in severe early-onset preeclampsia with IUGR. J Perinat Med. 2006; 34:272–279. [PubMed: 16856814]

Reiter LA, Freeman-Cook KD, Jones CS, Martinelli GJ, Antipas AS, Berliner MA, Datta K, Downs JT, Eskra JD, Forman MD, Greer EM, Guzman R, Hardink JR, Janat F, Keene NF, Laird ER, Liras JL, Lopresti-Morrow LL, Mitchell PG, Pandit J, Robertson D, Sperger D, Vaughn-Bowser ML, Waller DM, Yocum SA. Potent, selective pyrimidinetrione-based inhibitors of MMP-13. Bioorg Med Chem Lett. 2006; 16:5822–5826. [PubMed: 16942871]

Renkiewicz R, Qiu L, Lesch C, Sun X, Devalaraja R, Cody T, Kaldjian E, Welgus H, Baragi V. Broad-spectrum matrix metalloproteinase inhibitor marimastat-induced musculoskeletal side effects in rats. Arthritis Rheum. 2003; 48:1742–1749. [PubMed: 12794843]

Rodriguez-Manzaneque JC, Westling J, Thai SN, Luque A, Knauper V, Murphy G, Sandy JD, Iruela-Arispe ML. ADAMTS1 cleaves aggrecan at multiple sites and is differentially inhibited by metalloproteinase inhibitors. Biochem Biophys Res Commun. 2002; 293:501–508. [PubMed: 12054629]

Rodriguez JA, Orbe J, Martinez de Lizarrondo S, Calvayrac O, Rodriguez C, Martinez-Gonzalez J, Paramo JA. Metalloproteinases and atherothrombosis: MMP-10 mediates vascular remodeling promoted by inflammatory stimuli. Front Biosci. 2008; 13:2916–2921. [PubMed: 17981764]

Roman-Garcia P, Coto E, Reguero JR, Cannata-Andia JB, Lozano I, Avanzas P, Moris C, Rodriguez I. Matrix metalloproteinase 1 promoter polymorphisms and risk of myocardial infarction: a case-control study in a Spanish population. Coron Artery Dis. 2009; 20:383–386. [PubMed: 19620856]

Romero-Perez D, Fricovsky E, Yamasaki KG, Griffin M, Barraza-Hidalgo M, Dillmann W, Villarreal F. Cardiac uptake of minocycline and mechanisms for in vivo cardioprotection. J Am Coll Cardiol. 2008; 52:1086–1094. [PubMed: 18848143]

Rossello A, Nuti E, Catalani MP, Carelli P, Orlandini E, Rapposelli S, Tuccinardi T, Atkinson SJ, Murphy G, Balsamo A. A new development of matrix metalloproteinase inhibitors: twin hydroxamic acids as potent inhibitors of MMPs. Bioorg Med Chem Lett. 2005; 15:2311–2314. [PubMed: 15837315]

Rouis M, Adamy C, Duverger N, Lesnik P, Horellou P, Moreau M, Emmanuel F, Caillaud JM, Laplaud PM, Dachet C, Chapman MJ. Adenovirus-mediated overexpression of tissue inhibitor of metalloproteinase-1 reduces atherosclerotic lesions in apolipoprotein E-deficient mice. Circulation. 1999; 100:533–540. [PubMed: 10430768]

Rozanov DV, Ghebrehiwet B, Postnova TI, Eichinger A, Deryugina EI, Strongin AY. The hemopexin-like C-terminal domain of membrane type 1 matrix metalloproteinase regulates proteolysis of a multifunctional protein, gC1qR. J Biol Chem. 2002; 277:9318–9325. [PubMed: 11773076]

Ruiz S, Henschen-Edman AH, Nagase H, Tenner AJ. Digestion of C1q collagen-like domain with MMPs-1,-2,-3, and -9 further defines the sequence involved in the stimulation of neutrophil superoxide production. J Leukoc Biol. 1999; 66:416–422. [PubMed: 10496311]

Rundhaug JE. Matrix metalloproteinases and angiogenesis. J Cell Mol Med. 2005; 9:267–285. [PubMed: 15963249]

Ryu OH, Fincham AG, Hu CC, Zhang C, Qian Q, Bartlett JD, Simmer JP. Characterization of recombinant pig enamelysin activity and cleavage of recombinant pig and mouse amelogenins. J Dent Res. 1999; 78:743–750. [PubMed: 10096449]

Saarialho-Kere U, Kerkela E, Jahkola T, Suomela S, Keski-Oja J, Lohi J. Epilysin (MMP-28) expression is associated with cell proliferation during epithelial repair. J Invest Dermatol. 2002; 119:14–21. [PubMed: 12164918]

Sadowski T, Dietrich S, Koschinsky F, Ludwig A, Proksch E, Titz B, Sedlacek R. Matrix metalloproteinase 19 processes the laminin 5 gamma 2 chain and induces epithelial cell migration. Cell Mol Life Sci. 2005; 62:870–880. [PubMed: 15868410]

Sadowski T, Dietrich S, Koschinsky F, Sedlacek R. Matrix metalloproteinase 19 regulates insulin-like growth factor-mediated proliferation, migration, and adhesion in human keratinocytes through proteolysis of insulin-like growth factor binding protein-3. Mol Biol Cell. 2003a; 14:4569–4580. [PubMed: 12937269]

Sadowski T, Dietrich S, Muller M, Havlickova B, Schunck M, Proksch E, Muller MS, Sedlacek R. Matrix metalloproteinase-19 expression in normal and diseased skin: dysregulation by epidermal proliferation. J Invest Dermatol. 2003b; 121:989–996. [PubMed: 14708597]

Sakalihasan N, Delvenne P, Nusgens BV, Limet R, Lapiere CM. Activated forms of MMP2 and MMP9 in abdominal aortic aneurysms. J Vasc Surg. 1996; 24:127–133. [PubMed: 8691515]

Sangiorgi G, D'Averio R, Mauriello A, Bondio M, Pontillo M, Castelvecchio S, Trimarchi S, Tolva V, Nano G, Rampoldi V, Spagnoli LG, Inglese L. Plasma levels of metalloproteinases-3 and -9 as markers of successful abdominal aortic aneurysm exclusion after endovascular graft treatment. Circulation. 2001; 104:I288–295. [PubMed: 11568071]

Sansilvestri-Morel P, Fioretti F, Rupin A, Senni K, Fabiani JN, Godeau G, Verbeuren TJ. Comparison of extracellular matrix in skin and saphenous veins from patients with varicose veins: does the skin reflect venous matrix changes? Clin Sci (Lond). 2007; 112:229–239. [PubMed: 17020541]

Savani RC, Wang C, Yang B, Zhang S, Kinsella MG, Wight TN, Stern R, Nance DM, Turley EA. Migration of bovine aortic smooth muscle cells after wounding injury. The role of hyaluronan and RHAMM. J Clin Invest. 1995; 95:1158–1168. [PubMed: 7533785]

