Chapter 14
MMP-Mediated Collagen Remodeling and Vessel Functions

Agnès Noel and Nor Eddine Sounni

14.1 Introduction

Blood vessels are highly organized structures in which the extracellular matrix (ECM) of the vessel wall and the perivascular interstitium contribute substantially to their diverse functions. Synthesis and degradation of ECM components in vascular wall or perivascular stroma are tighly controlled mechanisms. Matrix metabolism perturbation is sufficient to significantly affect vascular system physiology leading to several vascular disorders including diabetic retinopathy (Turley 2001), hemorrhagic telangiectasia (Arteaga-Solis et al. 2000), hypertensive heart diseases (Morwood and Nicholson 2006), atherosclerosis and fibrosis (Diez 2007; Radisky et al. 2007). Vascular abnormalities are also associated with cancer progression and metastatic dissemination (Berk et al. 2007). The ECM in the vascular wall contains a variety of molecules including collagens, elastic fibers, glycoproteins and proteoglycans that provide structural and mechanical support to cells. Vascular cells are connected to these structural matrix components by cell surface receptors of integrins and non-integrins types (Davis and Senger 2008). Matrix receptor interactions influence vascular cell shape, behavior and response to cytokines and growth factors (Boudreau and Jones 1999). Alterations of vessel matrix have thus profound impact on blood vessel integrity affecting thereby the extravasation of fluids and plasma proteins into the interstitium (Wiig et al. 2008). ECM molecules play a major role of in maintaining mature tubular structures in vascular and lymphatic systems (Bergers and Benjamin 2003; Oliver and Detmar

A. Noel • N.E. Sounni (✉)
Laboratory of Tumor and Developmental Biology, Groupe Interdisciplinaire de Génoprotéomique Appliquée-Cancer (GIGA-Cancer), B23, University of Liège, 4000 Liège, Belgium
e-mail: nesounni@ulg.ac.be

K. Brix and W. Stöcker (eds.), *Proteases: Structure and Function*,
DOI 10.1007/978-3-7091-0885-7_14,

2002). For instance, genetic studies show that mutations in *COL3A1* gene lead to Ehlers-Dahlos syndrome type IV, a connective tissue disorder characterized predominantly by arterial dilation and rupture (Arteaga-Solis et al. 2000). On other hand, a mutation in the *Fibrillin-1* (*FBN1*) gene in Marfan syndrome, results in deficiency of elastic fibers that regulate cell attachment in vessel walls to the neighboring ECM (Neptune et al. 2003). Thus proper metabolism, assembly in vascular tissues regulates maintenance of tissue homeostasis. Functional and structural vascular remodeling involve several enzymes among which MMPs produced by endothelial, inflammatory, or malignant cells are key players. The present review will describe the contribution of MMPs in the remodeling of collagens that are essential vessel components. Understanding the complex role of MMPs in vessel wall assembly and functions in homeostasis or diseases is mandatory to provide new therapy to maintain vessel stability and proper function.

14.2 Collagenolytic Activities of MMPs

MMPs are a family of zinc-dependent endopeptidases composed of 24 currently known human enzymes that share several functional domains. MMPs are often referred to soluble (MMPs) or membrane type-MMPs (MT-MMPs) that are anchored to the cell surface through transmembrane domain or glycosylphosphatidylinositol (GPI) linker. For a description of the structure, function and regulation of MMPs and MT-MMPs, the reader is referred to previous reviews (Kessenbrock et al. 2010; Page-McCaw et al. 2007; Sohail et al. 2008; Sounni and Noel 2005; Strongin 2010; Zucker et al. 2003). Interstitial collagenases are the only known mammalian enzymes able of degrading triple-helical fibrillar collagen into distinctive tropocollagen A (TCA) (3/4) and (TCB) (1/4) fragments as a consequence of a specific proteolysis of all three α-chains at a single locus three-quarters from the N-terminus. Collagenolytic MMPs include soluble MMPs (MMP1, MMP8, MMP13) and the membrane-associated MMP14/MT1-MMP. More recently, MMP2 has been identified as an interstitial collagenase that can cleave native type I collagen in a distinctive way from other collagenases without generating the classical TCA fragment (Egeblad et al. 2007). MMP-2 and MMP-9 (initially referred to as gelatinase A and gelatinase B, respectively) cleave type IV collagen present in basement membrane and the degradation products generated by the action of interstitial collagenases. These MMPs produced by endothelial cells, fibroblasts, smooth muscle cells (VSMCs) and inflammatory cells play pivotal roles in multiple physiological and pathological processes involving extensive and aberrant collagenolysis (Fig. 14.1). Latest technological progresses have obviously advanced our consideration of MMPs as key regulators that operate in complex cellular and molecular networks. In addition to the mentioned collagenolytic activities, MMPs contribute to the proteolytic cleavage of an increasing repertoire of substrates that includes at least, almost all ECM components, chemokines/cytokines, growth factors and cell surface receptors (Butler and

