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Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease

Xi Wang and **Raouf A. Khalil**

Vascular Surgery Research Laboratories, Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA 02115, USA

Abstract

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that degrade various proteins in the extracellular matrix (ECM). Typically, MMPs have a propeptide sequence, a catalytic metalloproteinase domain with catalytic zinc, a hinge region or linker peptide, and a hemopexin domain. MMPs are commonly classified on the basis of their substrates and the organization of their structural domains into collagenases, gelatinases, stromelysins, matrilysins, membrane-type (MT)-MMPs, and other MMPs. MMPs are secreted by many cells including fibroblasts, vascular smooth muscle (VSM) and leukocytes. MMPs are regulated at the level of mRNA expression and by activation through removal of the propeptide domain from their latent zymogen form. MMPs are often secreted in an inactive proMMP form which is cleaved to the active form by various proteinases including other MMPs. MMPs degrade various protein substrates in ECM including collagen and elastin. MMPs could also influence endothelial cell function as well as VSM cell migration, proliferation, Ca^{2+} signaling and contraction. MMPs play a role in vascular tissue remodeling during various biological processes such as angiogenesis, embryogenesis, morphogenesis and wound repair. Alterations in specific MMPs could influence arterial remodeling and lead to various pathological disorders such as hypertension, preeclampsia, atherosclerosis, aneurysm formation, as well as excessive venous dilation and lower extremity venous disease. MMPs are often regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs), and the MMP/TIMP ratio often determines the extent of ECM protein degradation and tissue remodeling. MMPs may serve as biomarkers and potential therapeutic targets for certain vascular disorders.

Keywords

angiogenesis; aneurysm; atherosclerosis; cell signaling; extracellular matrix; hypertension; smooth muscle; TIMPs

Correspondence and Reprints: Raouf A Khalil, MD, PhD, Harvard Medical School, Brigham and Women's Hospital, Division of Vascular Surgery, 75 Francis Street, Boston, MA 02115, Tel : (617) 525-8530, Fax : (617) 264-5124, raouf_khalil@hms.harvard.edu.

CONFLICT OF INTEREST

None

1. INTRODUCTION

MMPs are a family of zinc-dependent endoproteases with multiple roles in tissue remodeling and degradation of various proteins in the extracellular matrix (ECM). MMPs promote cell proliferation, migration, and differentiation and could play a role in angiogenesis, cell apoptosis, and tissue repair. MMPs may also affect bioactive molecules on the cell surface and modulate various cellular and signaling pathways. Alterations in MMP expression and activity occur in normal biological processes e.g. during pregnancy and wound healing, but have also been observed in cardiovascular diseases such as atherosclerosis, aneurysms, and chronic venous disease.

In this chapter, we will use data reported in PubMed and other scientific databases as well as data from our laboratory to provide a general overview of the biochemical and biological properties of MMPs with emphasis on MMP structure, tissue distribution, and protein substrates. We will also discuss the regulation of MMP activity by endogenous tissue inhibitors of metalloproteinases (TIMPs) and other synthetic MMP inhibitors. We will then describe specific classes of MMPs and provide examples of their role in cardiovascular diseases. We will conclude the chapter by highlighting the potential benefits of MMPs as biomarkers and therapeutic targets in cardiovascular conditions. Additional information regarding specific MMP functions can be found in other reports (Raffetto and Khalil, 2008; Kucukguven and Khalil, 2013; MacColl and Khalil, 2015; Mittal et al., 2016).

2. MMP STRUCTURE

MMPs were first identified as a collagen proteolytic activity that causes ECM protein degradation during resorption of the tadpole tail (Gross and Lapiere, 1962). MMPs are now grown to a large family of endopeptidases or matrixins that belong to the metzincins superfamily of proteases. MMPs are highly homologous, multidomain, zinc (Zn^{2+}) containing metalloproteinases that degrade various protein components of ECM. The MMP family shares 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 or hinge region of variable length, and a hemopexin domain of about 200 amino acids (Fig. 1) (Ohuchi et al., 1997; Holmbeck et al., 1999; Nagase et al., 2006; Cauwe et al., 2007).

Most MMPs also share three characteristics. First, MMPs show homology to collagenase-1 (MMP-1). 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. Second, MMPs contain a cysteine switch motif PRCGXPD in which the cysteine sulfhydryl group chelates the active site Zn^{2+} thus keeping MMPs in their inactive proMMP form. Third, the catalytic domain of MMPs harbors a Zn^{2+}-binding motif to which Zn^{2+} is bound by three histidines from the conserved sequence HEXXHXXGXXH, with the assistance of a conserved glutamate, and a conserved methionine sequence XBMX (Met-turn) located 8-residues down from the Zn^{2+} binding motif that supports the structure surrounding the catalytic Zn^{2+} (Fig. 1) (Bode et al., 1993; Bode et al., 1999; Visse and Nagase, 2003).

In vertebrates, the MMP family comprises 28 members, at least 23 are expressed in human tissues, and 14 of those MMPs are expressed in the vasculature (Table 1) (Visse and Nagase, 2003). MMPs are commonly classified on the basis of their substrates and the organization of their structural domains into collagenases, gelatinases, stromelysins, matrilysins, membrane-type (MT)-MMPs, and other MMPs. Different classes of MMPs have additional specific structural features that distinguish them from the typical MMP structure (Fig. 1) (Pei et al., 2000; English et al., 2001; Kucukguven and Khalil, 2013). For instance, while the topology of MMPs could be well conserved, a major difference between MMPs lies in the S1′ subsite, a well-defined hydrophobic pocket of variable depth that is critical for the interaction of an MMP with its specific substrate (Gall et al., 2001).

3. SOURCES and TISSUE DISTRIBUTION of MMPS

MMPs are produced by multiple tissues and cells (Table 1). MMPs are secreted by connective tissue, pro-inflammatory, and uteroplacental cells including fibroblasts, osteoblasts, endothelial cells, vascular smooth muscle (VSM), macrophages, neutrophils, lymphocytes, and cytotrophoblasts.

Dermal fibroblasts and leukocytes are major sources of MMPs, especially MMP-2 (Saito et al., 2001), and platelets are important sources of MMP-1, MMP-2, MMP-3, and MMP-14 (Seizer and May, 2013). In general, MMPs are either secreted from the cells or anchored to the plasma membrane by proteoglycans such as heparan sulfate glycosaminoglycans or by special trans-membrane domains as in MT-MMPs and MMP-23 (Visse and Nagase, 2003).

Because MMPs play a major role in ECM remodeling, they are highly distributed in most connective tissues. MMPs have also been localized in many cell types, suggesting other biological roles for MMPs. MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13, and MT1-MMP and MT3-MMP are expressed in various vascular tissues and cells (Chen et al., 2013). In the rat inferior vena cava, MMP-2 and MMP-9 are localized in different layers of the venous wall including the intima, media and adventitia, suggesting interaction with different molecules and signaling pathways in endothelial cells, VSM, and ECM, respectively (Raffetto et al., 2008). Other studies have shown specific distribution of MMP-1, MMP-2, MMP-3, and MMP-7 in endothelial cells and VSMCs, MMP-2 in the adventitia (Sansilvestri-Morel et al., 2007), MMP-9 in endothelial cells, medial VSMCs, and adventitial microvessels, and MMP-12 in VSMCs and fibroblasts of human great saphenous vein (Woodside et al., 2003).

4. MMP ACTIVATION

MMPs are regulated at multiple levels including mRNA expression, activation of the proenzyme to the active form, and the generally counteracting inhibitory actions of endogenous TIMPs. MMPs are synthesized as pre-proMMPs, from which the signal peptide is removed during translation to generate proMMPs. In these zymogens or proMMPs, the cysteine from the propeptide PRCGXPD ‘cysteine switch’ motif coordinates with the catalytic Zn^{2+} to keep the proMMP in a latent inactive form (Nagase et al., 2006). In order to process and activate these zymogens or proMMPs, the cysteine switch is cleaved and the

propeptide domain is detached often by other proteolytic enzymes such as serine proteases, the endopeptidase furin, plasmin, or other MMPs to produce the active MMP form (Nagase et al., 2006). Furin-containing MMPs such as MMP-11, MMP-21, and MMP-28 and MT-MMPs have a furin-like pro-protein convertase recognition sequence at the C-terminus of the propeptide and therefore are activated intracellularly by furin (Fig. 1) (Pei and Weiss, 1995). MT-MMPs first undergo intracellular activation by furin, then proceed to the cell surface where they can cleave and activate other proMMPs (English et al., 2001). TIMPs may be important for the formation of non-inhibitory proMMP/TIMP/MT-MMP complexes. Non-inhibitory complexes between progelatinases and TIMPs are restricted to proMMP-2 and TIMP-2, TIMP-3, or TIMP-4, and to MMP-9 and TIMP-1 (Morgunova et al., 2002). For example, TIMP-2 first forms a complex with proMMP-2 by binding to its hemopexin domain, and the complex then localizes to the cell surface where it binds to the active site of a MT1-MMP molecule (Strongin et al., 1995; Sato et al., 1996; Butler et al., 1998; Zucker et al., 1998). This ternary proMMP-2/TIMP-2/MT1-MMP complex then facilitates the cleavage and activation of its bound proMMP-2 to active MMP-2 by another “free” MT1-MMP molecule. This non-inhibitory complex is different from the inhibitory complex of TIMP-2/active MMP-2, as it is formed between the C-terminal domain of TIMP-2 and the C-terminal hemopexin of MMP-2, such that both molecules maintain their inhibitory and proteolytic properties, respectively (Kolkenbrock et al., 1991; Fridman et al., 1993; Morgunova et al., 2002). The activation of MMP-2 on the cell surface allows it to accumulate pericellularly where it reaches marked collagenolytic activity locally in the extracellular space (Visse and Nagase, 2003). Similarly, the stromelysins MMP-3 and MMP-10 are secreted from the cells as inactive proMMPs, but are then activated on the cell surface. MMPs can also be activated by various physicochemical agents including heat, low pH, thiol-modifying agents such as 4-aminophenylmercuric acetate, mercury chloride, N-ethylmaleimide, oxidized glutathione, sodium dodecyl sulfate, and chaotropic agents. Most of these activators disrupt the cysteine-Zn^{2+} coordination at the cysteine switch motif of the MMP molecule. Other MMP activators include plasmin which activates MMP-9. Also, both MMP-3 and hypochlorous acid activate MMP-7, and MMP-7 could activate MMP-1 (Kucukguven and Khalil, 2013).

MMP expression/activity can also be influenced by hormones, growth factors, and cytokines (Verma and Hansch, 2007). For example, ovarian sex hormones affect the expression/activity of various MMPs which could in turn participate in endometrial tissue remodeling and shedding during the menstrual and estrous cycles. Also, increases in estrogen and progesterone as well as vascular endothelial growth factor (VEGF) and placental growth factor during pregnancy could promote the expression/activity of uteroplacental MMPs and in turn facilitate cytotrophoblast tissue invasion and uteroplacental growth and vascularization. MMPs are regulated by growth factors in other cells and tissues (Hollborn et al., 2007). For example, overexpression of VEGFa in SNU-5 cells increases MMP-2 expression, while downregulation of VEGFa decreases MMP-2 expression (Mao et al., 2014). Also, platelet derived growth factor-BB (PDGF-BB) increases MMP-2 expression in rat VSMCs, possibly via Rho-associated protein kinase, extracellular signal-regulated kinases (ERK), and phosphorylation of p38 mitogen-activated protein kinase (MAPK) (Cui et al., 2014). In carotid artery plaques, epidermal growth factor (EGF) upregulates MMP-1

and MMP-9 mRNA transcripts and increases MMP-9 activity in VSMCs (Rao et al., 2014). In contrast, transforming growth factor-β1 (TGF-β1) downregulates MMPs via a TGF-β1 inhibitory element in the MMP promoter. Interestingly, MMP-2 does not have this element, and therefore may not be affected, or in some instances upregulated, by TGF-β1.

MMP expression/activity also increases during the inflammatory process. MMPs are secreted by pro-inflammatory cells and their secretion is promoted by pro-inflammatory cytokines.

5. MMP SUBSTRATES

The ECM is composed of fibers, proteoglycans and polysaccharides. Fibers are largely glycoproteins and include collagen, elastin, laminin, fibronectin, vitronectin, aggrecan, entactin, fibrin and tenascin. Collagen is the main ECM protein. Elastin is not glycosylated and provides plasticity and flexibility to certain tissues particularly the arteries, lungs and skin. Laminin is localized in the basal lamina of the epithelium. Fibronectin is used by cells to bind to ECM, and can modulate the cytoskeleton to facilitate or hinder cell movement. Proteoglycans have more carbohydrates than proteins, and attract water to keep the ECM hydrated. Proteoglycans also facilitate binding of growth factors to the ECM milieu. Syndecan-1 is a proteoglycan and integral transmembrane protein that bind chemotactic cytokines during the inflammatory process. Other ECM components include polysaccharides such as hyaluronic acid (Kucukguven and Khalil, 2013).

MMPs promote tissue remodeling and the turnover of various ECM proteins including collagen, elastin, gelatin, and other glycoproteins and proteoglycans. Collagen and elastin are essential for the structural integrity of the vascular wall and are important MMP substrates. MMPs break down collagen type I, II, III, IV, V, VI, VII, VIII, IX, X, and XIV with different efficacies. MMP degrades other ECM protein substrates such as aggrecan, entactin, fibronectin, tenascin, laminin, myelin basic protein, and vitronectin (Table 1). Casein is not a physiological MMP substrate, but is digested by and used to measure the activity of several MMPs in zymography assays (Kucukguven and Khalil, 2013).

The hemopexin domain may confer most of the MMP substrate specificity and may be essential in the recognition and catalytic degradation of fibrillar collagen (Patterson et al., 2001; Suenaga et al., 2005). On the other hand, the catalytic domain may be sufficient in the degradation of non-collagen substrates (Visse and Nagase, 2003). MMPs catalytic activity generally requires Zn^{2+} and a water molecule flanked by three conserved histidine residues and a conserved glutamate, with a conserved methionine acting as a hydrophobic base to support the structure surrounding the catalytic Zn^{2+} in the MMP molecule (Fig. 2). During the initial transition states of the MMP-substrate interaction, Zn^{2+} is penta-coordinated with a substrate's carbonyl oxygen atom, one oxygen atom from the MMP glutamate-bound water, and the three conserved histidines in the MMP molecule. The Zn^{2+}-bound water then performs a nucleophilic attack on the substrate, resulting in the breakdown of the substrate and the release of a water molecule (Fig. 2) (Bode et al., 1999; Pelmenschikov and Siegbahn, 2002; Park et al., 2003; Jacobsen et al., 2010). The MMP-substrate interaction may involve alternative transition state whereby Zn^{2+} is penta-coordinated with a substrate's

carbonyl oxygen atom, two oxygen atoms from the MMP conserved glutamate, and two of the three conserved histidines. One oxygen from glutamate then performs a nucleophilic attack and causes breakdown of the substrate (Manzetti et al., 2003). Peptide catalysis and substrate degradation is also influenced by specific subsites or pockets (S) within the MMP molecule that interact with corresponding substituents (P) in the substrates (Fig. 2). The most important pocket for substrate specificity and binding is the MMP S1' pocket, which is extremely variable and could have a shallow, intermediate, or deep location (Bode et al., 1999; Park et al., 2003; Jacobsen et al., 2010). MMP-1 and MMP-7 have shallow S1' pocket. MMP-2, MMP-9, and MMP-13 have intermediate S1' pocket, while MMP-3, MMP-8, and MMP-12 have deep S1' pocket (Park et al., 2003). S2' and S3' pockets are shallower and, therefore, more exposed to solvents than S1' pocket (Jacobsen et al., 2010). Second to the S1' pocket, the S3 pocket may contribute to substrate specificity (Nagase et al., 2006).

Examination of the crystal structure of the MMP-11 catalytic domain during the interaction with a phosphinic inhibitor mimicking a D,L-peptide has suggested that the MMP-11 S1′ pocket forms a tunnel running through the enzyme. This open channel is filled by the MMP inhibitor P1′ group which adopts a constrained conformation to fit the MMP-11 S1′ pocket, together with two water molecules interacting with the MMP-11 specific residue Gln215. The presence of a water molecule interacting with one oxygen atom of the MMP inhibitor phosphinyl group and the proline residue of the MMP Met-turn suggests how the intermediate formed during proteolysis may be stabilized. Furthermore, the hydrogen bond distance observed between the methyl of the phosphinic group and the carbonyl group of Ala182 mimics the interaction between this carbonyl group and the amide group of the cleaved peptidic bond. This crystal structure provides a good model to study the mechanism of proteolysis by MMPs (Gall et al., 2001).

MMPs show significant substrate specificity. Stromelysin-1 and stromelysin-2 (MMP-3 and MMP-10) do not cleave interstitial collagen, but degrade other ECM protein substrates and cleave certain proMMPs to their active form. MMP-3 and MMP-10 have similar substrate specificity, but MMP-3 has greater proteolytic efficiency than MMP-10. Stromelysin-3 (MMP-11) is distantly related to stromelysin-1 and stromelysin-2. While MMP-11 does not cleave interstitial collagen, it has very weak proteolytic activity toward other ECM protein substrates (Pei and Weiss, 1995). Different MMPs may cooperate in order to completely degrade a protein substrate. For example, the collagenases MMP-1, MMP-13, and MMP-18 first unwind triple helical collagen and hydrolyze the peptide bonds of fibrillar collagen type I, II and III into ¾ and ¼ fragments (Chung et al., 2004; Nagase et al., 2006). The resulting single α-chain gelatins are further degraded by the gelatinases MMP-2 and MMP-9 into smaller oligopeptides (Patterson et al., 2001). Of note, gelatinases have three type-II fibronectin repeats in their catalytic domain that allow them to bind gelatin as well as collagen and laminin. Therefore, while MMP-2 is primarily a gelatinase, it can function much like the collagenase MMP-1, although in a weaker manner (Nagase et al., 2006). MMP-2 can degrade collagen in two steps; first by inducing a weak interstitial collagenase-like collagen degradation into ¾ and ¼ fragments, then by promoting gelatinolysis using the fibronectin-like domain (Aimes and Quigley, 1995). MMP-9 could also act as a collagenase

and gelatinase. As a collagenase, MMP-9 binds the α2 chains of collagen IV with high affinity even when it is inactive, making the substrate readily available (Olson et al., 1998).