Sawicki G, Radomski MW, Winkler-Lowen B, Krzymien A, Guilbert LJ. Polarized release of matrix metalloproteinase-2 and -9 from cultured human placental syncytiotrophoblasts. Biol Reprod. 2000; 63:1390–1395. [PubMed: 11058543]

Sayer GL, Smith PD. Immunocytochemical characterisation of the inflammatory cell infiltrate of varicose veins. Eur J Vasc Endovasc Surg. 2004; 28:479–483. [PubMed: 15465368]

Schafer-Somi S, Ali Aksoy O, Patzl M, Findik M, Erunal-Maral N, Beceriklisoy HB, Polat B, Aslan S. The activity of matrix metalloproteinase-2 and -9 in serum of pregnant and non-pregnant bitches. Reprod Domest Anim. 2005; 40:46–50. [PubMed: 15655000]

Seah CC, Phillips TJ, Howard CE, Panova IP, Hayes CM, Asandra AS, Park HY. Chronic wound fluid suppresses proliferation of dermal fibroblasts through a Ras-mediated signaling pathway. J Invest Dermatol. 2005; 124:466–474. [PubMed: 15675969]

Sesso R, Franco MC. Abnormalities in metalloproteinase pathways and IGF-I axis: a link between birth weight, hypertension, and vascular damage in childhood. Am J Hypertens. 23:6–11. [PubMed: 19893495]

Shalinsky DR, Brekken J, Zou H, McDermott CD, Forsyth P, Edwards D, Margosiak S, Bender S, Truitt G, Wood A, Varki NM, Appelt K. Broad antitumor and antiangiogenic activities of AG3340, a potent and selective MMP inhibitor undergoing advanced oncology clinical trials. Ann N Y Acad Sci. 1999; 878:236–270. [PubMed: 10415735]

Shi ZD, Ji XY, Berardi DE, Qazi H, Tarbell JM. Interstitial flow induces MMP-1 expression and vascular SMC migration in collagen I gels via an ERK1/2-dependent and c-Jun-mediated mechanism. Am J Physiol Heart Circ Physiol. 298:H127–135. [PubMed: 19880665]

Shimizu C, Matsubara T, Onouchi Y, Jain S, Sun S, Nievergelt CM, Shike H, Brophy VH, Takegawa T, Furukawa S, Akagi T, Newburger JW, Baker AL, Burgner D, Hibberd ML, Davila S, Levin M, Mamtani M, He W, Ahuja SK, Burns JC. Matrix metalloproteinase haplotypes associated with coronary artery aneurysm formation in patients with Kawasaki disease. J Hum Genet. 55:779–784. [PubMed: 20827277]

Shipley JM, Wesselschmidt RL, Kobayashi DK, Ley TJ, Shapiro SD. Metalloelastase is required for macrophage-mediated proteolysis and matrix invasion in mice. Proc Natl Acad Sci U S A. 1996; 93:3942–3946. [PubMed: 8632994]

Shokry M, Omran OM, Hassan HI, Elsedfy GO, Hussein MR. Expression of matrix metalloproteinases 2 and 9 in human trophoblasts of normal and preeclamptic placentas: preliminary findings. Exp Mol Pathol. 2009; 87:219–225. [PubMed: 19716817]

Silence J, Collen D, Lijnen HR. Reduced atherosclerotic plaque but enhanced aneurysm formation in mice with inactivation of the tissue inhibitor of metalloproteinase-1 (TIMP-1) gene. Circ Res. 2002; 90:897–903. [PubMed: 11988491]

Silence J, Lupu F, Collen D, Lijnen HR. Persistence of atherosclerotic plaque but reduced aneurysm formation in mice with stromelysin-1 (MMP-3) gene inactivation. Arterioscler Thromb Vasc Biol. 2001; 21:1440–1445. [PubMed: 11557669]

Sinha I, Bethi S, Cronin P, Williams DM, Roelofs K, Ailawadi G, Henke PK, Eagleton MJ, Deeb GM, Patel HJ, Berguer R, Stanley JC, Upchurch GR Jr. A biologic basis for asymmetric growth in descending thoracic aortic aneurysms: a role for matrix metalloproteinase 9 and 2. J Vasc Surg. 2006; 43:342–348. [PubMed: 16476613]

Skiles JW, Gonnella NC, Jeng AY. The design, structure, and therapeutic application of matrix metalloproteinase inhibitors. Curr Med Chem. 2001; 8:425–474. [PubMed: 11172697]

Skoog T, Ahokas K, Orsmark C, Jeskanen L, Isaka K, Saarialho-Kere U. MMP-21 is expressed by macrophages and fibroblasts in vivo and in culture. Exp Dermatol. 2006; 15:775–783. [PubMed: 16984259]

Slater SC, Koutsouki E, Jackson CL, Bush RC, Angelini GD, Newby AC, George SJ. R-cadherin:beta-catenin complex and its association with vascular smooth muscle cell proliferation. Arterioscler Thromb Vasc Biol. 2004; 24:1204–1210. [PubMed: 15117735]

Somerville RP, Oblander SA, Apte SS. Matrix metalloproteinases: old dogs with new tricks. Genome Biol. 2003; 4:216. [PubMed: 12801404]

Stefanidakis M, Koivunen E. Cell-surface association between matrix metalloproteinases and integrins: role of the complexes in leukocyte migration and cancer progression. Blood. 2006; 108:1441–1450. [PubMed: 16609063]

Steinhusen U, Weiske J, Badock V, Tauber R, Bommert K, Huber O. Cleavage and shedding of E-cadherin after induction of apoptosis. J Biol Chem. 2001; 276:4972–4980. [PubMed: 11076937]

Stoneman VE, Bennett MR. Role of apoptosis in atherosclerosis and its therapeutic implications. Clin Sci (Lond). 2004; 107:343–354. [PubMed: 15230690]

Stracke JO, Fosang AJ, Last K, Mercuri FA, Pendas AM, Llano E, Perris R, Di Cesare PE, Murphy G, Knauper V. Matrix metalloproteinases 19 and 20 cleave aggrecan and cartilage oligomeric matrix protein (COMP). FEBS Lett. 2000; 478:52–56. [PubMed: 10922468]

Strickland DK, Ashcom JD, Williams S, Burgess WH, Migliorini M, Argraves WS. Sequence identity between the alpha 2-macroglobulin receptor and low density lipoprotein receptor-related protein suggests that this molecule is a multifunctional receptor. J Biol Chem. 1990; 265:17401–17404. [PubMed: 1698775]

Subramaniam R, Haldar MK, Tobwala S, Ganguly B, Srivastava DK, Mallik S. Novel bis-(arylsulfonamide) hydroxamate-based selective MMP inhibitors. Bioorg Med Chem Lett. 2008; 18:3333–3337. [PubMed: 18442906]