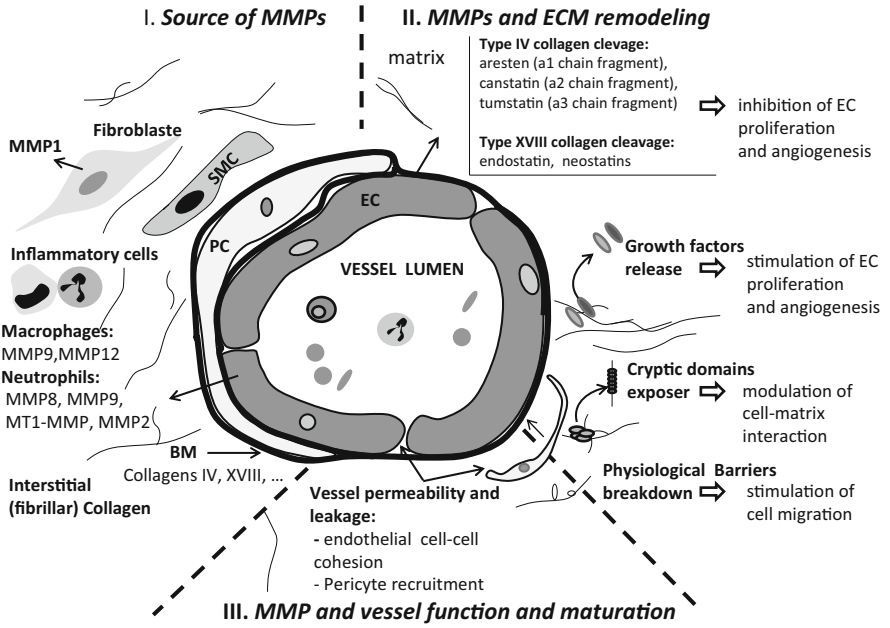

Fig. 14.1 MMP effects on vessel function and maturation. MMPs are produced in perivascular stroma by endothelial (EC), pericyte (PC) inflammatory cells, and fibroblasts (I). They regulate vessel function and maturation through different mechanisms which relay on their proteolytic activity. MMPs increase growth factor availability in perivascular stroma, unmask cryptic sites within extracellular matrix molecules and generate angiogenesis inhibitor form basement membrane (BM) and collagens (II). MMPs activity controls the vascular homeostasis and regulates vessel permeability and leakage in vascular diseases (III)

Overall 2009; Hu et al. 2007). Under normal conditions, MMP activities are controlled through transcriptional regulation, activation of pro-MMP precursor zymogens and inhibition by physiological tissue inhibitor of matrix metalloproteinases (TIMPs) that bind MMP in a 1:1 stoichiometry (Kessenbrock et al. 2010; Lopez-Otin and Overall 2002). Four TIMPs have been identified in vertebrates and their expression is regulated during development and tissue remodeling (Nagase et al. 2006). More recently some MMPs and TIMPs were described as targets of epigenetic regulation via CpG methylation and histones modifications (Chernov et al. 2009; Liu et al. 2007; Pulukuri et al. 2007).