6. TISSUE INHIBITORS OF METALLOPROTEINASES (TIMPs)

MMPs are inhibited by both endogenous and exogenous inhibitors. TIMPs are endogenous MMP inhibitors that bind MMPs in a 1:1 stoichiometry (Fig. 3) (Bode et al., 1999; Nagase et al., 2006). 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 Cys1 is important for 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+}. The TIMP molecule wedges into the active-site cleft of MMP in a manner similar to that of the substrate (Fig. 3). Four homologous TIMPs have been identified and termed as TIMP-1, TIMP-2, TIMP-3 and TIMP-4. TIMP-1 and TIMP-3 are glycoproteins, while TIMP-2 and TIMP-4 do not contain carbohydrates. TIMPs can inhibit multiple MMPs with different efficacies. For example, TIMP-2 and TIMP-3 inhibit MT1-MMP and MT2-MMP, whereas TIMP-1 is a poor inhibitor of MT1-MMP, MT3-MMP, MT5-MMP and MMP-19 (Baker et al., 2002). Also, while TIMP-1 and TIMP-2 bind MMP-10 (stromelysin-2), the binding is 10-fold weaker than that to MMP-3 (stromelysin-1) (Batra et al., 2012). TIMP-1 has a threonine-2 (Thr2) residue that interacts with the MMP S1’ pocket in a manner similar to that of a substrate P1’ substituent, largely determining the affinity to MMP-3. Substitutions at Thr2 affect the stability of the TIMP-MMP complex and the TIMP specificity to different MMPs. For instance, substitution of Thr2 by alanine results in a 17-fold decrease in the ability of TIMP-1 to bind MMP-1 compared with MMP-3 (Meng et al., 1999).

TIMPs are widely distributed in many tissues and organs. A change in either MMP or TIMP levels could alter the MMP/TIMP ratio and cause a net change in MMP activity. MMP inhibition by TIMPs would decrease degradation of ECM proteins. Serine proteinases such as neutrophil elastase could inactivate TIMPs, spare MMPs from inhibition by TIMPs, and in turn favor breakdown of ECM proteins (Desrochers et al., 1992; Liu et al., 2000).

In addition to inhibiting MMPs, TIMPs can inhibit a broader spectrum of metalloproteinases. TIMP-1 inhibits a disintegrin and metalloproteinase-10 (ADAM-10) while TIMP-2 inhibits ADAM-12 (Amour et al., 2000; Kveiborg et al., 2010). TIMP-3 has a much broader metalloproteinase inhibition profile including ADAM-10, ADAM-12, and ADAM-17 as well as a disintegrin and metalloproteinase with thrombospondin motif ADAMTS-1, ADAMTS-2, ADAMTS-4 and ADAMTS-5 (Amour et al., 2000; Kashiwagi et al., 2001; Rodriguez-Manzaneque et al., 2002; Jacobsen et al., 2008). This broad-spectrum metalloproteinase inhibition by TIMP-3 is best illustrated by the observation that TIMP-3 ablation in mice is associated with emphysema-like alveolar damage and faster apoptosis of mammary epithelial cells after weaning, whereas TIMP-1 or TIMP-2-null mice do not exhibit such abnormalities (Fata et al., 2001; Leco et al., 2001).

7. OTHER BIOLOGICAL AND PLEIOTROPIC MMP INHIBITORS

In addition to endogenous TIMPs, α2-Macroglobulin is another endogenous MMP inhibitor found in blood and tissue fluids. Human α2-Macroglobulin is a glycoprotein consisting of four identical subunits and a wide-spectrum proteinase inhibitor that inhibits most endopeptidases including MMPs, by entrapping them within the macroglobulin. The complex is then rapidly internalized and cleared by endocytosis via low density lipoprotein receptor-related protein-1 (Strickland et al., 1990).

Other proteinase inhibitors may inhibit MMPs by unclear mechanisms (Murphy and Nagase, 2008). For instance, a secreted form of β-amyloid precursor protein or a C-terminal fragment of procollagen C-proteinase enhancer protein can inhibit MMP-2. Reversion-inducing-cysteine-rich protein with kazal motifs (RECK) is a glycosyl phosphatidylinositol (GPI)-anchored glycoprotein expressed in many cells including vascular smooth muscle cells (VSMCs), and inhibits MMP-2, MMP-9 and MMP-14 when expressed in human fibrosarcoma-derived cell line HT1080 (Oh et al., 2001). Tissue factor pathway inhibitor-2 is a serine proteinase inhibitor that can inhibit MMP-1 and MMP-2.(Herman et al., 2001)

Monoclonal antibodies have high specificity and affinity for specific MMPs and can detect MMPs in the body fluids and tissues. Monoclonal antibodies REGA-3G12 and REGA-2D9 react specifically with MMP-9, and do not cross-react with MMP-2. MMP inhibition by REGA-3G12 involves the catalytic domain and not the Zn^{2+} binding region or the fibronectin region. REGA-1G8 is less specific and cross reacts with serum albumin. Patients with Crohn's disease suffer from recurring fistulae, and MMP-9 is upregulated in crypt abscesses and around fistulae, suggesting a role in fistula formation. In a mouse heterotopic xenograft model of intestinal fibrosis, treatment with anti-MMP-9 monoclonal antibody reduced collagen deposition and hydroxyproline content in day-14 intestinal grafts, suggesting reduced fibrosis. Anti-MMP-9 antibody may be a promising therapeutic strategy for fibrosis-related complications of inflammatory bowel disease (Goffin et al., 2016).

The hemopexin domain could be a potential target for MMP antibodies. The hemopexin domain of MMP-1 is essential for the specificity of its catalytic domain to cleave collagen. Also, MMP-2 is localized at extracellular sites by its fibronectin domains and MT1-MMP (MMP-14) requires the hemopexin domain for cell surface clustering and ability to activate proMMP-2 (Suenaga et al., 2005). The hemopexin domain can also be used to protect specific MMP substrates from degradation by MMPs. Studies have generated glutathione-S-transferase (GST) fusion proteins containing MMP-9 hemopexin domain or truncated forms corresponding to the specific structural blades B1-B4 of the MMP-9 hemopexin domain. GST-MMP-9 hemopexin domain inhibited MMP-9-dependent degradation of gelatin, but not other MMP-9 substrates such as a fluorogenic peptide, αB crystalline, or nonmuscular actin. The MMP-9 hemopexin domain may shield gelatin and prevent its binding to and degradation by MMP-9. GST-MMP-9 hemopexin domain also abolishes the degradation of gelatin by MMP-2, confirming that it is not an MMP-9 antagonist. ELISA assays demonstrated that GST-B4 and GST-B1 specifically bound to gelatin. These findings suggest new functions of MMP-9 hemopexin domain and its blades B4 and B1 that could help in designing specific inhibitors of gelatin degradation (Ugarte-Berzal et al., 2016).

Small interfering RNA (siRNA) can be used to assess the role of a specific MMP in a biological process. MMP-2 siRNA inhibits the transcriptional product of MMP-2 (Chetty et al., 2006). Targeted delivery of MMP siRNA could decrease MMP expression and unrestrained ECM turnover and tissue remodeling in localized pathological conditions such as aneurysm, varicose veins, osteoarthritis and tumors. For instance, specific inhibition of either MMP-2 or MT1-MMP by specific shRNAs hampers melanoma cell migration and invasion (Marusak et al., 2016). Gene therapy has shown some success in animal models, and with the design of efficient and safe gene delivery into target tissues downregulation of MMPs using siRNA or overexpression of TIMPs may have clinical applications (van der Laan et al., 2003).

Sulodexide (SDX) is a highly purified glycosaminoglycan containing fast-moving heparin fraction (80%) and dermatan sulfate (20%). SDX has pro-fibrinolytic, anti-thrombotic, anti-inflammatory and endothelial protective activity in the vascular system that could be partly related to its effects on MMPs. SDX decreases MMP-9 secretion from white blood cells without MMP prodomain displacement (Mannello et al., 2013), and may inhibit proteases with cysteine residues such as MMP-2 and MMP-9 (Serra et al., 2014).

The intracellular signaling pathways and the upstream inducers and downstream transcription factors that affect MMP or TIMP mRNA expression may serve as potential targets for MMP inhibition. Extracellular matrix metalloproteinase inducer (EMMPRIN) is a widely expressed membrane protein of the immunoglobulin superfamily (Biswas et al., 1995) that has been implicated in tissue remodeling (Huet et al., 2008b) and various cardiovascular pathological conditions including heart failure (Spinale et al., 2000) and atherosclerosis (Major et al., 2002). Anti-EMMPRIN antibody directed against a specific epitope inhibits the production of MMP-9 in tumor cell-macrophage *in vitro* co-culture systems. The EMMPRIN antibody also inhibited *in vivo* tumor progression in both the RENCA renal cell carcinoma and CT26 colon carcinoma subcutaneous tumor models, and reduced tumor size and number of metastatic foci in the 4T1 orthotopic model. This was achieved by inhibiting angiogenesis as assessed by immunohistochemical staining for the endothelial marker CD31, by inhibiting tumor cell proliferation as assessed by staining for Ki-67, and by enhancing tumor cell apoptosis as assessed by the TUNEL assay. The EMMPRIN antibody also recruited more macrophages into the tumor, and skewed the tumor microenvironment for macrophages from TGF-β-dominated anti-inflammatory microenvironment to a less immunosuppressive one, thus allowing stimulated macrophages to perform antibody-dependent cell cytotoxicity and to kill tumor cells. These findings suggest that EMMPRIN antibody maps the epitope capable of inducing MMPs, and place EMMPRIN as a potential target to modulate MMPs in cancer therapy and cardiovascular disease (Walter et al., 2015). Blockade of mitogen-activated protein kinase (MAPK), NF-κB or activator protein (AP)-1 has shown some efficacy *in vitro* and in animal models of arthritis, partly due to changes in MMP expression (Mix et al., 2004). Also, biologics may block inflammatory cytokines and reduce MMP expression in different tissues. Statins may inhibit MMPs through pleiotropic effects. For instance, atorvastatin inhibits MMP-1, MMP-2, and MMP-9 expression in human retinal pigment epithelial cells (Dorecka et al., 2014), and MMP-1, MMP-2, MMP-3, and MMP-9 secretion from rabbit macrophages and cultured rabbit aortic and human saphenous vein VSMCs (Luan et al., 2003). Also, in a rat

model of heart failure, pravastatin suppressed the increase in myocardial MMP-2 and MMP-9 activity (Ichihara et al., 2006).

8. SYNTHETIC MMP INHIBITORS

Divalent ions can influence MMP release and activity. Cu^{2+} ion decreases the secretion of MMP-2 (Guo et al., 2005). Deep sea water components such as Cu^{2+}, Mg^{2+}, and Mn^{2+} inhibit proliferation and migration of cultured rat aortic smooth muscle cells (RASMCs) by inhibiting not only extracellular signal–regulated kinase (ERK1/2) and MAPK kinase (MEK) phosphorylation, but also MMP-2 activity (Li et al., 2014a), a mechanism that may involve interference with Zn^{2+} binding at the MMP catalytic active site. Zn^{2+} chelators deprive MMPs from the Zn^{2+} ion critical for their activity (Newsome et al., 2007). Utilizing the Zn^{2+} binding property, several MMP inhibitors have been developed (Benjamin and Khalil, 2012). MMP inhibitors often have a Zn^{2+} binding group, e.g. hydroxamic acid, carboxylic acid, sulfhydryl group (Hu et al., 2007). Zn^{2+} binding globulins (ZBGs) displace the Zn^{2+}-bound water molecule in a MMP and inactivate the enzyme. A ZBG is also an anchor that keeps the MMP inhibitor in the MMP active site and allows the backbone of the MMP inhibitor to enter the MMP substrate-binding pockets (Jacobsen et al., 2010). Hydroxamic acids include succinyl, sulfonamide, and phosphinamide hydroxamates (Scozzafava and Supuran, 2000; Pochetti et al., 2006; Hu et al., 2007). Batimastat (BB-94), marimastat (BB-2516), and ilomastat (GM6001) are broad spectrum succinyl hydroxamates with a structure mimicking collagen, and inhibit MMPs by bidentate chelation of Zn^{2+} (Wojtowicz-Praga et al., 1997; Hu et al., 2007). Other ZBGs include carboxylic acids, sulfonylhydrazides, thiols, aminomethyl benzimidazole-containing ZBGs, phosphorous- and nitrogen-based ZBGs, and heterocyclic bidentate chelators (Skiles et al., 2001; Puerta et al., 2004; Jacobsen et al., 2010). Tetracyclines such as doxycycline and mechanism-based MMP inhibitors such as SB-3CT also inhibit MMPs by chelating Zn^{2+} (Hu et al., 2007). SB-3CT (compound 40) coordinates with the MMP Zn^{2+}, thus allowing the conserved Glu202 to perform a nucleophilic attack and form a covalent bond with the compound (Jacobsen et al., 2010). When compared to the traditional competitive Zn^{2+} chelating MMP inhibitors, the strong covalent bond in SB-3CT prevents dissociation of the MMP inhibitor and decreases the rate of catalytic turnover, and therefore reduces the amount of MMP inhibitor needed to saturate the MMP active site (Bernardo et al., 2002).

Some MMP inhibitors such as compound 37 do not have ZBGs and do not bind to the highly conserved Zn^{2+} binding group (Johnson et al., 2007). Instead, these MMP inhibitors undergo non-covalent interaction with the S1’, S2’, S3’, and S4’ pockets in the MMP molecule in a fashion similar to that of the substrate P1’, P2’, P3’, and P4’ substituents. The specificity and efficacy of the MMP inhibitor are determined by which pockets it blocks in the MMP molecule (Hu et al., 2007).

Several synthetic MMP inhibitors have been developed and some of them have been evaluated as investigational or therapeutic tools for degenerative diseases and vascular disorders (Jacobsen et al., 2010). However, because of the inherent flexibility in the MMP active-site, accurate modeling of specific MMP–inhibitor complexes has been markedly limited (Verma and Hansch, 2007). Despite the marked advances in the design of MMP

inhibitors, doxycycline is the only FDA-approved MMP inhibitor (Chen et al., 2013). MMP inhibitors have the potential to be used clinically in cardiovascular disease if their selectivity toward specific MMPs is enhanced and their side effects are minimized using targeted delivery (Li et al., 2005).

9. ROLE OF MMPS IN VASCULAR BIOLOGY

MMPs play a role in many biological processes such as tissue remodeling and growth as well as tissue defense mechanisms and immune response. Increased expression of MMPs has been detected during different stages of mammalian development, from embryonic implantation to the morphogenesis of different tissues and organs including lung, bone and blood vessels (Harvey et al., 1995; Vu and Werb, 2000; Page-McCaw et al., 2007). MMPs participate in vascular tissue remodeling, cell growth, proliferation, migration, and differentiation, and tissue invasion and vascularization (Fig. 4). Induction of MMP activity contributes to the disassembly of intercellular junctions and the degradation of ECM, thus overcoming the physical constraint to cell movement (Mauris et al., 2014). Also, MMPs have been localized in most vascular cell types, suggesting that these cells could be a source of the MMPs released in ECM, and that MMPs may play a role in vascular cell signaling and intracellular pathways (Raffetto et al., 2010; Lim et al., 2011).

9.1. MMPs and Smooth Muscle growth and Proliferation

MMPs regulate VSMC growth and proliferation by several mechanisms including proteolytic cleavage of growth factors so that they become available to cells that are not in direct physical contact, degradation of ECM so that founder cells can move across the tissues into nearby stroma, and regulated receptor cleavage in order to terminate migratory signaling and cell migration (Chang and Werb, 2001). MMPs facilitate VSMC proliferation by promoting permissive interactions between VSMCs and components of ECM, possibly via integrin-mediated pathways (Morla and Mogford, 2000; Walker et al., 2003). MMPs induce the release of growth factors by cleaving the growth factor-binding proteins and matrix molecules (Zhang et al., 2004). 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 such as fibroblast growth factor-1 (FGF-1) and FGF-2, are potent mitogens for VSMCs that are released through the action of MMPs on ECM proteoglycans (Visse and Nagase, 2003). Together with ADAMs, MMPs could facilitate the release of cell surface heparin-bound epidermal growth factor (HB-EGF), which in turn stimulates VSMC proliferation (Hollenbeck et al., 2004; Lucchesi et al., 2004). MMPs also activate transforming growth factor-h (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 focal adhesion kinase (FAK), these processes upregulate and/or stabilize key regulators of the cell cycle. Dismantling of cadherin-catenin complex occurs in balloon-injured rat carotid arteries leading to increased expression of the cell cycle gene cyclin D1 which stimulates VSMC proliferation (Slater et al., 2004). 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).

MMP inhibition is used to assess the role of MMPs in VSMC proliferation. Pretreatment of human aortic smooth muscle cells (ASMCs) with extract of Buddleja officinalis attenuates high-glucose-induced cell proliferation by suppressing MMP-9 activity (Lee et al., 2010). Also, MMP-9 knockout is associated with inhibition of VSMC proliferation in mouse model of filament loop arterial injury (Cho and Reidy, 2002). However, MMP-9 knockout is not associated with decreased VSMC proliferation in mouse model of carotid artery occlusion (Galis et al., 2002), likely due to compensatory activation of other proteases (Newby, 2005). Some studies have reported excess neointima formation in rat model of carotid arteries balloon injury after treatment with the MMP inhibitor GM-6001 (Bendeck et al., 1996; Zempo et al., 1996). Other studies have shown that synthetic MMP inhibitors 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, decreased h-catenin nuclear translocation and decreased proliferation of cultured human VSMCs. Tetracycline-based MMP inhibitors reduce VSMC migration and neointima formation in rat model of carotid artery balloon injury (Bendeck et al., 2002; Islam et al., 2003). Collectively, experimental evidence largely points to a stimulatory effect of MMPs on VSMC proliferation, and reversal of this effect by MMP inhibitors.

9.2. MMPs and Smooth Muscle Migration

MMPs play a role in VSMC migration. MMP-induced ECM proteolysis can modulate cell-ECM adhesion either by removal of sites of adhesion or by exposing a binding site and in turn facilitate VSMC migration. In rat ASMCs cultured on collagen I gel to mimic ECM, exposure to interstitial flow enhanced cell motility. MMP-1 increase human ASMC migration (Jin et al., 2008; Shi et al., 2010). Upregulation of MMP-1 enhances flow-induced cell motility, and ERK1/2 phosphorylation and increased expression of activator protein-1 (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). MMP-2 activation may also be involved in chemokine-induced chemotaxis in monolayers of human VSMCs (Haque et al., 2004). Young human ASMCs produce active MMP-2 and show a greater migratory capability than aged cells. The activation of pro-MMP-2 in young cells is likely due to an increase in MT1-MMP. In contrast, aged cells produce only inactive proMMP-2. Upregulation of TIMPs could also reduce MMP-2 activity in aged cells. Interestingly, treatment of young cells with TIMP-1 or TIMP-2 leads to a migratory behavior that mimics that of aged cells (Vigetti et al., 2008). Also, MMP-2 knockout decreases VSMC migration and neointima formation in the mouse carotid ligation model (Cheng et al., 2004; Johnson and Galis, 2004).