Suenaga N, Mori H, Itoh Y, Seiki M. CD44 binding through the hemopexin-like domain is critical for its shedding by membrane-type 1 matrix metalloproteinase. Oncogene. 2005; 24:859–868. [PubMed: 15558018]

Suzuki K, Enghild JJ, Morodomi T, Salvesen G, Nagase H. Mechanisms of activation of tissue procollagenase by matrix metalloproteinase 3 (stromelysin). Biochemistry. 1990; 29:10261–10270. [PubMed: 2176865]

Suzuki M, Raab G, Moses MA, Fernandez CA, Klagsbrun M. Matrix metalloproteinase-3 releases active heparin-binding EGF-like growth factor by cleavage at a specific juxtamembrane site. J Biol Chem. 1997; 272:31730–31737. [PubMed: 9395517]

Takase S, Bergan JJ, Schmid-Schonbein G. Expression of adhesion molecules and cytokines on saphenous veins in chronic venous insufficiency. Ann Vasc Surg. 2000; 14:427–435. [PubMed: 10990550]

Tan J, Hua Q, Xing X, Wen J, Liu R, Yang Z. Impact of the metalloproteinase-9/tissue inhibitor of metalloproteinase-1 system on large arterial stiffness in patients with essential hypertension. Hypertens Res. 2007; 30:959–963. [PubMed: 18049028]

Tarin C, Gomez M, Calvo E, Lopez JA, Zaragoza C. Endothelial nitric oxide deficiency reduces MMP-13-mediated cleavage of ICAM-1 in vascular endothelium: a role in atherosclerosis. Arterioscler Thromb Vasc Biol. 2009; 29:27–32. [PubMed: 18988893]

Tayebjee MH, Karalis I, Nadar SK, Beevers DG, MacFadyen RJ, Lip GY. Circulating matrix metalloproteinase-9 and tissue inhibitors of metalloproteinases-1 and -2 levels in gestational hypertension. Am J Hypertens. 2005; 18:325–329. [PubMed: 15797648]

Terashima M, Akita H, Kanazawa K, Inoue N, Yamada S, Ito K, Matsuda Y, Takai E, Iwai C, Kurogane H, Yoshida Y, Yokoyama M. Stromelysin promoter 5A/6A polymorphism is associated with acute myocardial infarction. Circulation. 1999; 99:2717–2719. [PubMed: 10351963]

Teti A. Regulation of cellular functions by extracellular matrix. J Am Soc Nephrol. 1992; 2:S83–87. [PubMed: 1318112]

Thanabalasundaram G, Pieper C, Lischper M, Galla HJ. Regulation of the blood-brain barrier integrity by pericytes via matrix metalloproteinases mediated activation of vascular endothelial growth factor in vitro. Brain Res. 1347:1–10. [PubMed: 20553880]

Thompson AR, Drenos F, Hafez H, Humphries SE. Candidate gene association studies in abdominal aortic aneurysm disease: a review and meta-analysis. Eur J Vasc Endovasc Surg. 2008; 35:19–30. [PubMed: 17920311]

Toth M, Bernardo MM, Gervasi DC, Soloway PD, Wang Z, Bigg HF, Overall CM, DeClerck YA, Tschesche H, Cher ML, Brown S, Mobashery S, Fridman R. Tissue inhibitor of metalloproteinase (TIMP)-2 acts synergistically with synthetic matrix metalloproteinase (MMP) inhibitors but not with TIMP-4 to enhance the (Membrane type 1)-MMP-dependent activation of pro-MMP-2. J Biol Chem. 2000; 275:41415–41423. [PubMed: 10998420]

Tsai JH, Hwang JM, Ying TH, Shyu JC, Tsai CC, Hsieh YS, Wang YW, Liu JY, Kao SH. The activation of matrix metalloproteinase-2 induced by protein kinase C alpha in decidualization. J Cell Biochem. 2009; 108:547–554. [PubMed: 19693770]

Uglow EB, Slater S, Sala-Newby GB, Aguilera-Garcia CM, Angelini GD, Newby AC, George SJ. Dismantling of cadherin-mediated cell-cell contacts modulates smooth muscle cell proliferation. Circ Res. 2003; 92:1314–1321. [PubMed: 12775583]

Ulrich D, Lichtenegger F, Unglaub F, Smeets R, Pallua N. Effect of chronic wound exudates and MMP-2/-9 inhibitor on angiogenesis in vitro. Plast Reconstr Surg. 2005; 116:539–545. [PubMed: 16079688]

Uzui H, Harpf A, Liu M, Doherty TM, Shukla A, Chai NN, Tripathi PV, Jovinge S, Wilkin DJ, Asotra K, Shah PK, Rajavashisth TB. Increased expression of membrane type 3-matrix metalloproteinase in human atherosclerotic plaque: role of activated macrophages and inflammatory cytokines. Circulation. 2002; 106:3024–3030. [PubMed: 12473546]

Vaalamo M, Mattila L, Johansson N, Kariniemi AL, Karjalainen-Lindsberg ML, Kahari VM, Saarialho-Kere U. Distinct populations of stromal cells express collagenase-3 (MMP-13) and collagenase-1 (MMP-1) in chronic ulcers but not in normally healing wounds. J Invest Dermatol. 1997; 109:96–101. [PubMed: 9204962]

Valentin F, Bueb JL, Kieffer P, Tschirhart E, Atkinson J. Oxidative stress activates MMP-2 in cultured human coronary smooth muscle cells. Fundam Clin Pharmacol. 2005; 19:661–667. [PubMed: 16313278]

van de Ven WJ, Voorberg J, Fontijn R, Pannekoek H, van den Ouweland AM, van Duijnhoven HL, Roebroek AJ, Siezen RJ. Furin is a subtilisin-like proprotein processing enzyme in higher eukaryotes. Mol Biol Rep. 1990; 14:265–275. [PubMed: 2094803]

van der Laan WH, Quax PH, Seemayer CA, Huisman LG, Pieterman EJ, Grimbergen JM, Verheijen JH, Breedveld FC, Gay RE, Gay S, Huizinga TW, Pap T. Cartilage degradation and invasion by rheumatoid synovial fibroblasts is inhibited by gene transfer of TIMP-1 and TIMP-3. Gene Ther. 2003; 10:234–242. [PubMed: 12571631]

van Laake LW, Vainas T, Dammers R, Kitslaar PJ, Hoeks AP, Schurink GW. Systemic dilation diathesis in patients with abdominal aortic aneurysms: a role for matrix metalloproteinase-9? Eur J Vasc Endovasc Surg. 2005; 29:371–377. [PubMed: 15749037]

Van Lint P, Wielockx B, Puimege L, Noel A, Lopez-Otin C, Libert C. Resistance of collagenase-2 (matrix metalloproteinase-8)-deficient mice to TNF-induced lethal hepatitis. J Immunol. 2005; 175:7642–7649. [PubMed: 16301674]