MMP-9 may also be involved in VSMC migration (Jin et al., 2008; Shi et al., 2010). Tanshinone IIA, a major constituent of Salvia miltiorrhiza bunge, inhibits tumor necrosis factor-α (TNF-α)-induced human ASMC 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 downregulation of NF-κB may also mediate the inhibitory effects of curcumin on migration of human ASMCs (Yu and Lin, 2010). Also, MMP-9 knockout is associated with reduced

VSMC migration and neointima formation in mouse models of filament loop injury (Cho and Reidy, 2002) and carotid artery occlusion (Galis et al., 2002).

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

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

MMP inhibitors have been used to study the effect of MMPs on VSMC migration. TIMPs 1–4 delivered directly or by gene transfer inhibit SMC migration *in vitro*, reduce neointima formation in human saphenous vein in organ culture (George et al., 2000), and reduce neointma formation and intima thickening in *in vivo* models of vascular injury (Forough et al., 1996; Baker et al., 1998). TIMP gene transfer also preserves the tunica media basement membrane and inhibits VSMC migration to the intima. Synthetic MMP inhibitors inhibit migration of VSMC in cultured baboon arterial explant (Kenagy et al., 1996) and early VSMC migration in the rat model of carotid balloon injury (Islam et al., 2003). Also the MMP inhibitor GM-6001 attenuates flow-induced cell migration (Shi et al., 2010). Collectively, evidence supports that MMPs enhance VSMC migration via proteolytic degradation of ECM as well as direct cellular effects, and MMP inhibitors reduce VSMC migration.

9.3. MMPs and Smooth Muscle Relaxation

MMPs may affect VSM contraction mechanisms. Studies have suggested that MMPs via PI_3K and ATP synthesis may transactivate EGFR and contribute to the α-adrenergic receptor-induced vascular tone. Inhibition of the expression of MMP-2 or MMP-7 blunted the phosphorylation of Akt by PI_3K and thus inhibited the response to phenylephrine in rat mesenteric artery (Nagareddy et al., 2009). We have shown that phenylephrine-induced contraction of rat aorta is inhibited ~50% by MMP-2 and ~70% by MMP-9 (Chew et al., 2004). The MMP-induced inhibition of aortic contraction was concentration- and time-dependent. The inhibitory effects of MMP-2 and MMP-9 on phenylephrine-induced contraction were reversible upon washing out the MMPs, suggesting that the actions of MMPs are specific and are not solely due to irreversible degradation of ECM protein. Also, the inhibitory effects of MMPs on VSM contraction are not likely due to degradation of

phenylephrine 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 Ca^{2+} release from the intracellular stores in the sarcoplasmic reticulum and Ca^{2+} entry from the extracellular space through different types of Ca^{2+} channels. We have shown that MMP-2 and MMP-9 do not inhibit phenylephrine-induced contraction of aortic segments incubated in Ca^{2+}-free solution, suggesting little effect on Ca^{2+} release from the intracellular stores. On the other hand, MMP-2 and MMP-9 cause relaxation of phenylephrine-precontracted aortic segments, and inhibit phenylephrine-induced Ca^{2+} influx (Chew et al., 2004). Similarly, MMP-2 inhibits Ca^{2+}-dependent contraction mechanisms in isolated segments of rat inferior vena cava (Raffetto et al., 2010). The mechanism by which MMPs inhibit Ca^{2+} entry could involve direct effects on the Ca^{2+} channels. In rat inferior vena cava, MMP-2 induced relaxation is abolished in high KCl depolarizing solution, which prevents K^+ movement out of the cell via K^+ channels. Also, blockade of large conductance Ca^{2+}-activated K^+ channels (BK_{Ca}) by iberiotoxin inhibits MMP-2 induced relaxation of rat inferior vena cava, suggesting that MMP-2 actions may involve activation of BK_{Ca} and membrane hyperpolarization, which inhibit Ca^{2+} influx through voltage-gated Ca^{2+} channels (Raffetto et al., 2007). MMPs are known to 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). Further studies are needed to define the role of integrins and PARs as possible mechanisms via which MMPs could inhibit VSM contraction.

While MMP-2 and MMP-9 reduce Ca^{2+} influx in both arteries and veins (Chew et al., 2004; Raffetto et al., 2010), veins differ from arteries in their structure and function, and the effects of MMPs on the veins should not always be generalized to the arteries. Veins have fewer layers of VSMCs compared to the several layers of VSMCs in the arteries. Also, venous and arterial VSMCs originate from distinct embryonic locations and are exposed to different pressures and hemodynamic effects in the circulation (Deng et al., 2006). Studies have shown that MMP-2 expression is greater in cultured VSMCs from human saphenous vein compared with those from human coronary artery. In contrast, MMP-3, MMP-10, MMP-20, and MMP-26 expression is less in saphenous vein than coronary artery VSMCs (Deng et al., 2006). Interestingly, while some studies suggest that MMP-2 and MMP-9 levels could be similar in cultured saphenous vein and internal mammary artery VSMCs, venous VSMCs exhibit more proliferation, migration and invasion compared to arterial VSMCs (Turner et al., 2007). Similarly, the levels of TIMP-1, TIMP-2, and TIMP-3 are greater in cultured human saphenous vein than coronary artery VSMCs (Deng et al., 2006). These observations highlight the importance of further studying the differences in the expression/activity of MMPs and TIMPs in veins versus arteries and in venous versus arterial disease.

9.4. MMPs and Endothelial Cell Function

The endothelium controls vascular tone by releasing relaxing factors including nitric oxide and prostacyclin, and through hyperpolarization of the underlying VSMCs by endothelial-derived hyperpolarizing factor (EDHF) (Feletou and Vanhoutte, 2006). Protease-activate receptors (PARs 1–4) are G-protein coupled receptors and important targets of MMPs. MMP-1 and MMP-13 activate PAR-1 (Ahn et al., 2003; Trivedi et al., 2009; Austin et al., 2013). PAR-1 is expressed on a number of different types of cells including endothelial cells, platelets, leukocytes and smooth muscle cells (McNamara et al., 1993; Coughlin, 2000), and is an important target for MMP-1 and MMP-13 (Coughlin, 2001; Macfarlane et al., 2001; Coughlin, 2005). PAR-2 stimulates NO production via a pathway that targets phosphorylation of Ser1177 in endothelial nitric oxide synthase, and in turn contributes to vasodilation (Maruyama et al., 2015).

EDHF-mediated relaxation involves the opening of small and intermediate conductance Ca^{2+}-activated K^+ channels and hyperpolarization of endothelial cells. Endothelial cell hyperpolarization spreads via myoendothelial gap junctions and causes relaxation of VSMCs. EDHF could also cause hyperpolarization through opening of BK_{Ca} in VSM (Feletou and Vanhoutte, 2006). MMP-2 may increase EDHF release and enhance K^+ efflux via BK_{Ca}, leading to venous tissue hyperpolarization and relaxation (Raffetto et al., 2007). In contrast, MMP-3 may impair endothelium-dependent vasodilation (Lee et al., 2008), making it important to further examine the effects of MMPs on EDHF.

9.5. MMPs and Angiogenesis

Angiogenesis is the process of forming new blood vessels. Angiogenesis requires degradation of the vascular basement membrane and ECM remodeling to allow endothelial cells to migrate into the surrounding tissue. Angiogenesis plays a role in several biological processes and pathological conditions including the progression of atherosclerotic plaques and tumor growth (Khatri et al., 2004; Folkman, 2006). MMPs, by virtue of their proteolytic activity, mediate the effects of several pro-angiogenic factors. Angiogenic growth factors such as FGF, TGF-α, TGF-β, VEGF and angiogenin are secreted by endothelial cells and other cells, and act in an autocrine or paracrine fashion to promote angiogenesis. Treatment of human umbilical vein endothelial cells (HUVECs) with VEGF increases the expression of MMP-1, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-13, and MMP-19. VEGF 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 promote 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 endothelial cell-cell adhesions.

MMP-14 (MT1-MMP) plays a role in angiogenesis (Pepper, 2001b; Mimura et al., 2009). Semaphorin 4D is overexpressed in cancer and promotes neovascularization upon stimulation of its Plexin-B1 receptor on endothelial cells. MMP-14 releases semaphorin 4D from its inactive membrane bound form to act in a paracrine fashion on endothelial cells

(Basile et al., 2007). Also, MMP-14-dependent TGF-β signaling facilitates prostaglandin E_2-induced endothelial cord formation in cultured HUVECs (Alfranca et al., 2008).

MMPs play a role in adipose tissue angiogenesis (Hausman and Richardson, 2004). Also, upregulation of MMPs has been positively linked to tumor size and the increased angiogenic and metastatic potential of tumors. Expression of MMP-2 and MMP-9 and VEGF is positively correlated to tumor 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 endothelial cells. MMP-2 inhibition causes apoptotic cell death *in vitro*, and suppresses tumor growth of pre-established 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 the FGF-2/FGFR-2 pathway in the mouse angiogenesis model (Ardi et al., 2009), and downregulation of MMP-9 expression inhibits tumor growth in nude mice (Ezhilarasan et al., 2009). Also, MMP-3 mediates matriptase/MT-SP1-induced tumor growth and angiogenesis by enhancing ECM degradation in tumor cell microenvironment (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 endothelial cell basement membranes to release b-FGF. Connective tissue growth factor forms an inactive complex with VEGF165, and cleavage of connective tissue growth factor by MMP-1, MMP-3, MMP-7 or MMP-13 releases active VEGF165. MMP-2, MMP-3, and MMP-7 degrade the ECM proteoglycan decorin and release latent TGF-1, and MMP-2 and MMP-9 cleave the latency-associated peptide to activate TGF-β1 (Chung and Kao, 2009).

Dormant tumors may secrete TIMPs to prevent the tumor from switching to the angiogenic phenotype and thereby arrest tumor growth (Handsley and Edwards, 2005; Moller et al., 2010). Also, MMPs may exert anti-angiogenic 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 and thus decreases angiogenesis in hormone dependent ovarian cancer (Bendrik et al., 2010). MMP-7, MMP-9 and MMP-12 may block angiogenesis by converting plasminogen to angiostatin, a potent angiogenesis inhibitor. 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.

9.6. MMPs and Cell Apoptosis

Apoptosis is a form of cell death that involves activation of the intracellular cysteine proteases, caspases. Several factors promote apoptosis including death signals originating from outside the cell as well as intracellular factors such as DNA damage, cell cycle status

and the levels of tumor suppressors such as p53 (Stoneman and Bennett, 2004). In contrast, survival signals maintain cell 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 platelet-derived growth factor (PDGF), HB-EGF and IGF-1 act via tyrosine kinase receptors to stimulate the PI_3K/Akt pathway. MMP-2, MMP-7 and MMP-9 cleave cell surface pro-HB-EGF and liberate the soluble active growth factor which binds to EGF-R and promotes growth (Hao et al., 2004; Lucchesi et al., 2004). In human coronary VSMCs, oxidized low density lipoprotein and 4-hydroxynonenal activate PDGFR-β and the ERK1/2 pathway and in turn increase the production of MMP-1 (Akiba et al., 2006). MMP-1, MMP-2, MMP-8 and MMP-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 (Frisch and Screaton, 2001). ECM–integrin interactions trigger FAK activation and induce the p53 survival pathway (Ilic et al., 1998; Almeida et al., 2000). MMPs favor FAK activation and survival signaling. On the other hand, excess MMPs could degrade ECM proteins or integrins and promote apoptosis (Levkau et al., 2002). For example, MMP-7 is involved in the cleavage of N-cadherin and modulation of VSMC apoptosis. MMPs may also modulate apoptosis by cleaving death ligands such as TNF-α and Fas ligand and their receptors. MMP-1, MMP-2, MMP-9, MMP-8 and MMP-13 and the MT-MMPs 14, 15, 16 and 17 can cleave pro-TNF-α (Somerville et al., 2003; Visse and Nagase, 2003). Similarly, MMP-7 sheds Fas-L from the cell surface (Bond et al., 2000; Mannello et al., 2005). Caspase-mediated cleavage of the DNA repair enzyme poly(ADP-ribose) polymerase is an important step in apoptosis. MMP-2 has been localized in the nuclei of isolated cardiac myocytes and may be involved in cleaving nuclear poly(ADP-ribose) polymerase (Kwan et al., 2004).

TIMP-3 and TIMP-4, but not TIMP-1 or TIMP-2, stimulate apoptosis in many cell types including VSMCs (Baker et al., 1998; Bond et al., 2000; Guo et al., 2004). Thus, MMPs regulate VSMC apoptosis and cell survival via several pathways, and MMP inhibitors could oppose the effects of MMPs on cell survival and promote apoptosis.

9.7. MMPs, Tissue Repair and Wound Healing

Dynamic modulation of the physical contacts between neighboring cells is integral to epithelial cell growth and tissue repair. MMPs participate in tissue repair after acute injury (Garcia-Irigoyen et al., 2015). Tissue repair and wound healing are associated with increased expression of MMPs (Ravanti and Kahari, 2000). MMP-8 is the first collagenase to appear during dermal wound-healing and its levels peak earlier than that of MMP-1, supporting time-dependent expression of different MMPs during wound healing (Nwomeh et al., 1998). Mice deficient in MMP-8 show delayed healing of cutaneous wounds, and increased inflammatory responses, supporting that MMP-8 is a necessary component in dermal wound healing and the regulation of the inflammatory process (Gutierrez-Fernandez et al., 2007). MMP-10 is expressed by macrophages and epithelium in response to injury. In wounds of MMP-10 KO mice, collagen deposition and skin stiffness is increased, with no change in collagen expression or reepithelialization. Increased collagen deposition in MMP-10 KO

wounds was accompanied by less collagenolytic activity and reduced expression of MMP-8 and MMP-13, where MMP-13 was the key collagenase. Ablation and adoptive transfer approaches and cell-based models demonstrated that the MMP-10-dependent collagenolytic activity was a product of alternatively activated (M2) resident macrophages. These observations suggest a role for MMP-10 in controlling the tissue remodeling activity of macrophages and moderating scar formation during wound repair (Rohani et al., 2015).

MMP-19 is a potent basement membrane-degrading enzyme that plays a role in tissue remodeling, wound healing and epithelial cell migration by cleaving laminin-5γ2 chain (Stracke et al., 2000; Sadowski et al., 2005) Angiostatin, a proteolytic fragment of plasminogen, is a potent angiogenesis antagonist that inhibits migration and proliferation of endothelial cells. MMP-19 may exhibit anti-angiogenic effects on endothelial cells by processing human plasminogen in a characteristic cleavage pattern to generate three angiostatin-like fragments, with a molecular weight of 35, 38, and 42 kDa, that decrease the phosphorylation of c-met, inhibit the proliferation of human microvascular endothelial cells and reduce formation of capillary-like structures (Brauer et al., 2011).

MMP-28 is highly expressed in the epidermis. Immunohistochemical staining show epilysin in the basal and suprabasal epidermis of intact skin. In injured skin, epilysin staining is seen in basal keratinocytes both at and some distance from the wound edge, a pattern distinct from that of other MMPs expressed during tissue repair. MMP-28 may function in tissue homeostasis and repair.(Lohi et al., 2001; Saarialho-Kere et al., 2002)

9.8. Vascular and Placental MMPs during Pregnancy

Normal pregnancy is associated with significant hemodynamic, vascular and uteroplacental changes to ensure adequate placentation of the embryo, and sufficient blood and nutrient supply to the developing fetus. Adequate placentation and uterine vascularization are critical during normal pregnancy. Extravillous trophoblasts invade the maternal decidua and remodels spiral arteries to achieve maximal vasodilation and adequate nutrient supply to the embryo. 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 cytotrophoblasts (Cohen et al., 2010). Trophoblast invasion into the decidual stroma my require degradation of ECM proteins by MMPs. MMP-2 and MMP-9 play a role in endometrial tissue remodeling during the menstrual cycle and pregnancy (Mishra et al., 2010; Zhang et al., 2010; Ulbrich et al., 2011). MMP-2 and MMP-9 may be involved in ECM remodeling and trophoblast invasion of the spiral arteries during pregnancy (Shimonovitz et al., 1994; Isaka et al., 2003; Suman and Gupta, 2012; Su et al., 2016). MMP-2 and MMP-9 are abundantly expressed in invading extravillous trophoblast cells (Shimonovitz et al., 1994; Isaka et al., 2003; Suman and Gupta, 2012; Su et al., 2016). Studies have shown that the endometrium produces proMMP-2, proMMP-3, proMMP-7, proMMP-9, and active MMP-2 (Jones et al., 2006). The matrilysin MMP-7 could play a role in endometrial tissue remodeling during the menstrual cycle and pregnancy (Roy and Ghosh, 2010). Also, cytotrophoblasts and VSM release MMP-12,

which could mediate elastolysis and remodeling of the uterine spiral arteries during pregnancy (Harris et al., 2010). 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 MMP-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 may 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). Plasma levels of MMPs are increased during pregnancy, suggesting a role in the pregnancy-related changes in vascular function (Merchant and Davidge, 2004). MMP-2 is the main MMP in the umbilical cord, and serum MMP-9 level is elevated in pregnant women (Montagnana et al., 2009). Also, factors that promote trophoblast invasion may regulate MMPs. For instance, EGF–mediated induction of trophoblast invasion is associated with increased expression/activity of MMP-2 and MMP-9 (Qiu et al., 2004; Biadasiewicz et al., 2011).

Experimental studies support a role of MMPs during pregnancy. The serum activity of MMP-2 and MMP-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).