Van Wart HE, Birkedal-Hansen H. The cysteine switch: a principle of regulation of metalloproteinase activity with potential applicability to the entire matrix metalloproteinase gene family. Proc Natl Acad Sci U S A. 1990; 87:5578–5582. [PubMed: 2164689]

Velasco G, Pendas AM, Fueyo A, Knauper V, Murphy G, Lopez-Otin C. Cloning and characterization of human MMP-23, a new matrix metalloproteinase predominantly expressed in reproductive tissues and lacking conserved domains in other family members. J Biol Chem. 1999; 274:4570–4576. [PubMed: 9988691]

Venturi M, Bonavina L, Annoni F, Colombo L, Butera C, Peracchia A, Mussini E. Biochemical assay of collagen and elastin in the normal and varicose vein wall. J Surg Res. 1996; 60:245–248. [PubMed: 8592422]

Vigetti D, Moretto P, Viola M, Genasetti A, Rizzi M, Karousou E, Clerici M, Bartolini B, Pallotti F, De Luca G, Passi A. Aortic smooth muscle cells migration and the role of metalloproteinases and hyaluronan. Connect Tissue Res. 2008; 49:189–192. [PubMed: 18661340]

Vihinen P, Ala-aho R, Kahari VM. Matrix metalloproteinases as therapeutic targets in cancer. Curr Cancer Drug Targets. 2005; 5:203–220. [PubMed: 15892620]

Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res. 2003; 92:827–839. [PubMed: 12730128]

Voils SA, Evans ME, Lane MT, Schosser RH, Rapp RP. Use of macrolides and tetracyclines for chronic inflammatory diseases. Ann Pharmacother. 2005; 39:86–94. [PubMed: 15562139]

von Steinburg SP, Kruger A, Fischer T, Mario Schneider KT, Schmitt M. Placental expression of proteases and their inhibitors in patients with HELLP syndrome. Biol Chem. 2009; 390:1199–1204. [PubMed: 19663680]

Vu TH, Werb Z. Matrix metalloproteinases: effectors of development and normal physiology. Genes Dev. 2000; 14:2123–2133. [PubMed: 10970876]

Waitkus-Edwards KR, Martinez-Lemus LA, Wu X, Trzeciakowski JP, Davis MJ, Davis GE, Meininger GA. alpha(4)beta(1) Integrin activation of L-type calcium channels in vascular smooth muscle causes arteriole vasoconstriction. Circ Res. 2002; 90:473–480. [PubMed: 11884378]

Wakisaka Y, Chu Y, Miller JD, Rosenberg GA, Heistad DD. Spontaneous intracerebral hemorrhage during acute and chronic hypertension in mice. J Cereb Blood Flow Metab. 30:56–69. [PubMed: 19724290]

Walker HA, Whitelock JM, Garl PJ, Nemenoff RA, Stenmark KR, Weiser-Evans MC. Perlecan up-regulation of FRNK suppresses smooth muscle cell proliferation via inhibition of FAK signaling. Mol Biol Cell. 2003; 14:1941–1952. [PubMed: 12802066]

Wall SJ, Sampson MJ, Levell N, Murphy G. Elevated matrix metalloproteinase-2 and -3 production from human diabetic dermal fibroblasts. Br J Dermatol. 2003; 149:13–16. [PubMed: 12890189]

Wang X, Chow FL, Oka T, Hao L, Lopez-Campistrous A, Kelly S, Cooper S, Odenbach J, Finegan BA, Schulz R, Kassiri Z, Lopaschuk GD, Fernandez-Patron C. Matrix metalloproteinase-7 and ADAM-12 (a disintegrin and metalloproteinase-12) define a signaling axis in agonist-induced hypertension and cardiac hypertrophy. Circulation. 2009; 119:2480–2489. [PubMed: 19398663]

Wang Z, Juttermann R, Soloway PD. TIMP-2 is required for efficient activation of proMMP-2 in vivo. J Biol Chem. 2000; 275:26411–26415. [PubMed: 10827175]

Weckroth M, Vaheri A, Lauharanta J, Sorsa T, Konttinen YT. Matrix metalloproteinases, gelatinase and collagenase, in chronic leg ulcers. J Invest Dermatol. 1996; 106:1119–1124. [PubMed: 8618050]

Whitlock GA, Dack KN, Dickinson RP, Lewis ML. A novel series of highly selective inhibitors of MMP-3. Bioorg Med Chem Lett. 2007; 17:6750–6753. [PubMed: 18029177]

Williamson RA, Marston FA, Angal S, Koklitis P, Panico M, Morris HR, Carne AF, Smith BJ, Harris TJ, Freedman RB. Disulphide bond assignment in human tissue inhibitor of metalloproteinases (TIMP). Biochem J. 1990; 268:267–274. [PubMed: 2163605]

Wilson CL, Ouellette AJ, Satchell DP, Ayabe T, Lopez-Boado YS, Stratman JL, Hultgren SJ, Matrisian LM, Parks WC. Regulation of intestinal alpha-defensin activation by the metalloproteinase matrilysin in innate host defense. Science. 1999; 286:113–117. [PubMed: 10506557]

Wilson WR, Anderton M, Choke EC, Dawson J, Loftus IM, Thompson MM. Elevated plasma MMP1 and MMP9 are associated with abdominal aortic aneurysm rupture. Eur J Vasc Endovasc Surg. 2008a; 35:580–584. [PubMed: 18226564]

Wilson WR, Anderton M, Schwalbe EC, Jones JL, Furness PN, Bell PR, Thompson MM. Matrix metalloproteinase-8 and -9 are increased at the site of abdominal aortic aneurysm rupture. Circulation. 2006; 113:438–445. [PubMed: 16432074]

Wilson WR, Choke EC, Dawson J, Loftus IM, Thompson MM. Plasma matrix metalloproteinase levels do not predict tissue levels in abdominal aortic aneurysms suitable for elective repair. Vascular. 2008b; 16:248–252. [PubMed: 19238864]

Wilson WR, Schwalbe EC, Jones JL, Bell PR, Thompson MM. Matrix metalloproteinase 8 (neutrophil collagenase) in the pathogenesis of abdominal aortic aneurysm. Br J Surg. 2005; 92:828–833. [PubMed: 15918165]

Woodside KJ, Hu M, Burke A, Murakami M, Pounds LL, Killewich LA, Daller JA, Hunter GC. Morphologic characteristics of varicose veins: possible role of metalloproteinases. J Vasc Surg. 2003; 38:162–169. [PubMed: 12844106]

Xiong W, Knispel RA, Dietz HC, Ramirez F, Baxter BT. Doxycycline delays aneurysm rupture in a mouse model of Marfan syndrome. J Vasc Surg. 2008; 47:166–172. discussion 172. [PubMed: 18178469]

Yan YL, Cohen SM. Efficient synthesis of 5-amido-3-hydroxy-4-pyrones as inhibitors of matrix metalloproteinases. Org Lett. 2007; 9:2517–2520. [PubMed: 17521196]