Normal pregnancy is associated with vasodilation of the maternal uterine, renal and systemic vessels (Conrad, 2011) and reduction in the mechanisms of vascular contraction (Khalil et al., 1998; Crews et al., 1999). MMPs could play a role in the uterine artery remodeling during pregnancy. MMP-2, MMP-3, MMP-14 and TIMP-1 transcripts are elevated in the uterine artery of early pregnant rats (day 7). In late pregnant rats (day 21), mRNA expression of MMP-2, MMP-3, MMP-7, MMP-9, MMP-12, MMP-13, MT1-MMP, and TIMP-1 and TIMP-2 is increased. TIMP-1 and MMP-3 mRNA expression return to control virgin levels in the post-partum period, whereas MMP-9 and MMP-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 elevation of the levels of some MMPs post-partum may contribute to vessel regression and return to a non-pregnant state (Kelly et al., 2003). The levels/activity of MMP-2 and MMP-9 are increased in the aorta of normal pregnant rats, suggesting a role of MMPs in the pregnancy-associated

vascular remodeling (Yin et al., 2012; Dang et al., 2013). 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). Gelatinases may function upstream of the endothelial endothelin B receptor and promote the NO pathway and the renal vasodilatory response during pregnancy (Jeyabalan et al., 2007).

The pregnancy-associated vasodilation and increase in vascular MMPs could be related to increased plasma levels of estrogen and progesterone (Risberg et al., 2009). Estrogen causes relaxation of VSM of the rat aorta and uterine artery (Crews and Khalil, 1999; Scott et al., 2007). Also, progesterone inhibits contraction of rat blood vessels (Crews and Khalil, 1999). We have shown that the expression/activity of MMP-2 and MMP-9 are increased in the aorta of pregnant rats (Dang et al., 2013). Also, consistent with reports that estrogen enhances the release of MMP-2 from human VSMCs (Wingrove et al., 1998), we found that estrogen +progesterone enhanced MMP-2 and MMP-9 expression/activity in the aorta of virgin rats. The pregnancy-associated increases in vascular MMPs could play a role in vascular remodeling, angiogenesis, and the systemic changes in blood vessels (Pepper, 2001a). In addition to their proteolytic effects, MMPs may affect membrane receptors and cell signaling. For instance, MMP-2 and MMP-9 cause relaxation of precontracted rat aorta (Chew et al., 2004). The increases in vascular MMPs together with demonstrated effects of MMPs on vascular remodeling and contraction mechanisms are consistent with a role in the reduced vascular contraction and enhanced systemic vasodilation during pregnancy.

The extracellular MMP inducer EMMPRIN may affect MMP expression during pregnancy. EMMPRIN release from the luminal epithelium may regulate the expression of stromal MMP-2 and MMP-14, and thereby affect the adhesion and fusion of embryo to luminal epithelium (Mishra et al., 2010). EMMPRIN stimulates the production of MMP-1, MMP-2, MMP-3, and MMP-9 (Huet et al., 2008a) and may regulate MMPs in endothelial cells and tumors (Foda et al., 2001). We have shown that EMMPRIN expression is increased in the uterus and aorta of late-pregnant compared with virgin and mid-pregnant rats. EMMPRIN expression was also increased in the aorta and uterus of virgin rats treated with estrogen +progesterone. The sex hormone-induced increases in uterine and aortic MMP-2 and MMP-9 were blocked by EMMPRIN neutralizing antibody, supporting a role of EMMPRIN in the increases in uterine and vascular MMPs (Dang et al., 2013).

In contrast with the pregnancy-associated increases in MMPs in the uterus and aorta, a decrease in the expression/activity of placental MMP-2 and MMP-9 was observed in late compared with mid-pregnancy in rats (Dang et al., 2013). Some studies have shown an increase in MMP-2 and MMP-9 in the placenta of diabetic rats at mid-gestation (Pustovrh et al., 2005), but did not follow the changes in MMPs during late-gestation. Other studies have suggested that MMPs are involved in placental remodeling during pregnancy (Pustovrh et al., 2005). The expression of MMP-2, MMP-14 and EMMPRIN is increased in the bovine placenta during late gestation (Mishra et al., 2012). MMP-28 transcript and protein are expressed in rhesus monkey placenta during early pregnancy. MMP-28 mRNA expression was shown by *in situ* hybridization after day 12 of pregnancy, and both the syncytial and the cytotrophoblastic cell layers of placental villi, the cytotrophoblast cells of the trophoblastic column, and the extravillous trophoblast cells of trophoblastic shell were primary producers

of MMP-28 transcript. MMP-28 mRNA was undetectable in the endovascular trophoblast cells, decidual cells, luminal and glandular epithelium, arterioles, and myometrium. The restricted distribution of MMP-28 in the villous and extravillous trophoblasts during rhesus monkey early pregnancy suggests a role in trophoblast invasion associated with embryo implantation (Li et al., 2003). The differences in the expression of MMPs in the rat versus bovine and non-human primate placenta could be related to species differences in the MMP regulation mechanisms or differences in the role of MMPs in early, mid, and late pregnancy. It is possible that the placenta as a potential source of MMPs may have finite capacity particularly during the late stages of pregnancy. Most of the placental remodeling takes place during the peri-implantation period and during fetal and organ development in early and mid-gestation, and further placental remodeling may not be needed during late pregnancy. Interestingly, we observed that the pregnancy-associated decrease in placental MMPs expression was associated with a decrease in the expression of placental EMMPRIN in late-pregnant compared with mid-pregnant rats, supporting a role of EMMPRIN as a critical inducer of MMPs during pregnancy (Dang et al., 2013).

10. ROLE OF MMPS IN VASCULAR PATHOLOGY

Altered MMP expression/activity and MMP/TIMP imbalance could cause unrestrained tissue remodeling and multiple pathological conditions including autoimmune and inflammatory disorders, osteoarthritis and cancer. MMPs play key roles in the spread of viral infection, inflammation and remodeling of the respiratory airways and tissue fibrosis (Hirakawa et al., 2013). MMPs may also participate in cancer development, progression, invasiveness and dissemination by promoting a pro-tumorigenic microenvironment and modulating the cell-ECM and cell-to-cell contacts (Garcia-Irigoyen et al., 2015). MMPs could break the cell-to-cell and cell-ECM adhesion, degrade ECM proteins, and promote angiogenesis, and thereby facilitate cancer invasion and metastasis (Zhang et al., 2014). Alterations in MMPs expression/activity may also be associated with cardiovascular disease such as hypertension, atherosclerosis, aneurysm and chronic venous disease (Fig. 5).

10.1. MMPs and Hypertension

Hypertension is a multifactorial disorder involving alterations in the renal, neuronal and vascular control mechanisms of blood pressure. Hypertension is often associated with vascular remodeling and rearrangement of various components of the vascular wall including ECM. Several MMPs and TIMPs may be involved in the vascular remodeling associated with hypertension. Elevated plasma levels of some MMPs in hypertension may cause excessive elastolysis or accumulation of collagen degradation products in the vascular wall. Increased MMP activity could result in increased degradation of elastin relative to collagen leading to decreased elasticity (Onal et al., 2009). On the other hand, decreased TIMP-1 activity could lead to accumulation of poorly cross-linked immature and unstable fibrin degradation products, resulting in misdirected deposition of collagen (Onal et al., 2009). Some studies have shown a correlation between MMP levels and hypertension. Other studies have shown low levels of MMPs and high levels of TIMPs levels in hypertension and suggested that decreased degradation of collagen type I could play a role in the development of hypertension. Studies have compared the effects of early and late hypertension on ECM

remodeling in Dahl rats of different age groups: young salt-resistant (control), young salt-sensitive (early hypertension), middle-age salt-resistant (aging), and middle-age salt-sensitive (late hypertension). In early hypertension, several MMPs decreased, TIMP-1 increased, and total collagen increased, consistent with increased fibrosis. MMP-8 activity decreased in young salt-sensitive rats. Also, MMP-14 correlated positively with changes in left ventricular mass in early hypertension. In contrast, late hypertension was associated with increased MMP-8 and MMP-14 and decreased total collagen levels. These findings suggest downregulation and upregulation of MMPs at early versus late stages of hypertension, and are consistent with the view that ECM remodeling in response to pressure overload is a dynamic process involving both ECM accumulation and degradation depending on the stage of hypertension (Lin et al., 2008).

In addition to regulation of ECM turnover, MMPs could affect vascular remodeling in hypertension 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 vasoconstriction and hypertension. Also, in fructose treated rat model of acquired systolic hypertension and insulin resistance, the insulin-resistant VSMCs showed increased expression/activity of MMP-2 and MMP-7, EGFR, the contractile proteins myosin light chain (MLC) kinase and MLC-II, and their transcriptional activators possibly through activation of ERK1/2. Disruption of MMP-EGFR signaling normalized the increased expression of contractile proteins and their transcriptional activators in insulin-resistant VSMCs and arteries and prevented the development of hypertension in fructose treated rats (Nagareddy et al., 2010). Also, in a study comparing the effects of treatment with angiotensin II (AngII) for 10 days in wild-type and MMP-9 knockout mice, baseline blood pressure was equivalent in both phenotypes, but AngII treatment increased systolic blood pressure to a greater extent in MMP-9 knockout than wild-type mice. In response to AngII treatment, the carotid artery pressure-diameter relationship and arterial compliance were increased in wild-type, but reduced in MMP-9 knockout mice. Also, maximal carotid artery diameter was greater in wild-type versus MMP-9 knockout mice. AngII treatment induced MMP-2 and increased carotid media thickness equally in both phenotypes. On the other hand, AngII treatment induced MMP-9 and enhanced MMP-9 *in situ* gelatinase activity only in wild-type mice, and vessels from these mice produced more collagen I breakdown products than MMP-9 knockout mice. Conversely, staining for collagen IV was enhanced in vessels from AngII-treated MMP-9 knockout mice. These findings suggest that the onset of AngII-induced hypertension is accompanied by increased MMP-9 activity in conductance vessels, MMP-9 deficiency results in vessel stiffness and increased pulse pressure, and MMP-9 activation may have a beneficial role in early hypertension by preserving vessel compliance and alleviating the increase in blood pressure (Flamant et al., 2007).

MMP/TIMP imbalance in blood vessels, particularly in the intima and media, may account for the increased proteolytic activity and maladaptive vascular remodeling in hypertension. Increased levels of MMP-2, MMP-9, and MMP-14 and enhanced gelatinolytic activity were observed in the aortas of two kidney-one clip (2K-1C) rat model of hypertension. Doxycycline treatment for 8 weeks attenuated 2K-1C hypertension, prevented the increase in the aortic intima and media thicknesses, attenuated the increases in MMP-2, MMP-9, and

MMP-14 in the intima and media, but did not change the levels of TIMPs 1–4 (Castro et al., 2010). MMP-2 may contribute to arterial remodeling in early hypertension by decreasing the actin-binding protein calponin-1. In a study of Sham-operated and 2K-1C rat model of hypertension, MMP-2 activity was increased in aortas from 2K-1C rats at 1 and 2 weeks of hypertension, followed by increased VSMC proliferation, and these effects were abolished by doxycycline. Increased aortic media to lumen ratio started in 2K-1C rats at 1 week of hypertension, and was established by 2 weeks. MMP-2 and calponin-1 co-localized in the cytosol of VSMCs. Aortas from 2K-1C rats showed a decrease in calponin-1 protein levels but not calponin-1 mRNA expression, at 1 week of hypertension, and doxycycline treatment prevented the decrease in calponin-1 protein level. Conversely, calponin-1 was upregulated in 2K-1C rats at 2 weeks of hypertension. These findings suggest that MMP-2 may contribute to the post-translational decrease in calponin-1. The decrease in calponin may be associated with VSMC phenotype switch and VSMC migration, and thereby contribute to maladaptive arterial remodeling in early hypertension (Belo et al., 2016). Studies in Dahl salt-sensitive rats fed high-salt diet for 6 weeks have shown that intraperitoneal treatment with the MMP inhibitor GM6001 1.2 mg/kg body weight on alternate days for 4 weeks reduced blood pressure. MMP-9 expression and activity were reduced in cerebral vessels of GM6001-treated Dahl salt-sensitive rats. GM6001 treatment ameliorated oxidative/nitrosative stress and tight junction proteins in cerebral vessels of Dahl salt-sensitive rats, suggesting restoration of vascular integrity. These findings suggest that inhibition of MMP-9 attenuates high blood pressure and hypertension-associated cerebrovascular pathology in salt-sensitive hypertension (Kalani et al., 2016). Also, in spontaneously hypertensive rats, induction of acute hypertension by AngII 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 hypertension, inhibited ADAM-12 expression, and prevented cardiac hypertrophy (Wang et al., 2009). In addition to cardiac hypertrophy, MMPs may play a role in other hypertensive complications such as intracranial hemorrhage (Franz et al., 2009; Castro et al., 2010; Wakisaka et al., 2010). In VSMCs from spontaneously hypertensive rats, TNF-α increased cell migration and MMP-9 expression. Upregulation of MMP-9 was 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 hypertension (Lee et al., 2009). Collectively, these studies support a role of MMPs in vascular tissue remodeling in hypertension (Lee et al., 2009). The effects of MMPs on ECM and non-ECM components and its contribution to VSMC reshaping and migration may contribute to hypertension-induced maladaptive vascular remodeling, which may be the first step in the development of other cardiovascular-renal diseases including atherosclerosis, stroke, heart failure, and renal failure.

10.2. Uteroplacental and Vascular MMPs in Preeclampsia

Preeclampsia is a major complication of pregnancy characterized by hypertension and often proteinuria (Ali and Khalil, 2015; Shah and Khalil, 2015). Preeclampsia is a major cause of maternal and fetal morbidity and mortality, fetal intrauterine growth restriction (IUGR), fetal programming of cardiovascular and metabolic disease, and predisposition to adulthood

hypertension and diabetes (Roberts and Gammill, 2005; Alexander, 2006; Uzan et al., 2011). Studies in preeclamptic women and animal models of hypertension in pregnancy have helped to uncover some of the pathogenic mechanisms (Losonczy et al., 1992; Crews et al., 2000; Alexander et al., 2001b; Davis et al., 2002; Orshal and Khalil, 2004). Reduction in uteroplacental perfusion pressure (RUPP) during late pregnancy in sheep, dog, rabbit and rat induces a hypertensive state that closely resembles preeclampsia (Crews et al., 2000; Alexander et al., 2001b; Khalil and Granger, 2002). Placental ischemia is also associated with increased release of bioactive factors (Levine et al., 2004; Gilbert et al., 2007; Gilbert et al., 2009; Reslan and Khalil, 2010; Palei et al., 2013b), which could target various vascular mediators and MMPs in ECM, endothelial cells and VSM leading to increased vasoconstriction and hypertension in pregnancy.

MMP-mediated vascular remodeling may play a role in the pathogenesis of preeclampsia (Merchant and Davidge, 2004). Higher plasma levels of MMPs such as MMP-2 and lower levels of TIMPs have been observed in women with preeclampsia or who subsequently develop preeclampsia (Narumiya et al., 2001; Myers et al., 2005; Lavee et al., 2009; Montagnana et al., 2009; Shokry et al., 2009). Increased MMP-2 activity may contribute to the endothelial dysfunction in preeclampsia (Myers et al., 2005). However, the proteases intrinsic to syncytiotrophoblast microvillous membranes are unlikely to be the cause of the endothelial changes (de Jager et al., 2003). Also, some clinical studies showed no association between MMP-2 levels and hypertension in pregnancy. A study enrolling 133 women showed no statistical difference in MMP-2 levels between patients with gestational hypertension or preeclampsia and normotensive control pregnant women (Galewska et al., 2008; Lavee et al., 2009). Another study enrolling 83 pregnant women showed no difference in pro-MMP-2 levels (Palei et al., 2008). On the other hand, some studies have shown higher serum levels of MMP-9 in preeclampsia than control pregnancies, and an association between serum MMP-9 and TNF-receptor levels, suggesting an underlying inflammatory process (Poon et al., 2009). MMP-7 and MMP-26 may contribute to ECM remodeling in the umbilical cord of preeclamptic pregnancies by activating MMP-9 (Galewska et al., 2010). MMP-9 may promote 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., 2008). These findings have suggested MMP-9 as one of the biomarkers of preeclampsia (Poon et al., 2010). However, other studies have shown higher plasma pro-MMP-9 levels and pro-MMP-9/TIMP-1 ratios in women with gestational hypertension, but not in preeclampsia (Palei et al., 2008). Also, the C(-1562)T polymorphism in MMP-9 gene showed an association with gestational hypertension, but not preeclampsia (Palei et al., 2010). In effect, some studies demonstrated reduced levels of MMPs and elevated TIMPs in preeclampsia and suggested that reduced degradation of ECM components results in intimal thickening, tissue hypoxia and preeclampsia biochemical and pathological cascade. Decreased levels/activity of MMP-1 and increased levels of TIMP-1 were detected in umbilical cord arteries of preeclamptic women (Galewska et al., 2006). Also, in cultured human decidual endothelial cells, basal and stimulated secretion of MMP-1 was reduced in cells from preeclamptic compared with normal pregnant women. The decreased MMP-1 expression in decidual endothelial cells from preeclamptic women may contribute to inhibition of endovascular invasion by

cytotrophoblasts and the relative failure of trophoblasts to invade maternal decidual blood vessels in preeclampsia (Gallery et al., 1999). MMP-9 expression may also be low in preeclamptic pregnancies (Shokry et al., 2009). Decreased levels of MMP-1, MMP-3 and MMP-9 were detected in extracts of human umbilical cord artery, and MMP-2 was the main collagenolytic enzyme in umbilical cord artery wall. Preeclampsia was associated with a reduction in levels/activity of those MMPs, which may reduce the breakdown of collagen, and the accumulation of collagen in conjunction with reduced elastin content of umbilical cord artery may reduce the elasticity of arterial wall and decrease blood flow to the fetus (Galewska et al., 2003). MMP-3 expression is also reduced in the placental invasive trophoblasts of patients with severe preeclampsia (Husslein et al., 2009).

Maternal immune cells in the placental bed may alter the cytokine environment, and result in disturbed trophoblast cell function, impaired MMP expression and reduced invasiveness. Expression of MMP-3 and MMP-7 by extravillous trophoblasts especially close to spiral arteries is reduced in preeclamptic patients. In contrast with healthy pregnancies, extravillous trophoblasts from preeclamptic pregnancies express the receptor for leukemia inhibitory factor. Leukemia inhibitory factor is produced by uterine natural killer cells that accumulate alongside the spiral arteries and suppresses MMP expression in the placental bed of preeclamptic patients (Reister et al., 2006).

Genetic polymorphisms in MMP-2 and MMP-9 transcription (Palei et al., 2013a), and decreased levels of MMP-9 have been observed in preeclamptic compared with normal placenta (Shokry et al., 2009; Omran et al., 2011). In preeclampsia, increased expression of miRNA-519d-3p and miRNA-204 (Choi et al., 2013) could target MMP-2 and MMP-9 and decrease trophoblast invasion of spiral arteries (Yu et al., 2015b). In first trimester trophoblasts suppression of MMP-9 expression inhibits the invasive capability of trophoblasts (Yu et al., 2015b). Also, MMP-9 knockout mice show a phenotype that mimics preeclampsia possibly due to impaired trophoblast differentiation and invasion (Plaks et al., 2013). In a study utilizing 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 hypertensive pregnant rats was associated with reduction in trophoblast invasion and 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). Collectively, these findings suggest a relationship between decreased MMP-2 and MMP-9 and impaired trophoblast invasion in preeclampsia. However, measurements of plasma levels of MMPs have not been consistent in preeclampsia, with some studies showing an increase in serum levels of MMP-2 and MMP-9 (Narumiya et al., 2001; Eleuterio et al., 2015), while other studies showing a decrease in circulating MMP-9 (Montagnana et al., 2009). Further measurements of the plasma levels of MMPs and their correlation with MMP levels in the placenta and other maternal tissues are needed in preeclampsia and animal models of hypertension in pregnancy.

Because collagen is a major substrate of MMPs, a decrease in MMP-2 and MMP-9 is expected to cause excessive collagen deposition, and in turn decrease uteroplacental

vascularization and spiral arteries remodeling (Li et al., 2014b). Also, we and others have shown additional effects of MMP-2 and MMP-9 on cell surface receptors and cell signaling. While some studies have shown that MMP-2 causes vasoconstriction in endothelium intact mesenteric arteries of rats (Fernandez-Patron et al., 1999; Abdalvand et al., 2013), we have shown that MMP-2 and MMP-9 cause relaxation of rat aorta and rat inferior vena cava (Chew et al., 2004; Raffetto et al., 2007; Raffetto et al., 2010). Of note, gelatinases mainly degrade collagen IV, and partially degrade collagen I, suggesting that other MMPs may be involved in collagen degradation and cell signaling in preeclampsai. The collagenase MMP-1 is expressed in cytotrophoblasts and syncytiotrophoblasts of the placenta and decidua and may play a role in trophoblast invasion. Some studies have shown low levels of MMP-1 in umbilical cord blood, placenta and decidua of preeclamptic versus normal pregnant women, and the low MMP-1 levels are correlated with the severity preeclampsia (Deng et al., 2015). Other studies suggest a role of MMP-1 in the pathogenesis of preeclampsia (Nugent et al., 2016). It has been shown that both pro- and active MMP-1 levels are elevated in the plasma of women with preeclampsia; there is increased expression of MMP-1 in blood vessels of women with preeclampsia; and MMP-1 is a potent vasoconstrictor of endothelium-intact omental arteries obtained from pregnant women (Estrada-Gutierrez et al., 2011).

We and others have measured the hemodynamic and uteroplacental changes in normal pregnant rats and the RUPP rat model of placental ischemia. Blood pressure was increased, and the litter size and individual pup weight were decreased in RUPP versus normal pregnant rats (Alexander et al., 2001a; Granger et al., 2002). We have examined whether alteration of MMP expression/activity is a potential pathogenic mechanism in the uteroplacental and vascular remodeling and placental ischemia in hypertension in pregnancy. We examined the specific changes in three important tissues during pregnancy; the uterus which undergoes remodeling to accommodate the growing fetus, the placenta which provides nutrient supply to the developing fetus, and the aorta for the vascular changes in the maternal circulation. The uterus, placenta, and aortic tissue weight was reduced in RUPP versus normal pregnant rats. Also, histological morphometry showed reduction in uterine, placental and aortic cross-sectional area in RUPP versus normal pregnant rats, supporting growth-restrictive remodeling in the uterus, placenta and vasculature of RUPP rats. Also, the fetal litter size and individual pup weight are decreased in RUPP compared with normal pregnant rats (Li et al., 2014b). In search for the mechanisms involved in the changes in uteroplacental and vascular remodeling, Western blots, gelatin zymography and immunohistochemical analysis revealed that MMP-2 and MMP-9 were abundantly expressed in tissues of normal pregnant rats, supporting a role of MMPs in the uteroplacental and vascular remodeling during normal pregnancy (Dang et al., 2013). MMPs immunostaining was particularly apparent in the aortic media, consistent with reports that VSMCs are a major source of MMPs (Li et al., 2012; Seo et al., 2013). Western blots and gelatin zymography revealed decreases in protein amount and gelatinase activity of MMP-2 and MMP-9 in the uterus, placenta and aorta of RUPP compared with normal pregnant rats. MMP-2 and MMP-9 immunostaining was also reduced in uterine and placenta tissue sections and less intense in the aortic media of RUPP versus normal pregnant rats. The decreases in MMP levels, in parallel with the decreases in uterine, placental, and aortic

tissue weight and cross-sectional area suggest a role for reduced MMPs in growth-restrictive remodeling in tissues of RUPP rats (Li et al., 2014b).

TIMP-1 is elevated in preeclampsia, and amniotic TIMP-2 levels are higher in women who developed a hypertensive disorder compared to normotensive women (Tayebjee et al., 2005; Lavee et al., 2009; Montagnana et al., 2009). A decrease in ECM remodeling could play a role in hemolysis, elevated liver enzyme and low platelet levels (HELLP) syndrome. The mRNA expression of MMP-2 and TIMP-2 were decreased, whereas TIMP-1 and TIMP-3 levels were unchanged in 11 females with HELLP syndrome and 8 controls matched for gestational age (von Steinburg et al., 2009). Other studies showed no statistical difference in TIMP-1 and TIMP-2 between preeclamptic and control samples (Galewska et al., 2008).

Collectively, studies suggest an imbalance between MMPs and TIMPs in hypertension in pregnancy, but the mechanisms via which this imbalance contributes to the preeclamptic pathology need to be further examined. Also, while the changes in MMPs in RUPP rats suggest a role in hypertension in pregnancy, the mechanisms linking localized RUPP to the systemic changes in MMPs and the potential bioactive factors involved need to be examined.

10.3. MMPs and Vascular Inflammation

MMPs play a major in the immune response and vascular inflammation. MMP-1 degrades collagen and gelatin. MMP-1 also cleaves proMMP-9 into its active form. As with many other MMPs, the levels of MMP-1 are very low in most cells under physiological conditions, but are upregulated in inflammatory conditions and autoimmune disease (Mittal et al., 2016). Increased levels and activities of MMP-1, MMP-8, and MMP-9 with relatively low levels of TIMP have been identified in slow-to-heal wounds (Ayuk et al., 2016). A systemic inflammatory response could occur after trauma and infection, leading to multiple organ dysfunction syndrome, an important cause of morbidity and mortality in intensive care units. Animal model studies have shown a high level of MMP-9 in the early stages of multiple organ dysfunction syndrome, which also correlated with the degree of renal, hepatic and pulmonary injury (Teng et al., 2012).

MMP-1 expression is augmented by inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) (Nam et al., 2011). Cytokines increase the production of reactive oxygen species (ROS), which could in turn affect MMP expression/activity. Studies in fibroblasts have suggested that MMP expression may be influenced by changes in NADPH oxidase-1 (Nox-1) levels (Arbiser et al., 2002). Urokinase may affect MMP-9 expression partly through increasing the generation of ROS (Zubkova et al., 2014). Leukocytes are not only a major source of MMPs, but they also generate ROS that can influence MMP activity. ROS may activate MMPs via oxidation of the MMP prodomain thiol followed by autolytic cleavage. On the other hand, ROS may inactivate MMPs by modifying the amino acids critical for catalytic activity, thus providing a feedback-mechanism that could control any bursts in MMP proteolytic activity (Fu et al., 2004). Calabriso and co-workers have sought to evaluate whether anti-oxidant supplementation with polyphenol-rich red grape skin extracts modulates the matrix-degrading capacity in cell models of vascular inflammation. Human endothelial and monocytic cells were incubated with increasing concentrations of Negroamaro and Primitivo red grape skin polyphenolic

extracts (NSPE and PSPE, respectively), before stimulation with inflammatory challenge. NSPE and PSPE inhibited endothelial invasion, MMP-2 and MMP-9 release in stimulated endothelial cells, and MMP-9 production in inflamed monocytes, without affecting tissue TIMP-1 or TIMP-2. Among the main polyphenols of grape skin extracts, trans-resveratrol, trans-piceid, kaempferol and quercetin exhibited the most significant inhibitory effects on MMPs enzyme activities. Their findings suggest grape skins as a rich source of polyphenols that prevent the dysregulation of vascular remodeling in degenerative and inflammatory diseases (Calabriso et al., 2016).

MMP-28 may regulate the inflammatory and ECM responses in cardiac aging. In a mouse model of myocardial infarction (MI) of the left ventricle induced by permanent coronary artery ligation, MMP-28 expression was decreased post-MI, and its cell source shifted from myocytes to macrophages. In MMP-28 KO mice, MMP-28 deletion increased day 7 mortality because of increased cardiac rupture post-MI. MMP-28 KO mice exhibited larger left ventricular volumes, worse left ventricular dysfunction, worse left ventricular remodeling index, and increased lung edema. Plasma MMP-9 levels were unchanged in the MMP-28 KO mice but increased in wild-type mice at day 7 post-MI. The mRNA levels of inflammatory and ECM proteins were attenuated in the infarct regions of MMP-28 KO mice, indicating reduced inflammatory and ECM responses. M2 macrophage activation was impaired in MMP-28 KO mice. MMP-28 deletion also led to decreased collagen deposition and fewer myofibroblasts. Collagen cross-linking was impaired as a result of decreased expression and activation of lysyl oxidase in the infarcts of MMP-28 KO mice. These findings suggest that MMP-28 deletion aggravated MI-induced left ventricular dysfunction and rupture as a result of defective inflammatory response and scar formation by suppressing M2 macrophage activation (Ma et al., 2013).

Vascular inflammation could take part in the vasculopathy associated with other vascular diseases such as atherosclerosis, coronary artery syndrome, peripheral arterial disease, aneurysm, and chronic venous disease.

10.4. MMPs and Atherosclerosis

Atherosclerosis is a multifactorial vascular disease. VSMC proliferation at sites of endothelial cell injury and subsequent lipid deposition play a role in atheroma formation, and MMPs appear to be involved in these processes. Dysfunctional endothelium recruits different inflammatory pathways leading to intimal differentiation, VSMC proliferation, ox-LDL deposition, platelet activation and aggregation, and the 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. Studies have suggested a role for MMPs in vascular wall remodeling and atherosclerosis (Vacek et al., 2015). MMP expression is increased 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, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-12 are produced by SMCs and macrophages in the arterial wall, and are highly expressed 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, MMP-3 and MMP-9. Activated gelatinases have been found in plaque extracts, and gelatinolytic and caseinolytic activities have been detected in atherosclerotic areas, but not in unaffected arterial tissue (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 hemodialysis develop atherosclerosis rapidly and show evidence of fibrinolysis/proteolysis imbalance in their plasma, and MMP-2 may play a role in the development of atherosclerosis in these patients (Pawlak et al., 2008). Plasma levels of MMP-1, MMP-3, and MMP-7 are higher in patients with high compared with those with low intima-media thickness. MMP-7 is positively associated with carotid calcification (Gaubatz et al., 2010) and plasma levels of MMP-8 are positively associated with the occurrence of carotid plaques (Djuric et al., 2010). MMP-10 is induced by C-reactive protein in endothelial cells, and is overexpressed in atherosclerotic lesions. Also, high serum levels of MMP-10 are associated with increased inflammatory markers, increased carotid intima-media thickness and atherosclerotic plaques (Rodriguez et al., 2008).

Certain genetic variants of MMPs have been associated with the progression and complications of atherosclerosis. Studies have shown associations of MMP-9 genotypes with different stages of carotid artery atherosclerosis (Rauch et al., 2008). Also, MMP-9 ablation reduced the size of atherosclerotic lesion in ApoE$^{-/-}$ mice (Luttun et al., 2004). Also, in the mouse carotid artery ligation model, the plaque burden was reduced in hypercholesterolemic MMP-9 knockout compared with wild-type mice (Choi et al., 2005).

MMPs contribute to the pathophysiology of atherosclerosis through several pathways. Vascular inflammation is an important factor in the atherogenic process and has been shown to promote MMP expression. In a study enrolling 18 patients with stable angina, 14 patients with unstable angina and non-ST-segment elevation myocardial infarction, 14 patients with ST-elevation myocardial infarction, and 16 healthy controls, the progression of coronary artery disease was paralleled with increased MMP-9/TIMP-1 ratio in circulating CD14+ monocytes and in the serum. Similar MMP/TIMP-1 imbalance was observed in monocyte-derived macrophages within the atherosclerotic plaques (Brunner et al., 2010). Cholesterol lowering 3-HMGcoA reductase inhibitors decrease the expression of various MMPs in atheromatous plaques by reducing vascular inflammation (Cevik et al., 2008). For example, rosuvastatin inhibits the expression of MMP-2 and MMP-9 (Guo et al., 2010).

VSMC migration and proliferation are also involved in atheroma formation. MMPs enhance VSMC migration to atherogenic areas where they proliferate and increase the size of the lesion. In rat ASMCs, the herb Salvia miltorrhia extract inhibits VSMC migration in part through downregulation of MMP-9 and TNF-α (Jin et al., 2006a). In a study using mice with genetically modified collagen that resists digestion by MMP collagenases, in an atherogenic background, the lesion size was similar in collagenase-resistant and control mice, but collagen was more abundant and SMC number was decreased in the intimal lesions of collagenase-resistant mice, suggesting a role for MMPs in regulating collagen turnover and SMC proliferation in the atheromatous plaque (Fukumoto et al., 2004).

MMP-1 may mediate ox-LDL induced activation of the PDGFR-β and ERK1/2 atherogenic pathways (Akiba et al., 2006). Ox-LDL also activates MMP-2 through upregulation of MT1-

MMP and increases in oxidative radicals generated by xanthine/xanthine oxidase (Valentin et al., 2005). AngII could play a role in atherosclerosis by increasing the expression of MMP-9 in VSMCs through angiotensin type 1 receptor and NF-κB pathways (Guo et al., 2008).. Collectively, these studies have shown an association between MMPs levels, genetic variants of certain MMPs and the atherosclerotic process.

Because MMPs degrade ECM proteins and because increased MMP levels have been detected in vulnerable atherosclerotic plaques, it is thought that MMPs could reduce the strength of the fibrous cap and contribute to plaque rupture. Apoptosis of VSMCs plays a role in attenuating intimal thickening and destabilizing atherosclerotic plaques (Geng and Libby, 2002; Stoneman and Bennett, 2004). High-mobility group box 1 is an intracellular gene regulator protein produced by activated VSMCs that promotes the progression and increases the vulnerability of atherosclerotic lesions to rupture by increasing the expression of MMP-2, MMP-3 and MMP-9 (Inoue et al., 2007). Areas of atherosclerotic plaque rupture show a decrease in VSMCs and increased macrophage-derived foam cells. Studies have 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, and concluded that MMP-12 supported lesion expansion and destabilization. MMP-7 had no effect on plaque growth or stability, although it was associated with decreased VSMCs in plaques, while MMP-3 and -9 appeared to play protective roles, limiting plaque growth and promoting a stable plaque phenotype (Johnson et al., 2005). MMP-1, MMP-12 and MMP-13 derived from intimal macrophages have been suggested to play a role in both plaque initiation and progression (Koike et al., 2008). On the other hand, transgenic mice that specifically express MMP-1 in macrophages show smaller plaques and no evidence of plaque rupture when compared with control littermates (Lemaitre et al., 2001). This is likely because these mice have altered MMP-1 from birth, which could reduce collagen accumulation. MMP-3 also appears to have a dual role. Mice lacking both MMP-3 and ApoE show extensive atheromas, but reduced aneurysm formation (Silence et al., 2001). MMP-3 deficiency is associated with increased collagen and fewer macrophages in plaques, which could contribute to greater stability of atheromatous 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 concept that MMPs adversely affect the stability of established plaques (Rouis et al., 1999). Estrogen supplementation late after menopause may destabilize established plaques due to estrogen's ability to upregulate MT1-MMP without a corresponding increase in TIMP-2, and consequently increase MMP-2 activation (Grandas et al., 2009). While MMP-induced degradation of ECM proteins could contribute to plaque instability, the ability of MMPs to promote VSMC migration and proliferation may contribute to atherosclerotic plaque cap growth and stability. MMP-2, MMP-9, MMP-13 and MMP-14 release growth factors such as TGF-h and VEGF that are stored in ECM (Mott and Werb, 2004). MMP-9 releases VEGF bound to proteoglycans in ECM, enhancing its bioavailability and thereby influencing plaque neovascularization. Collectively, evidence suggests dual role for MMPs in intimal thickening and atherogenesis as well as atherosclerotic plaque rupture (Newby, 2005).

TIMPs may play a role in atherosclerosis. TIMP-4 is detected in cardiovascular tissue areas populated by inflammatory 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 cell 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 (Zureik et al., 2005). In a study evaluating carotid wall thickness, lumen area, calcium area, lipid core, and fibrous cap measures for associations with plasma MMPs 1, 2, 3, 7, 8, and 9 and TIMP-1, the fibrous cap thickness was greater in individuals with elevated TIMP-1 levels. Also, TIMP-1 was positively associated with measures of lipid core (Gaubatz et al., 2010). TIMP-1 deficiency produces macrophage-rich lesions with active proteinases and medial destruction in ApoE$^{-/-}$ mice (Lemaitre et al., 2003). TIMP-1-deficient mice show 30% smaller atherosclerotic lesions but increased aneurysm formation compared with control mice (Silence et al., 2002). However, pharmacological MMP inhibitors do not appear to affect the lesion size in atheroma-prone mice (Prescott et al., 1999; Manning et al., 2003).