Ye S, Watts GF, Mandalia S, Humphries SE, Henney AM. Preliminary report: genetic variation in the human stromelysin promoter is associated with progression of coronary atherosclerosis. Br Heart J. 1995; 73:209–215. [PubMed: 7727178]

Yu YM, Lin HC. Curcumin prevents human aortic smooth muscle cells migration by inhibiting of MMP-9 expression. Nutr Metab Cardiovasc Dis. 20:125–132. [PubMed: 19447587]

Zamboni P, Scapoli G, Lanzara V, Izzo M, Fortini P, Legnaro R, Palazzo A, Tognazzo S, Gemmati D. Serum iron and matrix metalloproteinase-9 variations in limbs affected by chronic venous disease and venous leg ulcers. Dermatol Surg. 2005; 31:644–649. discussion 649. [PubMed: 15996413]

Zempo N, Koyama N, Kenagy RD, Lea HJ, Clowes AW. Regulation of vascular smooth muscle cell migration and proliferation in vitro and in injured rat arteries by a synthetic matrix metalloproteinase inhibitor. Arterioscler Thromb Vasc Biol. 1996; 16:28–33. [PubMed: 8548422]

Zervoudaki A, Economou E, Stefanadis C, Pitsavos C, Tsioufis K, Aggeli C, Vasiliadou K, Toutouza M, Toutouzas P. Plasma levels of active extracellular matrix metalloproteinases 2 and 9 in patients with essential hypertension before and after antihypertensive treatment. J Hum Hypertens. 2003; 17:119–124. [PubMed: 12574790]

Zhang YM, Fan X, Chakaravarty D, Xiang B, Scannevin RH, Huang Z, Ma J, Burke SL, Karnachi P, Rhodes KJ, Jackson PF. 1-Hydroxy-2-pyridinone-based MMP inhibitors: synthesis and biological evaluation for the treatment of ischemic stroke. Bioorg Med Chem Lett. 2008; 18:409–413. [PubMed: 17981034]

Zheng H, Takahashi H, Murai Y, Cui Z, Nomoto K, Niwa H, Tsuneyama K, Takano Y. Expressions of MMP-2, MMP-9 and VEGF are closely linked to growth, invasion, metastasis and angiogenesis of gastric carcinoma. Anticancer Res. 2006; 26:3579–3583. [PubMed: 17094486]

Zhou Z, Apte SS, Soininen R, Cao R, Baaklini GY, Rauser RW, Wang J, Cao Y, Tryggvason K. Impaired endochondral ossification and angiogenesis in mice deficient in membrane-type matrix metalloproteinase I. Proc Natl Acad Sci U S A. 2000; 97:4052–4057. [PubMed: 10737763]

Zhou Z, Shen T, Zhang BH, Lv XY, Lin HY, Zhu C, Xue LQ, Wang H. The proprotein convertase furin in human trophoblast: Possible role in promoting trophoblast cell migration and invasion. Placenta. 2009; 30:929–938. [PubMed: 19853298]

Zureik M, Beaudeux JL, Courbon D, Benetos A, Ducimetiere P. Serum tissue inhibitors of metalloproteinases 1 (TIMP-1) and carotid atherosclerosis and aortic arterial stiffness. J Hypertens. 2005; 23:2263–2268. [PubMed: 16269968]

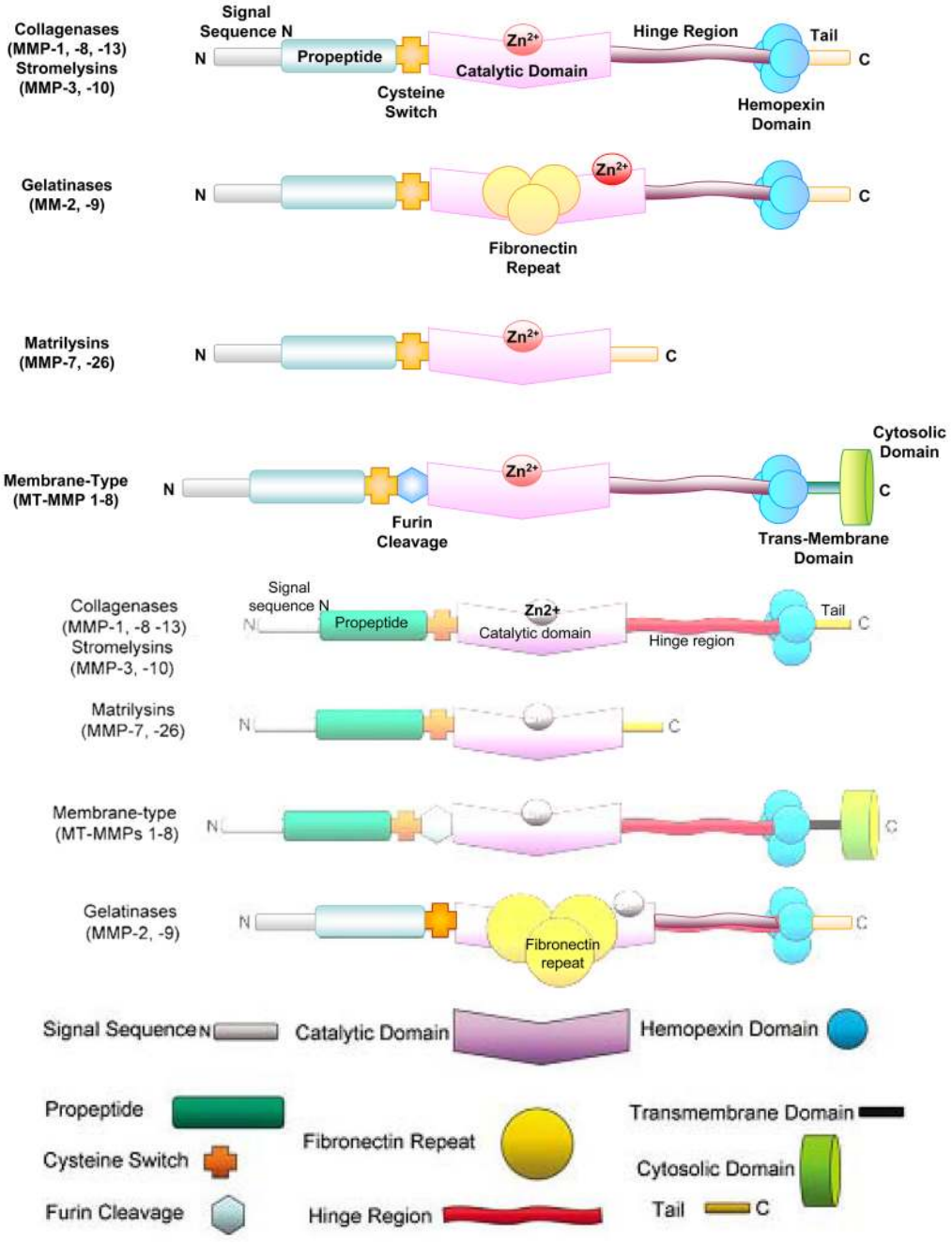

Fig. 1.