MMP-14 may promote vulnerable plaque morphology in mice, whereas TIMP-3 overexpression may be protective. High MMP-14 low TIMP-3 rabbit foam cells are more invasive and more prone to apoptosis than low MMP-14 high TIMP-3 cells. Proinflammatory stimuli increase MMP-14 and decrease TIMP-3 mRNA expression and protein levels in human macrophages. Conversion to foam-cells with oxidized LDL is associated with increased MMP-14 and decreased TIMP-3, independently of inflammatory mediators and partly through post-transcriptional mechanisms. Within atherosclerotic plaques, MMP-14 is prominent in foam-cells with either pro- or anti-inflammatory macrophage markers, whereas TIMP-3 is present in less foamy macrophages and colocalized with CD206. MMP-14 positive macrophages are more abundant whereas TIMP-3 positive macrophages are less abundant in plaques histologically designated as rupture prone. These findings suggest that foam-cells with high MMP-14 low TIMP-3 expression are prevalent in rupture-prone atherosclerotic plaques, independent of pro- or anti-inflammatory activation, and that reducing MMP-14 activity and increasing TIMP-3 could be valid therapeutic approaches to reduce plaque rupture and myocardial infarction. (Johnson et al., 2014).

MMP inhibitors have not been used extensively in cardiovascular clinical trials partly because cancer trials showed side effects such as tendinitis (possibly due to inhibition of ADAMs), lack of efficacy, and other adverse 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 retrieved by endarterectomy showed that doxycycline penetrated the atherosclerotic plaques, achieved acceptable tissue levels, and reduced MMP-1 levels, but had no effect on atheroma progression (Axisa et al., 2002). Also, most animal studies of post-angioplasty or in-stent stenosis have shown little or only short-term beneficial effects of MMP inhibitors.

10.5. MMPs, Coronary Artery Syndrome, and Myocardial infarction

Atherosclerosis in the coronary arteries could lead to acute coronary syndrome manifested as unstable anginas and myocardial infarction. Studies have shown an association between

MMPs and the development of acute coronary syndrome (Jones et al., 2003a). A case-control study on 261 patients who had suffered a myocardial infarction and 194 healthy controls, all Spanish male smokers, showed that MMP-1 promoter polymorphisms are associated with the risk of early myocardial infarction (Roman-Garcia et al., 2009). MMP-2 and MMP-9 were elevated following acute myocardial infraction in 91 patients compared to 172 control subjects with stable coronary artery disease. 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 a potential role of MMPs in coronary artery restenotic lesions (Ikeda and Shimada, 2003).

Certain genetic variants of MMPs have been associated with the progression and complications of coronary atherosclerosis. In a 3-year coronary atherosclerosis study, the 6A active variant of the MMP-3 promoter was correlated with progressive narrowing of coronary artery lumen (Ye et al., 1995) and acute myocardial infarction (Terashima et al., 1999). In a study on 139 patients with coronary artery disease and 119 healthy subjects, MMP-3 5A/6A genetic variant was associated with coronary artery disease, and the PON1 variant was correlated 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 myocardial infarction, 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 myocardial infarction (Du et al., 1999). Also, in a study of 1127 patients, higher serum levels of MMP-9 were associated with the T allele, but did not predict cardiovascular death (Blankenberg et al., 2003). Another study on coronary artery disease patients has shown increased serum levels of MMP-9 and suggested that coronary artery disease was conducive to 1562CG transformation of MMP-9 gene into genetic polymorphism, thus promoting arterial remodeling and increasing unstable atherosclerotic plaques (Yu et al., 2015a).

The levels of MMPs and TIMPs in early post-myocardial infarction period may provide an estimate of the extent of cardiac damage and remodeling. Urinary levels of MMP-9 and TIMP-1 are elevated in patients with atherosclerotic coronary artery and acute coronary syndrome compared with healthy volunteers (Fitzsimmons et al., 2007). MMP-9 and TIMP-1 correlate with echocardiographic parameters of left ventricular dysfunction after acute myocardial infarction and may identify patients at risk of subsequent left ventricular remodeling and adverse prognosis (Kelly et al., 2008).

10.6. MMPs, Cerebral Ischemia, and Ischemic Stroke

MMPs may play a role in cerebral ischemia and ischemic stroke. Evidence suggests associations between polymorphisms in MMP-1, MMP-2, MMP-3, MMP-9, and MMP-12 with ischemic stroke incidence, pathophysiology, and clinical outcome. Polymorphisms in the MMP genes can be influenced by racial and ethnic background., and could ultimately affect the presentation of ischemic stroke (Chang et al., 2016). MMP-12 may affect the blood-brain barrier after cerebral ischemia. In rats subjected to middle cerebral artery occlusion and reperfusion, MMP-12 was upregulated ~31-, 47-, and 66-fold in rats subjected

to 1-, 2-, or 4-hour ischemia, respectively, followed by 1-day reperfusion. MMP-12 suppression by infusion of nanoparticles of MMP-12 shRNA-expressing plasmid protected the blood-brain barrier integrity by inhibiting the degradation of tight-junction proteins, and reduced the percent Evans blue dye extravasation and infarct size. MMP-12 suppression reduced the levels of the other endogenous proteases tissue-type plasminogen activator and MMP-9, which are key players in blood-brain barrier damage. These findings demonstrate the adverse role of MMP-12 in acute brain damage after ischemic stroke and suggest that MMP-12 suppression could be a therapeutic target for cerebral ischemia (Chelluboina et al., 2015).

10.7. MMPs and Peripheral Arterial Disease

MMPs may be associated with peripheral arterial disease. Studies have analyzed MMP-10 levels in patients with lower limb arterial disease according to disease severity and cardiovascular risk factors and evaluated the prognostic value of MMP-10 for cardiovascular events and mortality after a 2 year follow-up period. Patients with peripheral arterial disease showed increased levels of MMP-10 and decreased levels of TIMP-1 compared with controls. Among patients with peripheral arterial disease, those with critical limb ischemia showed higher levels of MMP-10 compared with those with intermittent claudication, although the MMP-10/TIMP-1 ratio remained similar. The univariate analysis showed an association between MMP-10 levels, age, hypertension, and ankle-brachial index in peripheral arterial disease patients. Patients with the highest MMP-10 tertile had an increased incidence of all-cause mortality and cardiovascular mortality. These observations suggest that MMP-10 is associated with severity and poor outcome in peripheral arterial disease (Martinez-Aguilar et al., 2015).

10.8. MMPs and Aneurysm

MMPs have been associated with the pathophysiology, growth and rupture of thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA). High levels of MMP-2 and MMP-9 have been observed in patients with TAA, with MMP-9 predominantly expressed in the faster-growing anterior wall of the aneurysm and 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).. Studies in mice have shown that the expression of MT1-MMP, an important MMP for macrophage-mediated elastolysis, increases progressively after induction of TAA (Xiong et al., 2008; Jones et al., 2010) . Elevated levels of MMP-2, MMP-8, MMP-9 and MMP-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 MMP-9, and ADAM-10 and ADAM-17 (Geng et al., 2010). In the mouse model of Marfan syndrome, TAA was prevented in mice treated with the MMP inhibitor 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, vascular contraction and endothelium-dependent relaxation were impaired in the nontreated and atenolol-treated mice, but not doxycycline-treated mice (Chung et al., 2008). MMP/TIMP imbalance may be involved in TAA formation (Barbour et al., 2007), and

different degrees of MMP/TIMP imbalances were detected within TAA of patients with bicuspid versus tricuspid aortic valves (Ikonomidis et al., 2007).

MMPs may also play a role in the pathophysiology of AAA. AAA shows several histopathological changes in tunica intima and media including accumulation of lipids in foam cells, adventitial inflammatory infiltrate, extracellular free cholesterol crystals, calcifications, thrombosis, ulcerations and rupture of the vascular layers. Degradation of tunica media is a major pathophysiological feature in AAA. Loss of elastin may initiate AAA formation, and loss of collagen causes continued expansion of the aneurysm wall. Increased collagen turnover could be a major factor in growth and rupture of AAA. Medial neovascularization is characteristic of established AAA and involves proteolytic degradation of ECM by MMPs to facilitate endothelial cell proliferation and migration. Studies demonstrated upregulation of pro-angiogenic cytokines and increased medial neovascularization at the aneurysm rupture edge (Choke et al., 2006).

MMP-2 and MMP-9 appear to play a role in AAA formation (Petersen et al., 2000; Goodall et al., 2001). Patients with AAA show elevated plasma levels of MMP-2 and MMP-9 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. In a study examining circulating levels of MMPs in non-ruptured and ruptured AAA immediately prior to open repair, MMP-1 and MMP-9 levels were elevated in the plasma of patients with ruptured AAA versus non-ruptured AAA. A 4-fold elevation in preoperative plasma levels of MMP-9 were associated with non-survival at 30 days from rupture surgery compared with patients surviving for greater than 30 days (Wilson et al., 2008a). Secretion of MMP-2 and MMP-9 by human ASMCs is enhanced in tissues of AAA in response to hypoxia (Erdozain et al., 2010). MMP-2 and MMP-9 appear to be necessary to induce 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. MMP-8 levels are higher in infrarenal aortic biopsies taken from AAA compared with normal aorta. Immunohistochemistry localized MMP-8 to mesenchymal cells within the adventitia of the aortic wall. On the other hand, the levels of TIMP-1 and TIMP-2 were lower in AAA than in normal aortic samples, presenting a conducive environment for collagen degradation and aneurysm formation and expansion (Wilson et al., 2005).

MMPs may serve as biomarkers for estimation of aneurysmal area and proteolytic activity (Razavian et al., 2010). Plasma MMP-9 levels are correlated with aneurysmal size and expansion (Hackmann et al., 2008). In a study measuring the levels of MMP-9 in peripheral venous blood from 25 patients with AAA, 15 patients with atherosclerotic occlusive disease, and 5 control subjects, plasma MMP-9 levels were directly correlated with the amount of MMP-9 produced in the aneurysm tissue. Elevated MMP-9 levels were observed in one half of patients with AAA and less than 10% of those with atherosclerotic occlusive disease. Importantly, plasma MMP-9 levels decreased 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 AAA (Sangiorgi et al., 2001). However, normal MMP-9 levels may not exclude the presence of AAA (negative predictive value, 52%). Also, some studies showed no significant correlation between serum levels of MMP-9 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 levels of any MMP or TIMP and AAA diameter (Wilson et al., 2008b). 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). These conflicting observations make it important to further explore the validity and accuracy of measurement of MMP-9 or other MMPs as predictive tools for 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 MMP-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 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 MMP-induced degradation of ECM, causing further weakening of the aortic wall and aneurysm formation.

Small randomized clinical trials suggested favorable effects of MMP inhibition by doxycycline on retarding AAA expansion (Mosorin et al., 2001). One study demonstrated that two weeks doxycycline treatment in patients with advanced AAA resulted in reduction of aortic wall neutrophil and cytotoxic T-cell content, and suppression of the inflammatory cytokines IL-6 and IL-8 and the 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 an insignificant 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). Thus, MMP inhibitors may provide an alternative therapeutic approach for AAA.

In addition to the role of MMPs in TAA and AAA, there is an association between certain haplotypes of MMP-1, MMP-3, MMP-7, MMP-12 and MMP-13 and the risk of coronary artery aneurysms in patients with Kawazaki disease (Shimizu et al., 2010).

10.9. MMPs and Chronic Venous Disease

Chronic venous disease is a common disorder of the lower extremity venous system with major social and economic implications. Early stages of chronic venous disease are presented as telangiectasies or spider veins, varicose veins, and edema. Advanced stages of chronic venous disease, often termed as chronic venous insufficiency, are manifested as skin pigmentation or eczema, lipodermatosclerosis or atrophie blanche, healed ulcer or active ulcer (Eklof et al., 2004). Varicose veins affect approximately 25 million adults in the United States (Beebe-Dimmer et al., 2005). Varicose veins are presented as abnormally distended and tortuous superficial veins of the lower extremity, and often show incompetent venous valves and venous reflux. In addition to their socioeconomical impact and unsightly cosmetic appearance, varicose veins can lead to major complications such as thrombophlebitis, deep venous thrombosis, and venous leg ulcers (Eklof et al., 2004).

Varicose veins show imbalance in the protein components of ECM and changes in collagen and/or elastin content. Collagen measurements in varicose veins show marked variability ranging from an increase (Gandhi et al., 1993), to a decrease (Haviarova et al., 1999), or no change (Kockx et al., 1998). Experiments on cultured SMCs from varicose veins and cultured dermal fibroblasts from patients with chronic venous disease have shown an increase in the synthesis of type-I collagen and a decrease in the synthesis of type-III collagen, with no apparent change in gene transcription. These observations suggest that patients with varicose veins have post-translational inhibition of type-III collagen synthesis and may have a systemic abnormality in collagen production in various tissues. Type-III collagen is a critical factor in determining the elasticity and distensibility of blood vessels, and alterations in collagen synthesis and the collagen type-I/type-III ratio could cause marked changes in the vein wall integrity, leading to structural weakness in the vein wall, venous dilation, and formation of varicose veins (Sansilvestri-Morel et al., 2007). Some studies have suggested that a decrease in the elastin content could play a role in the pathogenesis of varicose veins, as it may cause a decrease in the vein wall elasticity and lead to vein wall dilation (Venturi et al., 1996). However, other studies have suggested that the elastin network may be increased in varicose veins (Sansilvestri-Morel et al., 2007).

Varicose veins show marked changes in MMP expression/activity (MacColl and Khalil, 2015). Studies have shown an increase in the levels of MMP-1, MMP-2, MMP-3, and MMP-7 in varicose veins (Sansilvestri-Morel et al., 2007). Increased plasma levels of MMP-10 and the hemostatic markers d-dimers, prothrombin fragments 1 and 2, von Willebrand factor, and activity of plasminogen activator inhibitor (PAI-1) have also been observed in patients with primary varicose veins, suggesting a prothrombotic and proinflammatory state (Dzieciuchowicz et al., 2015). Other studies have shown an increase

in MMP-1 protein level in the great saphenous vein, and an increase in the levels of MMP-1 and MMP-13 in the proximal versus distal segments of varicose veins, with no change in MMP mRNA expression, suggesting that the increased MMP levels are related to changes in MMP post-transcriptional modification or protein degradation (Gillespie et al., 2002). The levels of MMPs may also vary within the different tissue layers and cellular components of the varicose veins wall. Immunohistochemical analysis in tissue sections of varicose veins showed prominent localization of MMP-1 in fibroblasts, SMCs, and endothelial cells; MMP-9 in endothelial cells, medial SMCs and adventitial microvessels; and MMP-12 in SMCs and fibroblasts (Woodside et al., 2003). Other studies have shown increased MMP-1 expression in all layers and MMP-9 expression in the intimal and adventitial layers of varicose veins (Naik et al., 2016). The localization of MMPs in the tunica adventitia and fibroblasts is consistent with the role of MMPs in degradation of ECM proteins. Interestingly, studies also showed increased levels of MMP-2 levels in all layers of the vein wall, and of MMP-1, MMP-3 and MMP-7 in the tunica intima and media of varicose veins (Sansilvestri-Morel et al., 2007), suggesting additional effects of MMPs on the endothelium and VSM.

Although several studies have shown increases in the levels of certain MMPs in varicose veins, some studies have shown no change or even a decrease in the levels of MMPs. One study showed that the levels of active MMP-1 and both pro and active forms of MMP-2 are decreased in varicose veins (Gomez et al., 2014). The variability in the levels of MMPs may explain the variability in the measurements of collagen content in varicose veins wall which ranged from a decrease (Haviarova et al., 1999), to no change (Kockx et al., 1998), or even an increase (Gandhi et al., 1993). The variability in the levels of MMPs may be due to examining different vein segments from hypertrophic versus atrophic regions varicose veins, or examining vein specimens from patients at different stages of chronic venous disease, or inability to distinguish between pro- and active forms of MMPs.

Changes in MMP expression/activity have been associated with the progression of chronic venous disease and advanced stages of chronic venous insufficiency. Studies have shown elevated serum levels of MMP-2, ADAMTS-1 and ADAMTS-7 in the initial stages of chronic venous disease, whereas the serum levels of MMP-1, MMP-8, MMP-9, neutrophil gelatinase-associated lipocalin (NGAL), ADAM-10, ADAM-17 and ADAMTS-4 were particularly elevated during chronic venous insufficiency and skin changes (Serra et al., 2017). The collagenases MMP-1 and MMP-8 are overexpressed in the fluids and tissues of long lasting non-healing chronic venous ulcers (Amato et al., 2015), and their levels were higher in patients with infected ulcers than those with uninfected ulcers (Serra et al., 2016).

Increased lower extremity venous hydrostatic pressure is a major factor that could lead to increased expression/activity of MMPs in varicose veins. Studies have suggested that mechanical stretch may lead to increases in the expression of MMPs in endothelial cells, VSMCs and fibroblasts (Asanuma et al., 2003). We have shown that prolonged increases in mechanical tension or wall stretch of isolated rings of rat inferior vena cava are associated with increased expression of MMP-2 and MMP-9 in the tunica intima and increased MMP-9 in the tunica media of the vein wall. Prolonged stretch of rat inferior vena cava was also associated with decreased vein contraction. In inferior vena cava pretreated with MMP

inhibitors, prolonged mechanical stretch did not cause decreases in contraction. These observations suggested that prolonged increases in venous pressure/wall tension cause changes in MMP expression/activity, which in turn decrease vein contraction, and promote venous dilation (Raffetto et al., 2008). The factors linking the increased venous pressure to increased MMP expression in the vein wall are not clearly understood, but may include inflammation or hypoxia inducible factors (Lim et al., 2011).

Other MMP inducers/activators may promote MMP expression/activity in varicose veins. Studies have shown that high volume mechanical ventilation causes acute lung injury, and is associated with upregulation of MMP-2, MMP-9, and MT1-MMP as well as EMMPRIN (Foda et al., 2001). Also, EMMPRIN along with MMP-2, MT1-MMP and MT2-MMP are overexpressed in dermal structures of venous leg ulcers, which could lead to unrestrained activation of MMPs and enhanced ECM turnover (Norgauer et al., 2002).

TIMPs have been localized in different regions within the veins. Studies have tested whether histological changes in varicose veins wall may correlate with alterations in the expression of MMPs and TIMPs. Varicose veins were compared with great saphenous vein segments from arterial bypass, and with arm and neck veins from fistula and carotid operations. There was a higher expression of TIMP-2 and increased connective tissue accumulation in the tunica media of varicose veins compared with control arm and neck veins. TIMP-2 and -3 expression was higher in hypertrophic than atrophic segments, and in the thicker proximal segments compared to the distal segments of varicose veins. A higher TIMP expression would suppress protease activity, reduce ECM turnover, and favor deposition of connective tissue and thicker vein wall (Aravind et al., 2010). Other studies localized TIMP-1, TIMP-2, and TIMP-3 in the intima and TIMP-1 and TIMP-2 in the media of control veins, as compared to TIMP-1 and TIMP-3 in the intima and TIMP-1, TIMP-2, and TIMP-3 in the media of varicose veins (Sansilvestri-Morel et al., 2007).

An imbalance of MMP/TIMP ratio may contribute to the development of varicose veins. A change in either MMP or TIMP levels could alter the MMP/TIMP ratio and cause a net change in specific MMP activity. In one study, MMP-7 and MMP-9, and TIMP-1, TIMP-2 and TIMP-3 levels were only slightly modified, while MMP-1, MMP-2 and MMP-3 levels were increased, and these changes were accompanied by an increase in the elastic network and accumulation of collagen type I, fibrillin-1 and laminin in both the veins and the skin of patients with varicose veins compared with control subjects undergoing coronary bypass surgery. These findings suggest that an imbalance in MMP/TIMP ratio could lead to disruption of ECM production/degradation balance, and the observed remodeling in both the veins and the skin of patients with varicose veins suggests systemic alterations of the connective tissue (Sansilvestri-Morel et al., 2007). Other studies showed a decrease in MMP-2/TIMP-1 ratio in avulsed varicose veins and suggested that the decrease in MMP-2 proteolytic activity could be the cause of the extensive accumulation of ECM in hypertrophic regions of varicose veins (Badier-Commander et al., 2001). Also, marked increases in plasma levels of MMP-2 and MMP-9, TIMP-1 and TIMP-2, and the MMP-2/TIMP-2 ratio were observed in patients with leg venous ulcers compared with normal controls. In subjects with healed venous ulcers, there was a decrease in MMP-9 and TIMP-1 levels and in the MMP-2/TIMP-2 ratio compared to the baseline values (Caimi et al., 2015).

These observations highlight the importance of further examining the levels of TIMPs in comparison with MMPs in different regions of varicose veins at different stages of chronic venous disease.

In a recent study examining the effects of doxycycline in leg venous ulcer, patients were randomized into two groups, one group received the most appropriate basic treatment including compression therapy followed or not by vein surgery plus oral low dose of doxycycline 20 mg b.i.d. for 3 months, while the second group of patients received basic treatment only. Patients receiving basic treatment plus doxycycline showed a higher healing rate of venous ulcers compared with patients receiving basic treatment only. In patients receiving basic treatment only, the lower healing rate was associated with higher levels of MMP-9. NGAL and VEGF in plasma, wound fluid and biopsies. It was suggested that doxycycline administration through its immunomodulatory and anti-inflammatory actions, and inhibitory effects on MMP, could improve ECM function and speed venous leg ulcer and wound healing (Serra et al., 2015).

11. CONCLUSIONS AND PERSPECTIVE

MMPs are important regulators of the vascular ECM and other signaling pathways in the vasculature. MMPs are involved in many biological and vascular processes and could be important biomarkers for cardiovascular disease. One hurdle to understanding the role of specific MMPs in vascular pathology is that studies often examine few MMPs or TIMPs, and it is important to not generalize the findings to other MMPs and TIMPs. Because tissue remodeling is a dynamic process, an increase in one MMP in a certain region may be paralleled by a decrease of other MMPs in other regions. Also, because of the differences in the proteolytic activities of MMPs towards different substrates, MMP activity may vary during the course of disease. Therefore, it is important to examine different MMPs and TIMPs in various tissue regions and at different stages of the disease. Another challenge is that the topology of MMPs is well conserved, making it difficult to design highly specific MMP inhibitors. Endogenous TIMPs are not very specific and often inhibit multiple MMPs. Likewise, synthetic MMP inhibitors have poor selectivity and many biologic actions, and therefore often cause side effects (Hu et al., 2007). A major limitation of MMP inhibitors is that they cause musculoskeletal side effects manifested as joint inflammation, pain, stiffness, and tendonitis (Renkiewicz et al., 2003). New synthetic MMP inhibitors are being developed, and their effectiveness in cardiovascular disease needs to be examined. Another strategy is to target MMPs locally in the vicinity of a localized pathology, and thus minimize undesirable systemic effects. Localized MMP targeting may be advantageous in localized vascular pathology such as peripheral arterial disease, aneurysm, and varicose veins.

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List of Abreviations

BK_{Ca}	large conductance Ca^{2+}-activated K^+ channel
ECM	extracellular matrix
EDHF	endothelium-derived hyperpolarizing factor
EMMPRIN	extracellular matrix metalloproteinase inducer
ERK	extracellular signal-regulated kinase
GPI	glycosyl phosphatidylinositol
MAPK	mitogen-activated protein kinase
miR	microRNA
MMP	matrix metalloproteinase
MT-MMP	membrane-type MMP
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
PAR	protease-activated receptor
PMNs	polymorphonuclear leukocytes
PDGF	platelet-derived growth factor
PI_3K	phosphoinositide 3-kinase
RGD	Arg-Gly-Asp
siRNA	small interfering RNA
TGF-β	transforming growth factor-β
TIMP	tissue inhibitor of metalloproteinases
TNF-α	tumor necrosis factor-α
VEGF	vascular endothelial growth factor
VSM	vascular smooth muscle
VSMC	vascular smooth muscle cell
Zn^{2+}	zinc

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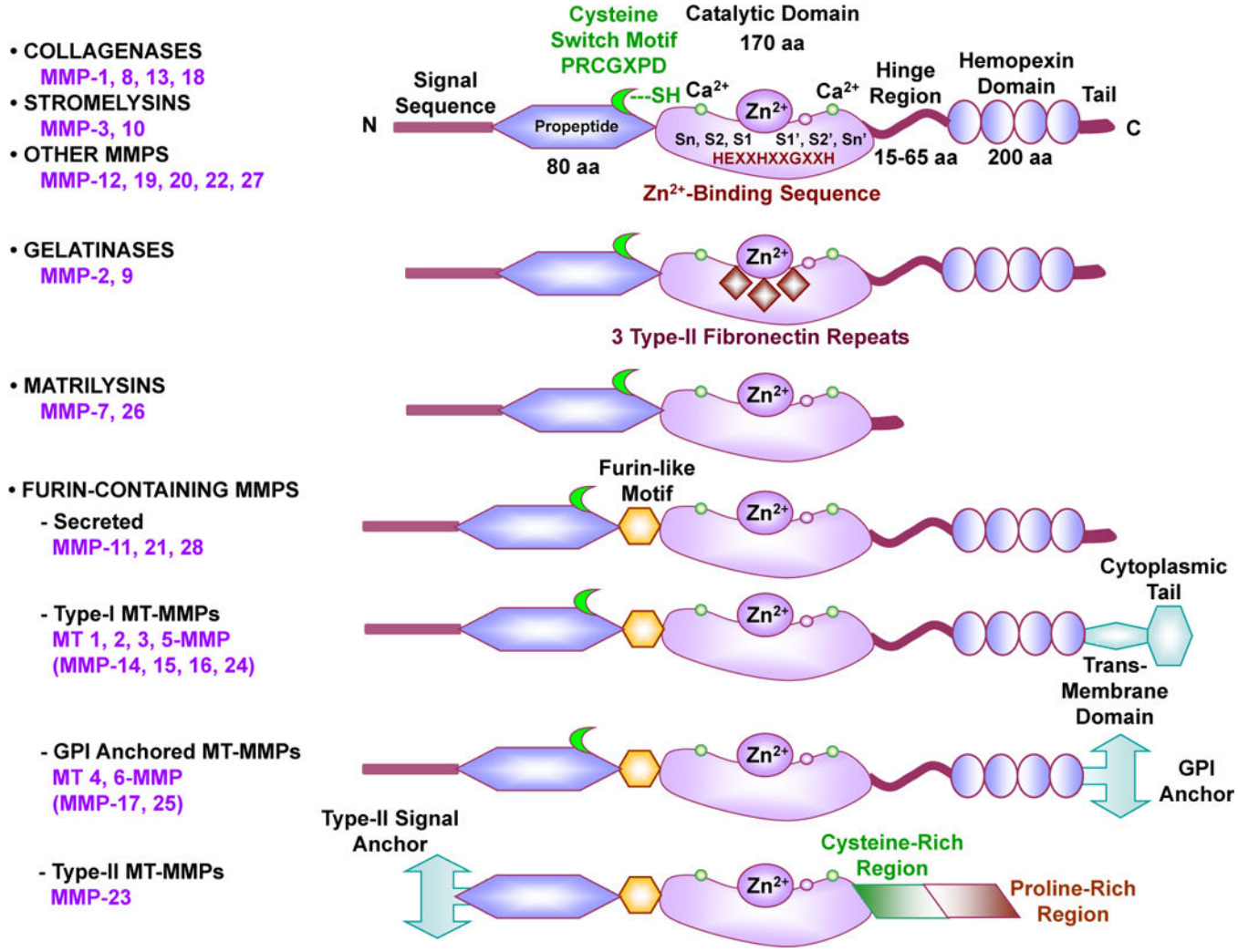

Fig. 1.

MMP subtypes and their structure. A typical MMP consists of a propeptide, a catalytic metalloproteinase domain, a linker peptide (hinge region), and a hemopexin domain. The propeptide has a cysteine switch PRCGXPD whose cysteine sulfhydryl (–SH) group chelates the active site Zn^{2+}, and keeps the MMP in its latent proMMP zymogen form. The catalytic domain contains the Zn^{2+} binding motif HEXXHXXGXXH, two Zn^{2+} ions (one catalytic and one structural), specific S1, S2,…Sn and S1', S2',…Sn' pockets, which confer specificity, and two or three Ca^{2+} ions for stabilization. Some MMPs show exceptions in their structures. Gelatinases have 3 type-II fibronectin repeats in the catalytic domain. Matrilysins have neither a hinge region nor a hemopexin domain. Furin-containing MMPs such as MMP-11, 21 and 28 have a furin-like pro-protein convertase recognition sequence in the propeptide C-terminus. MMP-28 has a slightly different cysteine switch motif PRCGVTD. Membrane-type MMPs (MT-MMPs) typically have a transmembrane domain and a cytosolic domain. MMP-17 and -25 have a glycosylphosphatidylinositol (GPI) anchor. MMP-23 lacks the consensus PRCGXPD motif, has a cysteine residue located in a different sequence ALCLLPA, may remain in the latent inactive proform through its type-II signal anchor, and has a cysteine-rich region and an immunoglobulin-like proline-rich region.

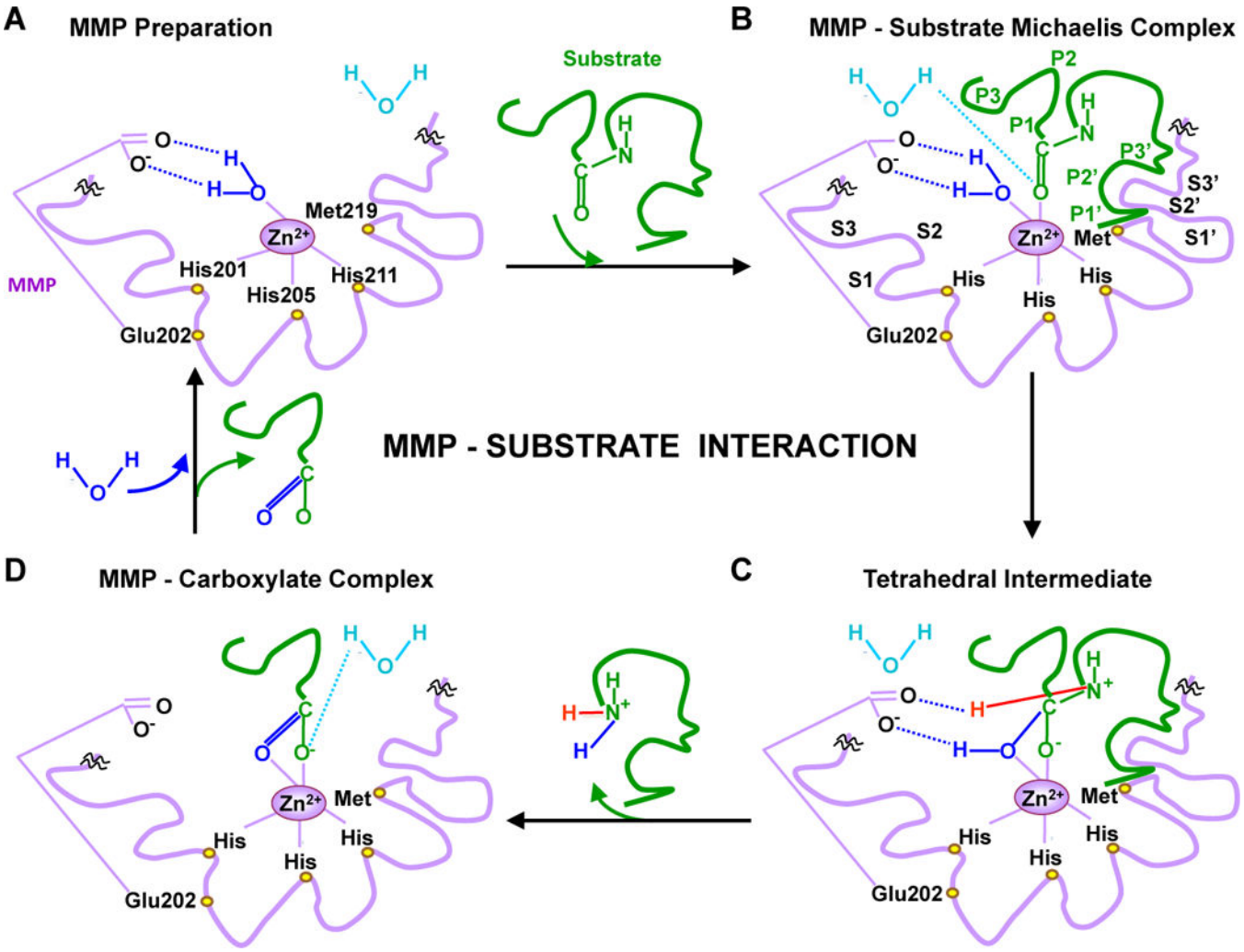

Fig. 2.

MMP-substrate interaction. MMP-3 is used as an example, and the MMP-substrate-interaction and the positions of the conserved His and Glu may vary in other MMPs. Only the MMP catalytic domain is illustrated, and the remaining part of the MMP molecule is truncated by squiggles. A) In the quiescent MMP molecule, the catalytic Zn^{2+} is supported in the HEXXHXXGXXH-motif by binding to the imidazole rings of the 3 histidines His201, 205, 211. Additionally, the methionine-219 (Met219) in the conserved XBMX Met-turn acts as a hydrophobic base to further support the structure surrounding the catalytic Zn^{2+}. In preparation for substrate binding, an incoming H_2O molecule is polarized between the MMP acidic Zn^{2+} and basic glutamate-202 (Glu202). B) Using H^+ from free H_2O, the substrate carbonyl group binds to Zn^{2+}, forming a Michaelis complex. This allows the MMP S1, S2, S3, …Sn pockets on the right side of Zn^{2+} and the primed S1', S2', S3', …Sn' pockets on the left side of Zn^{2+} to confer specific binding to the substrate P1, P2, P3, … Pn and the primed P1', P2', P3', … Pn' substituents, respectively. The MMP pockets are organized such that the S1 and S3 pockets are located away from the catalytic Zn^{2+}, while the S2 pocket is closer to Zn^{2+}. C) The substrate-bound H_2O is freed, the Zn^{2+}-bound oxygen from the Glu-bound H_2O executes a nucleophilic attack on the substrate carbon, and the Glu202

extracts a proton from the Glu-bound H_2O to form an N-H bond with the substrate N, resulting in a tetrahedral intermediate. D) Freed H_2O is taken up again, and the second proton from Glu-bound H_2O is transferred to the substrate, forming an additional N-H bond. As a result, the substrate scissile C-N bond breaks, thus releasing the N portion of the substrate while the carboxylate portion of the substrate remains in an MMP-carboxylate complex. Another H_2O is taken up, thus releasing the remaining carboxylate portion of the substrate, and the MMP is prepared to attack another substrate (A).

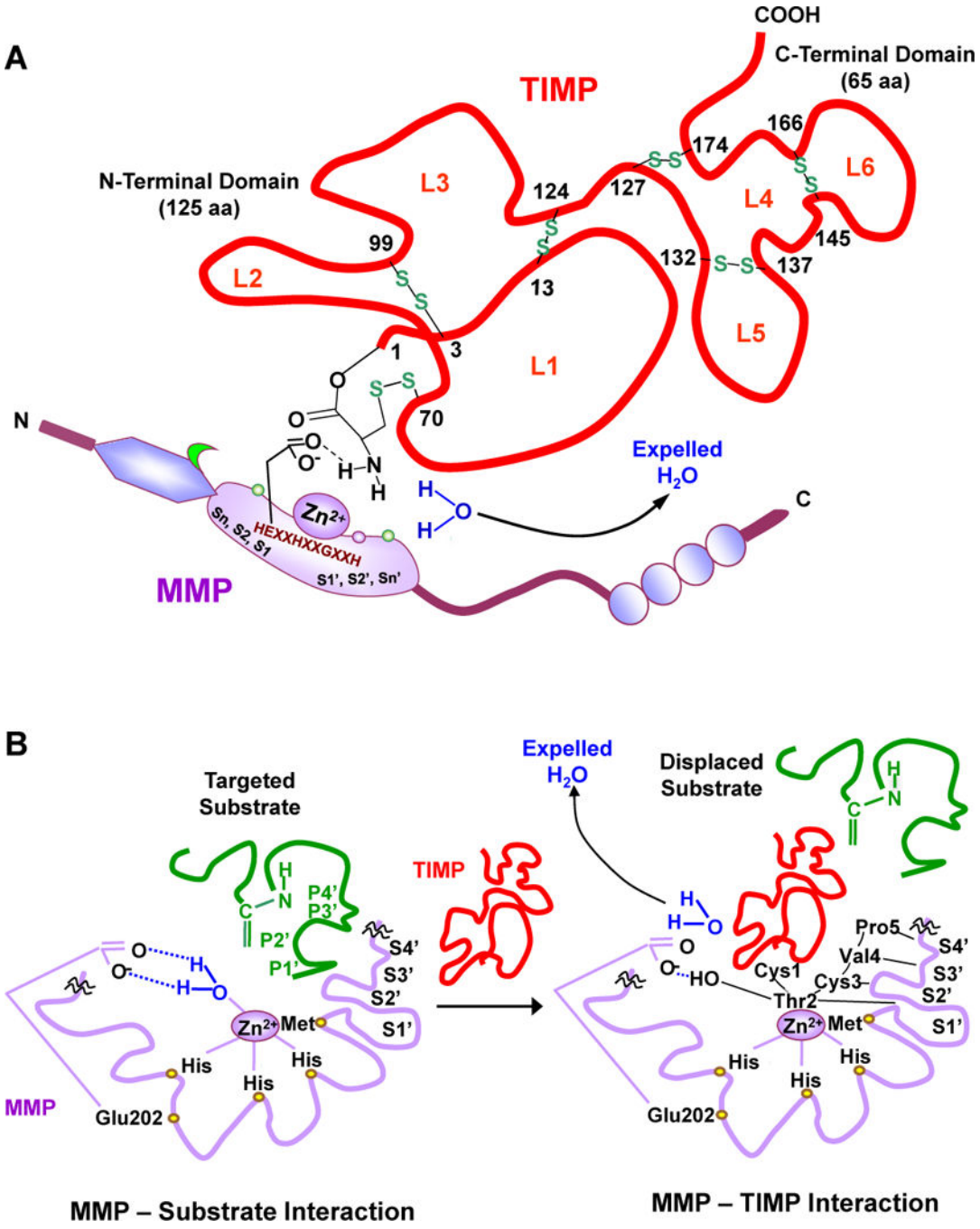

Fig. 3.