Structure of MMPs. Typically, MMPs consist of a propeptide of about 80 amino acids, a catalytic metalloproteinase domain of about 170 amino acids, a linker peptide (hinge region) of variable lengths and a hemopexin domain of about 200 amino acids. The catalytic domain contains the Zn^{2+} binding motif HEXXHXXGXXH. Matrilysins are exceptions as they lack the linker peptide and the hemopexin domain. Membrane-bound MMPs (MT-MMPs) have a furin-like proprotein convertase recognition sequence at the C-terminus of the propeptide.

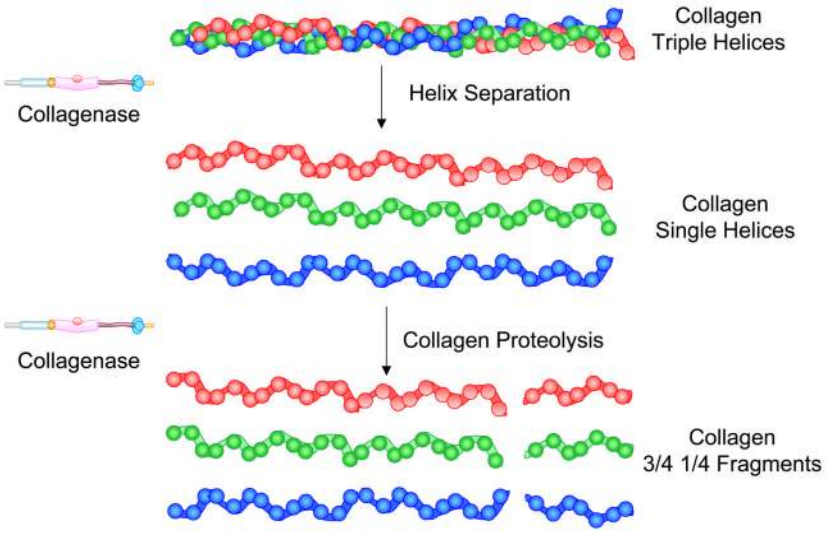

Fig. 2.

Collagenolytic activity of MMPs. Collagenases unwind triple helical collagen before they hydrolyze the peptide bonds breaking down collagen into 3/4 and 1/4 fragments. The MMPs hemopexin domains are essential for cleaving native fibrillar collagen.

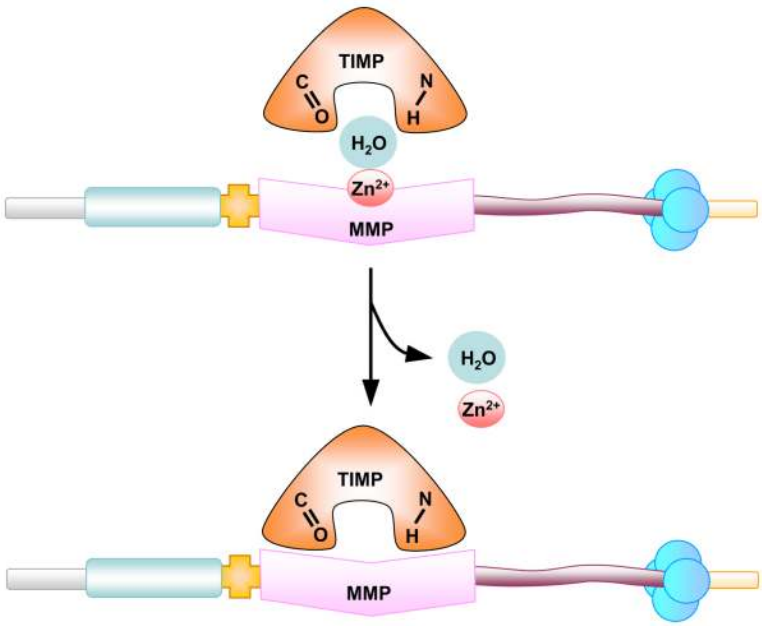

Fig. 3.

Endogenous inhibition of MMPs by TIMPs. The TIMP molecule wedges into the active-site cleft of MMP in a manner similar to that of the substrate. Cys1 is instrumental in chelating the active-site Zn^{2+} with its N-terminal α-amino group and carbonyl group, thereby expelling the water molecule bound to the catalytic Zn^{2+}.

Table 1

Members of the MMP Family and their Substrates

MMP (Other Name)	Tissue Distribution	Collagen Substrates	Non-Collagen ECM Substrates	Non-Structural ECM Component Substrates
Collagenases				
MMP-1 (Collagenase-1)	Fibroblast, Interstitial, Tissue Collagenase	I, II, III, VII, VIII, X, and gelatin	Aggrecan, casein, nidogen, serpins, versican, perlecan, proteoglycan link protein, tenascin-C	α1-antichymotrypsin, α1-antitrypsin, α1-proteinase inhibitor, IGFBP-3, IGFBP-5, IL-1β, L-selectin, ovostatin, recombinant TNF-α peptide, SDF-1
MMP-8 (Collagenase-2)	Neutrophil, or PMNL Collagenase	I, II, III, V, VII, VIII, X	Aggrecan, laminin, nidogen	α2-antiplasmin, pro-MMP-8
MMP-13 (Collagenase-3)	VV, SMC, preeclampsia	I, II, III, IV	Aggrecan, fibronectin, laminin, perlecan, tenascin	Plasminogen activator 2, pro-MMP-9, pro-MMP-13, SDF-1
Gelatinases				
MMP-2 (Gelatinase-A)	Aortic aneurysm, VV	I, II, III, IV, V, VII, X, XI	Aggrecan, elastin, fibronectin, laminin, nidogen, proteoglycan link protein, versican	Active MMP-9, active MMP-13, FGF R1, IGF-BP3, IGF-BP5, IL-1β, recombinant TNF-α peptide, TGF-β
MMP-9 (Gelatinase-B)	Aortic aneurysm, VV	IV, V, VII, X, XIV	Fibronectin, laminin, nidogen, proteoglycan link protein, versican	CXCL5, IL-1β, IL2-R, plasminogen, pro-TNFα, SDF-1, TGF-β
Stromelysins				
MMP-3 (Stromelysin-1)	VSMC, coronary artery disease, hypertension, tumor invasion	II, III, IV, IX, X, XI	Aggrecan, casein, decorin, elastin, fibronectin, laminin, nidogen, perlecan, proteoglycan, proteoglycan link protein, versican	α1-antichymotrypsin, α1-proteinase inhibitor, antithrombin III, E-cadherin, fibrinogen, IGF-BP3, L-selectin, ovostatin, pro-HB-EGF, pro-IL-1β, pro-MMP-1, pro-MMP-8, pro-MMP-9, pro-TNFα, SDF-1
MMP-10 (Stromelysin-2)	Atherosclerosis, uterine, preeclampsia	III, IV, V	Fibronectin, laminin, nidogen	Pro-MMP-1, pro-MMP-8, pro-MMP-10
Matrilysins				
MMP-7 (Matrilysin-1)	Uterine MMP	IV, X	Aggrecan, casein, elastin, enactin, laminin, proteoglycan link protein	β4 integrin, decorin, defensin, E-cadherin, Fas-L, plasminogen, pro-MMP-2, pro-MMP-7, pro-MMP-8, pro-TNFα, transferrin, and syndecan α2-antiplasmin
MMP-26 (Matrilysin-2, endometase)	Breast cancer cells	IV, gelatin	Casein, fibrinogen, fibronectin	Fibrin, fibronectin Pro-MMP-2 β 1-proteinase inhibitor
Membrane-Type MMPs				
MMP-14 (MT1-MMP)	Human fibroblasts, SMC, VSMC, uterine, angiogenesis	I, II, III	Aggrecan, dermatan proteoglycan, fibrin, fibronectin, laminin, nidogen, perlecan, tenascin, vitronectin	$\alpha_v\beta_3$ integrin, CD44, gC1qR, pro-MMP-2, pro-MMP-13, pro-TNFα, SDF-1, tissue transglutaminase
MMP-15 (MT2-MMP)	Human fibroblasts, leukocytes, preeclampsia	I	Aggrecan, fibronectin, laminin, nidogen, perlecan, tenascin, vitronectin	Pro-MMP-2, pro-MMP-13, tissue transglutaminase