TIMP-MMP Interaction. TIMP-1 and MMP-3 are used as prototypes. The amino acids involved in Zn^{2+}- and pocket-binding may vary with different MMPs and TIMPs. (A) TIMP is a ~190 aa protein, with an N-terminal domain (loops L1, L2, and L3) and C-terminal domain (loops L4, L5 and L6), which fold independently as a result of 6 disulfide bonds between 12 specific Cys residues. The N-terminal Cys1-Thr-Cys-Val4 and Glu67-Ser-Val-Cys70 are connected via a disulfide bond between Cys1 and Cys70 and are essential for MMP inhibition, as they enter the MMP active site and bidentately chelate the MMP Zn^{2+}.

The carbonyl oxygen and α-amino nitrogen in the TIMP Cys1 coordinate with the MMP Zn^{2+}, which is localized in the MMP molecule via the 3 histidines in the HEXXHXXGXXH motif. The TIMP α-amino group then expels Zn^{2+}-bound H_2O by binding the MMP H_2O binding site and forming a hydrogen bond with carboxylate oxygen from conserved MMP Glu202 (E in the HEXXHXXGXXH sequence). (B) TIMP Thr2 side chains enter the MMP S1' pocket in a manner similar to that of a substrate P1' substituent. Thr2 –OH group could also interact with Glu202, further contributing to expelling Zn^{2+}-bound H_2O and preventing substrate degradation. The TIMP Cys3, Val4 and Pro5 also interact with MMP S2′, S3', and S4′ pockets in a P2′, P3′, and P4'-like manner, further preventing substrate binding.

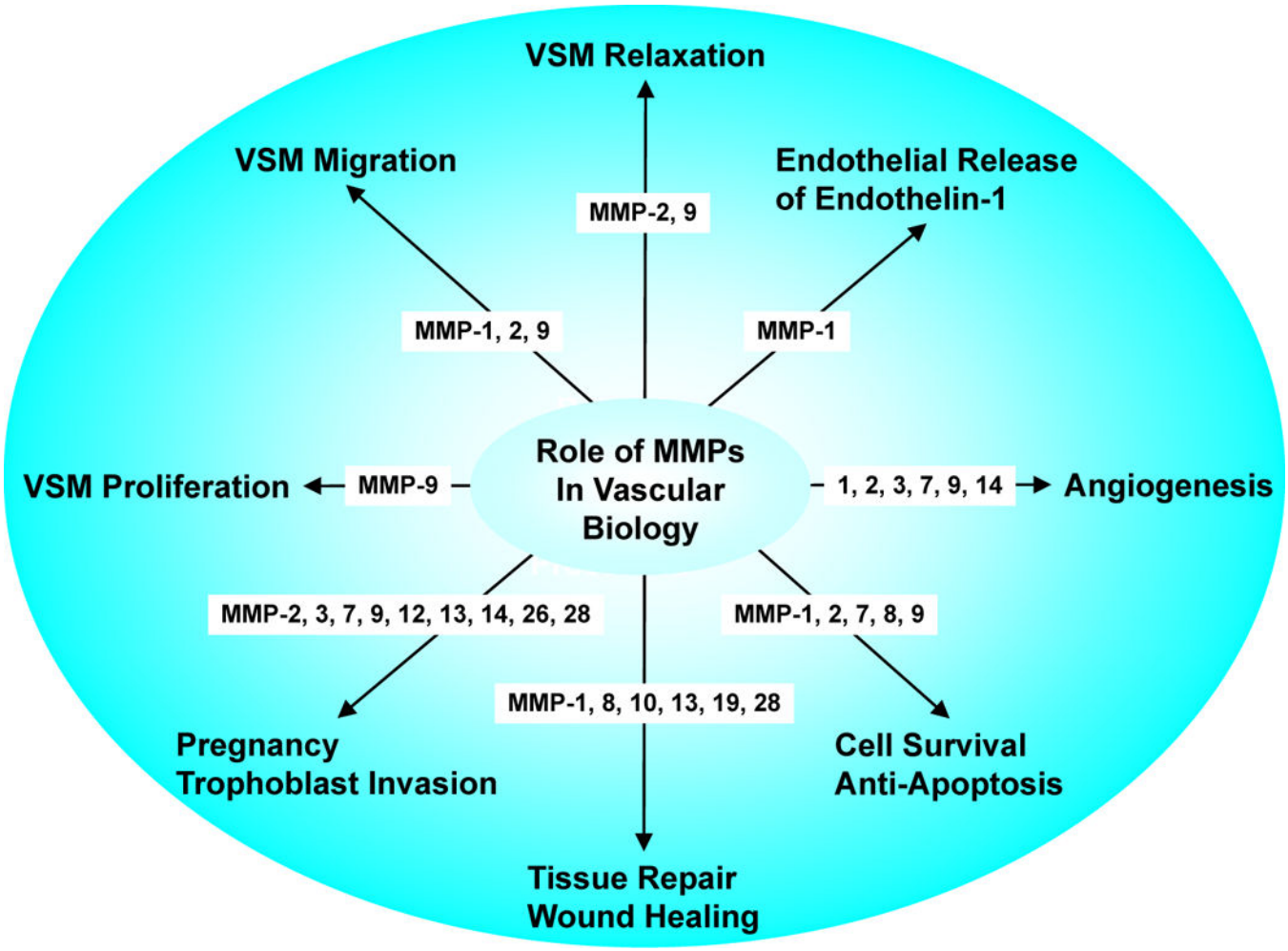

Fig. 4.
Representative roles of MMPs in vascular biology.

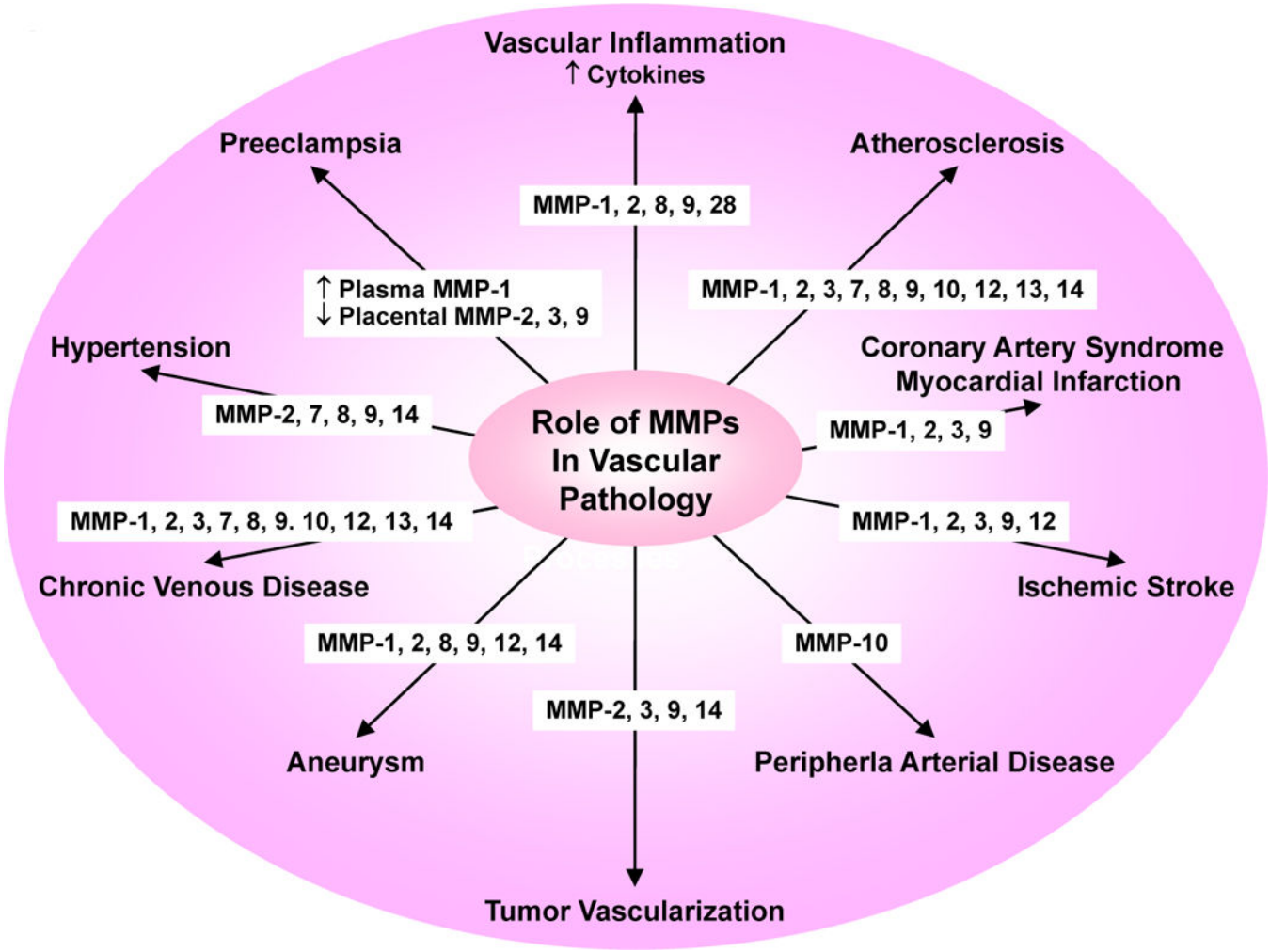

Fig. 5.
Representative roles of MMPs in vascular pathology.

Table 1

Members of the MMP family, gene locus, molecular weight, tissue distribution and substrates.

MMP (Other Name) Chromosome	MW kDa Pro/Active	Distribution	Collagen Substrates	Non-Collagen ECM Substrates	Other Targets and Substrates
Collagenases MMP-1 (Collagenase-1) 11q22.3	55/45	Endothelium, SMCs, fibroblasts, platelets, macrophages, varicose veins (interstitial/fibroblast collagenase)	I, II, III, VII, VIII, X, gelatin	Aggrecan, nidogen, perlecan, proteoglycan link protein, serpins, tenascin-C, versican	Casein, α1-antichymotrypsin, α1-antitrypsin, α1-proteinase inhibitor, IGF-BP-3 and -5, IL-1β, L-selectin, ovostatin, PAR-1, pro-TNF-α, SDF-1
MMP-8 (Collagenase-2) 11q22.3	75/55	Macrophages, neutrophils (PMNL or neutrophil collagenase)	I, II, III, V, VII, VIII, X, gelatin	Aggrecan, elastin, fibronectin, laminin, nidogen	α2-antiplasmin, proMMP-8
MMP-13 (Collagenase-3) 11q22.3	60/48	SMCs, macrophages, varicose veins, preeclampsia, breast cancer	I, II, III, IV, gelatin	Aggrecan, fibronectin, laminin, perlecan, tenascin	Casein, PAR-1, plasminogen activator 2, proMMP-9 and -13, SDF-1
MMP-18 (Collagenase-4) 12q14	70/53	*Xenopus* (amphibian, Xenopus collagenase) heart, lung, colon	I, II, III, gelatin		α1-antitrypsin
Gelatinases MMP-2 (Gelatinase-A, Type IV Collagenase) 16q13-q21	72/63	Endothelium, VSM, adventitia, platelets, leukocytes, aortic aneurysm, varicose veins	I, II, III, IV, V, VII, X, XI, gelatin	Aggrecan, elastin, fibronectin, laminin, nidogen, proteoglycan link protein, versican	Active MMP-9 and -13, FGF-R1, IGF-BP-3 and -5, IL-1β, pro-TNF-α, TGF-β
MMP-9 (Gelatinase-B, Type IV Collagenase) 20q11.2-q13.1	92/86	Endothelium, VSM, adventitia, microvessels, macrophages, aortic aneurysm, varicose veins	IV, V, VII, X, XIV, gelatin	Aggrecan, elastin, fibronectin, laminin, nidogen, proteoglycan link protein, versican	CXCL5, IL-1β, IL2-R, plasminogen, pro-TNF-α, SDF-1, TGF-β
Stromelysins MMP-3 (Stromelysin-1) 11q22.3	57/45	Endothelium, intima, VSM, platelets, coronary artery disease, hypertension, varicose veins, synovial fibroblasts, tumor invasion	II, III, IV, IX, X, XI, gelatin	Aggrecan, decorin, elastin, fibronectin, laminin, nidogen, perlecan, proteoglycan, proteoglycan link protein, versican	Casein, α1-antichymotrypsin, α1-proteinase inhibitor, antithrombin III, E-cadherin, fibrinogen, IGF-BP-3, L-selectin, ovostatin, pro-HB-EGF, pro-IL-1β, proMMP-1, -8 and -9, pro-TNF-α, SDF-1
MMP-10 (Stromelysin-2) 11q22.3	57/44	Atherosclerosis, uterus, preeclampsia, arthritis, carcinoma cells	III, IV, V, gelatin	Aggrecan, elastin, fibronectin, laminin, nidogen	Casein, proMMP-1, -8 and -10
MMP-11 (Stromelysin-3) 22q11.23	51/44	Brain, uterus, angiogenesis	Does not cleave	Aggrecan, fibronectin, laminin	α1-antitrypsin, α1-proteinase inhibitor, IGF-BP-1
Matrilysins MMP-7 (Matrilysin-1) 11q21-q22	29/20	Endothelium, intima, VSM, uterus, varicose veins (PUMP)	IV, X, gelatin	Aggrecan, elastin, enactin, fibronectin, laminin, proteoglycan link protein	Casein, β4 integrin, decorin, defensin, E-cadherin, Fas-ligand, plasminogen, proMMP-2, -7 and -8, pro-TNF-α, syndecan, transferrin

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MMP (Other Name) Chromosome	MW kDa Pro/Active	Distribution	Collagen Substrates	Non-Collagen ECM Substrates	Other Targets and Substrates
MMP-26 (Matrilysin-2, Endometase) 11p15	28/19	Breast cancer, endometrial tumors	IV, gelatin	Fibrinogen, fibronectin, vitronectin	Casein, β1-proteinase inhibitor, fibrin, fibronectin, proMMP-2
Membrane-Type MMP-14 (MT1-MMP) 14q11-q12	66/56	VSM, fibroblasts, platelets, brain, uterus, angiogenesis	I, II, III, gelatin	Aggrecan, elastin, fibrin, fibronectin, laminin, nidogen, perlecan, proteoglycan, tenascin, vitronectin	$\alpha_v\beta_3$ integrin, CD44, proMMP-2 and -13, pro-TNF-α, SDF-1, α1-proteinase inhibitor, tissue transglutaminase
MMP-15 (MT2-MMP) 16q13	72/50	Fibroblasts, leukocytes, preeclampsia	I, gelatin	Aggrecan, fibronectin, laminin, nidogen, perlecan, tenascin, vitronectin	ProMMP-2 and -13, tissue transglutaminase
MMP-16 (MT3-MMP) 8q21.3	64/52	Leukocytes, angiogenesis	I	Aggrecan, fibronectin, laminin, perlecan, vitronectin	Casein, proMMP-2 and -13
MMP-17 (MT4-MMP) 12q24.3	57/53	Brain, breast cancer	Gelatin	Fibrin	
MMP-24 (MT5-MMP) 20q11.2	57/53	Leukocytes, lung, pancreas, kidney, brain, astrocytoma, glioblastoma	Gelatin	Chondroitin sulfate, dermatin sulfate, fibrin, fibronectin, N-cadherin	ProMMP-2 and -13
MMP-25 (MT6-MMP) 16p13.3	34/28	Leukocytes (Leukolysin), anaplastic astrocytomas, glioblastomas	IV, gelatin		Fibrin, fibronectin, proMMP-2, α1-proteinase inhibitor
Other MMPs MMP-12 (Metalloelastase) 11q22.3	54/45 – 22	SMCs, fibroblasts, macrophages, great saphenous vein	IV, gelatin	Elastin, fibronectin, laminin	Casein, plasminogen
MMP-19 (RASI-1) 12q14	54/45	Liver	I, IV, gelatin	Aggrecan, fibronectin, laminin, nidogen, tenascin	Casein
MMP-20 (Enamelysin) 11q22.3	54/22	Tooth enamel	V	Aggrecan, cartilage oligomeric protein, amelogenin	
MMP-21 (Xenopus-MMP) 10q26.13	62/49	Fibroblasts, macrophages, placenta			α1-antitrypsin
MMP-22 (Chicken-MMP) 1p36.3	51	Chicken fibroblasts	Gelatin		
MMP-23 (CA-MMP) 1p36.3	28/19	Ovary, testis, prostate Other (type II) MT-MMP	Gelatin		
MMP-27 (Human MMP-22 homolog) 11q24		Heart, leukocytes, macrophages, kidney, endometrium, menstruation, bone, osteoarthritis, breast cancer			
MMP-28 (Epilysin) 17q21.1	56/45	Skin, keratinocytes			Casein

CA-MMP, cysteine array MMP; CXCL5, chemokine (C-X-C motif) ligand 5; FGF-R1, fibroblast growth factor receptor 1; IGF-BP, insulin-like growth factor binding protein; IL, interleukin; MW, molecular mass; PMNL, polymorphonuclear leukocytes; pro-HB-EGF, pro-heparin-binding epidermal growth factor-like growth factor; RASI-1, rheumatoid arthritis synovium inflamed-1; SDF-1, stromal cell-derived factor-1