MMP (Other Name)	Tissue Distribution	Collagen Substrates	Non-Collagen ECM Substrates	Non-Structural ECM Component Substrates
MMP-16 (MT3-MMP)	Human leukocytes, angiogenesis	I	Aggrecan, casein, fibronectin, laminin, perlecan, vitronectin	Pro-MMP-2, pro-MMP-13
MMP-24 (MT5-MMP)	Leukocytes		Chondroitin sulfate, dermatin sulfate, fibronectin	Pro-MMP2, pro-MMP-13
Other MMPs				
MMP-11 (Stromelysin-3)	Angiogenesis, uterine	Does not cleave	Laminin	α1-antitrypsin, α1-proteinase inhibitor, IGFBP-1
MMP-12 (metalloelastase)	Macrophages	IV	Elastin	Plasminogen
MMP-19 (RASI-1)		I, IV, gelatin	Aggrecan, casein, fibronectin, laminin, nidogen, tenascin	
MMP-20 (Enamelysin)	Tooth enamel		Aggrecan, amelogenin, cartilage oligomeric protein	
MMP-21	Macrophages, Fibroblasts, human placenta			α1-antitrypsin
MMP-23 (CA-MMP)	Ovary, testis, prostate	Gelatin		
MMP-25 (Leukolysin, MT6-MMP)		IV, gelatin		Fibrin, fibronectin, pro-MMP-2
MMP-28 (Epilysin)			Casein	

PMNL, polymorphonuclear leukocytes; SDF-1, stromal cell-derived factor-1; VSMC, vascular smooth muscle cell; VV, varicose veins

Table 2

ZBG MMP Inhibitors and their IC50 (μM, unless noted otherwise)

MMPI	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-11	MMP-12	MMP-13	MMP-14	Experimental Therapeutic Trials	Reference
1 (Batimastat)	3 nM	4 nM	20 nM		10 nM	10 nM						
2 Prinomastat AG3340	8.3 nM (Ki)	0.05 nM	0.3 nM	54 nM		0.26 nM			0.03 nM	0.33 nM	O_2-induced retinal neovascularization, neuronal hypoxic injury, ventilator-induced lung injury, lung cancer, uveal melanoma, gliomas, prostate cancer	(Price et al., 1999; Shalinsky et al., 1999; Foda et al., 2001; Garcia et al., 2002; Ozerdem et al., 2002; El-Bradey et al., 2004)
3	9 nM											(Borkakoti et al., 1994)
4 RS-104966	23 nM (Ki)								0.13 nM (Ki)			(Lovejoy et al., 1999)
5	>400	0.135	0.081	1.1	0.042	>7			1.8 nM	5	Osteoarthritis	(Hu et al., 2005)
6	>6		0.351		>22	1.3	0.002	0.120		1.1	Chronic obstructive pulmonary disease	(Li et al., 2009)
7	0.147	0.09 nM	0.050	>1	1.6 nM	6.7 nM				9.8 nM	Stop tumor invasion	(Rossello et al., 2005)
8	14	0.529	0.001			2.42				20.1	Chronic non-healing wounds	(Whitlock et al., 2007)
9	0.03	9.8 nM	1.7	0.475		0.003				17		(Ledour et al., 2008)
10	3.3	0.032	0.057									(Michaelides et al., 2001)
11	>50	>120	80		>120							(Michaelides et al., 2001; Campestre et al., 2006)
12			3.4									(Campestre et al., 2006)
13		58	200									(Campestre et al., 2006)
14	15											(Onaran et al., 2005)

MMPI	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-11	MMP-12	MMP-13	MMP-14	Experimental Therapeutic Trials	Reference
15	270											(Onaran et al., 2005)
16	0.049 (Ki)	1.1 nM	0.470	0.04		0.57 nM				0.024		(Hurst et al., 2005)
17	>100	0.005 1.2	0.04 >100		0.6 nM							(Pochetti et al., 2006)
18	0.160	0.02	0.150	1.4	1.1 nM	0.059			0.013	0.032	Acute liver disease, multiple sclerosis, breast cancer	(Van Lint et al., 2005; Biasone et al., 2007; Folgueras et al., 2008)
19		4.65 (Ki)			18.4	3.91	0.11		4.7	30.1		(Matziari et al., 2004)
20	>100	0.02	90		20	>100					Melanoma	(Breuer et al., 2004)
21	>100	4	>100		>100	20			>100	>100	Melanoma, prostate cancer	(Hoffman et al., 2008)
22	>500	N/A					6 (Ki)		N/A			(Cook et al., 2004)
23	16	0.01	1.8		0.015	0.012				0.01	Anti-angiogenic and anti-invasive in tumor models	(Grams et al., 2001; Maquoi et al., 2004)
24		0.14				0.14		0.22	0.36 nM		Osteoarthritis	(Reiter et al., 2006)
25	>50	>50	0.019									(Puerta et al., 2005)
26	>50	0.92	0.56	>50	0.086	27.1		0.018	4.1		Heart ischemia and reperfusion	(Romero-Perez et al., 2008)
27	>1	0.005	0.056			2.4 nM			2.5 nM		Brain edema following ischemia–reperfusion	(Jadhav et al., 2008)
28	>50	4.4	0.077	>50	0.248	32.3		0.085	6.6			(Romero-Perez et al., 2008)
29	>50	16.5	41.7	>50	3.8	>50		1.2	16.5			(Romero-Perez et al., 2008)

MMPI	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-11	MMP-12	MMP-13	MMP-14	Experimental Therapeutic Trials	Reference
30	>50	9.3	0.24	>50	0.064	>50		0.022	20.6			(Romero-Perez et al., 2008)
31	>50	7.6	>50	>50	5.0	>50		6.7	6.7			(Romero-Perez et al., 2008)
32 (100 μM)	21%	34%	34%			33%						(Yan and Cohen, 2007)
33 (50 μM)	52%	23%	45%			54%						(Yan and Cohen, 2007)

N/A, not active up to solubility limit.

Table 3

Non-ZBG and Mechanism-Based MMP Inhibitors and their IC50 (μM, unless noted otherwise)

MMPI	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-12	MMP-13	MMP-14	Experimental Therapeutic Trials	Reference
Non-ZBG MMP Inhibitors											
34	>100	>100	>100	>100	>100	>100	>100	0.03	>100	Osteoarthritis	(Johnson et al., 2007)
35	>100	0.39	1.7		0.98	1.4	0.014	0.27			(Morales et al., 2004)
36	>100	6.6			5.1	>100	24	4.9			(Morales et al., 2004)
37	>30	>30	>30	>30	>100	>100	>100	0.00067	>30	Osteoarthritis	(Johnson et al., 2007)
38								6.6			(Engel et al., 2005)
39								0.072			(Engel et al., 2005)
Mechanism-Based MMP Inhibitors											
40	73	0.028	4	67		0.400			0.110	Inhibits bone metastasis in prostate cancer, liver metastasis in T-cell lymphoma	(Kruger et al., 2005; Bonfil et al., 2006; Bonfil et al., 2007; Lee et al., 2007)
41		25				186					(Bernardo et al., 2002)
42		0.046	10			0.100			0.21		(Bernardo et al., 2002)
43	128	0.006	2.2	31		0.16			0.09		(Lee et al., 2007)
44											(Lee et al., 2007)
45	140	0.023	0.600	18.2		0.005			0.145		(Lee et al., 2009a)

Table 4

Vascular Effects of Specific MMP or TIMP Gene Ablation in Mice

MMP/TIMP Gene Ablated	Vascular Effects	Reference
MMP-2	Reduction of neointima formation in vascular injury. Protection from cardiac rupture post-myocardial Infarction.	(Johnson and Galis, 2004; Matsumura et al., 2005)
MMP-9	Reduction of neointima formation in vascular injury. Protection from cardiac rupture post-MI, vessel stiffness and increased pulse pressure.	(Ducharme et al., 2000; Johnson and Galis, 2004; Flamant et al., 2007)
MMP-11	Accelerated neointima formation in vascular injury	(Lijnen et al., 1999)
MMP-14	Defective angiogenesis	(Holmbeck et al., 1999; Zhou et al., 2000)
TIMP-1	Accelerated neointima formation in vascular injury. Spontaneous cardiac dilatation, augmented dysfunction post-MI.	(Creemers et al., 2003)
TIMP-3	Spontaneous dilated cardiomyopathy	(Fedak et al., 2004)

Table 5

Clinical studies of the association between MMPs and HTN and the effect of antihypertensives on MMP levels

Study Type/Yr	Subjects	Design	Results	Reference
Clinical Trial/1998	37 patients with never-treated essential HTN and 23 normotensive control subjects	Serum level of carboxy-terminal telopeptide of collagen type I as a marker of ECM collagen type I degradation, MMP-1, TIMP-1, and MMP-1/TIMP-1 ratio. Measurements repeated in 26 patients after 1 year treatment with lisinopril (ACE inhibitor)	Decreased baseline MMP-1 and increased baseline TIMP-1 in hypertensives vs. normotensives. No difference in baseline collagen type I between the two groups. HTN patients with baseline left ventricular hypertrophy exhibited lower free MMP-1 and collagen type I and higher free TIMP-1 than HTN patients without baseline left ventricular hypertrophy. Treated patients showed an increase in serum collagen type I and free MMP-1 and a decrease in free TIMP-1	(Laviades et al., 1998)
Clinical Trial/2003	42 HTN patients	6 Months treatment with amlodipine	Normalized plasma levels of MMP-9, but not MMP-2	(Zervoudaki et al., 2003)
Cross Sectional/2006	44 HTN patients and 44 controls	Measure plasma levels and activities of MMP-2, -9, and TIMP-1	Higher levels of MMP-2, -9, and TIMP-1 in HTN patients	(Derosa et al., 2006)
Cross Sectional/2007	202 HTN patients 54 control subjects	Measure carotid-femoral PWV and carotid-radial PWV to reflect arterial elasticity; serum MMP-9 and TIMP-1 levels measured by ELISA	HTN patients had higher levels of MMP-9 and TIMP-1. Age, systolic blood pressure, heart rate and TIMP-1 were independent predictors of carotid-femoral PWV in patients with essential HTN	(Tan et al., 2007)
Clinical Trial/2009	33 patients with stage 1 HTN and 16 age-matched control	Serum MMP-9 and TIMP-1 levels assessed in the hypertensive group before and after 3-month-antihypertensive therapy	Pre-treatment serum MMP-9 levels were higher in the hypertensive group while serum TIMP-1 levels were lower. Serum MMP-9 levels decreased and TIMP-1 levels increased after the antihypertensive treatment	(Onal et al., 2009)
RCT/2009	595 Nonhypertensive Framingham Offspring Study participants (mean age 55 yrs; 360 women) without prior heart failure or MI	Routine measurement of TIMP-1, MMP-9, and procollagen III N-terminal peptide for a period of 4 years	81 Participants (51 women) developed HTN, and 198 (114 women) progressed to a higher BP category. A 1-SD increment of log-TIMP-1 was associated with 50% higher incidence of HTN and 21% higher risk of BP progression. Individuals in the top TIMP-1 tertile had a 2.15-fold increased risk of HTN and 1.68-fold increased risk of BP progression relative to the lowest tertile. Individuals with detectable MMP-9 had 1.97-fold higher risk of BP progression than those with undetectable levels. Plasma procollagen III N-terminal peptide was not associated with HTN or BP progression. Higher TIMP-1 and MMP-9 levels were associated with BP progression on follow-up	(Dhingra et al., 2009)
Cross sectional/2010	64 children (34 male and 30 females)	Measure concentrations of MMP-2, -9 and TIMP-2, and insulin-like growth factor-I and its binding protein IGFBP-3	Changes in circulating levels of MMP-2 and -9 correlate with systolic BP and vascular function. MMP-2 was an independent predictor of systolic BP, whereas MMP-9 was an independent predictor of vascular dysfunction	(Sesso and Franco)2010)

PWV, pulse wave velocity