14.3 MMP-Mediated Collagen Remodeling for Vessel Structure and Functions

MMPs contribute to perivascular matrix remodeling during normal angiogenesis (Ucuzian and Greisler 2007). In pathological conditions, the vascular wall and perivascular interstitium are exposed to intensive MMP-mediated remodeling that can create a less restrictive microenvironment. A sustained MMP activity is associated with several vascular pathologies including aneurysm, atherosclerosis, hypertension and restinosis (Mott and Werb 2004; Page-McCaw et al. 2007). MMP-mediated collagen remodeling can regulate tissue architecture through different mechanisms. They can generate extracellular space for cell migration and unmask cryptic sites within ECM molecules modifying thereby cell to matrix adhesion. By promoting the release of matrix-associated growth factors or cytokines, they modulate the activity or bioavailability of signaling molecules during vascular response to physiological or pathological stimuli (Kessenbrock et al. 2010; Page-McCaw et al. 2007). MMP activities result also in the generation of matrix fragments displaying novel biological activity (Kessenbrock et al. 2010; Page-McCaw et al. 2007; Rundhaug 2005). It is now well recognized that collagen proteolysis may release a number of endogenous angiogenesis inhibitors, including type IV (arresten, canstatin, tumstatin), type V (restin) and type XVIII (endostatin, neostatins) collagen fragments among other fragments of ECM proteins that may display anti-angiogenic activity (Egeblad and Werb 2002; Kojima et al. 2008; Nyberg et al. 2005). These angio-inhibitory fragments regulate primarily endothelial cell proliferation and apoptosis by interfering with integrins. The contribution of such endogenous inhibitors in human pathologies is supported by the role played by endostatin in choroidal neovascularization (CNV) associated to age-related macular degeneration (AMD), the leading cause of blindness in elderly patients (Noel et al. 2007). MMPs release and activate endostatin from collagen XVIII present in vascular basement membranes and Bruch membrane (Ferreras et al. 2000; Zatterstrom et al. 2000). Endostatin levels are decreased in human eyes with AMD, and its deficiency was suggested to predispose to CNV formation (Bhutto et al. 2004). Accordingly, both external delivery of endostatin and endogenous endostatin inhibits experimental CNV (Marneros et al. 2007).

14.3.1 Type IV Collagen Remodeling

Type IV collagen is the main component of vascular basement membrane that forms a mesh-like structure with other molecules such as laminin, heparan sulfate proteoglycans, fibronectin and entactin. In addition to the release of endogenous angiogenic inhibitor (Fig. 14.1), specific cryptic type IV collagen epitopes can be exposed upon proteolysis. For instance, a cryptic site hidden within the three-dimensional structure of type IV collagen is exposed by MMP2 and promotes

in vivo angiogenesis (Xu et al. 2001). The recognition of a cryptic epitope (HU177) present exclusively in type IV collagen by a specific mouse antibody (HUIV26) inhibits endothelial cell proliferation and differentiation into tubule-like structures (Cretu et al. 2007). Interference with this epitope results in the expression of cyclin-dependent kinase (CDK) inhibitor p27kip1 in endothelial cells (Cretu et al. 2007). Cryptic activities embedded within intact type IV collagen molecules are also unmasked as a consequence of MT1-MMP, MT2-MMP and MT3-MMP action during morphogenesis (Rebustini et al. 2009). In eyes, exposure of cryptic collagen type IV epitopes is associated with increased CNV incidence. In line with this finding, the humanized antibody H8 directed against a cryptic collagen type IV epitope inhibits CNV progression (Gocheva et al. 2006).

14.3.2 Type I Collagen Remodeling

Type I collagen fibrils, the most abundant extracellular matrix (ECM) proteins in perivascular stroma (Di Lullo et al. 2002) is a heterotrimer molecule composed of two α1(I) and one α2(I) chains encoded by two separate genes: *Col1a1* and *Col1a2* (Shoulders and Raines 2009). Type I collagen remodeling in perivascular stroma represents an important step in cell migration and endothelial cell reorganization into tubular structure during normal and pathological angiogenesis. We have previously investigated the role of type I collagen proteolysis in perivascular stroma in transgenic mice carrying a mutation in *colla1* gene (*Col1a1r/r* mice) that renders type I collagen resistant to collagenase-mediated cleavage into the TCA and TCB fragments (Liu et al. 1995). These transgenic mice (*Col1a1r/r*) showed a dramatic reduction in steady state vascular leakage measured by plasma extravasation after quantification of Evans blue dye in interstitial space of skin tissue. Vessel structure analysis showed that these mice have reduced number of vascular openings within vessel wall and failed to develop normal vascular response after chemical stimulation of skin due to the lack of collagen remodelling in the perivascular stroma (Sounni et al. 2010a).

These data suggest that type I collagen remodelling is an important step in vascular response to tissue injuries and damage. Type I collagen is classically cleaved into characteristic TCA and TCB fragments by MMP1, MMP8, MMP13 and MT1-MMP (also called MMP14) (Ohuchi et al. 1997). Perturbations in collagen type I assembly, remodeling and synthesis is associated with increased tissue alterations such as atherosclerosis, fibrosis, and tumor. Type I collagen cleavage by MT1-MMP at endothelial cell surface stimulates migration, guidance and organization of endothelial cells into tubular structures (Collen et al. 2003). In the tumor microenvironment, type I collagen remodeling by MT1-MMP enables cancer cells to escape the mechanical barriers that confine them to collagen matrix and stimulates tumor growth *in vivo* (Hotary et al. 2003). The generation of MT1-MMP knockout mice delineated the role of MT1-MMP in collagen remodeling during development. Indeed, *Mt1-mmp*$^{-/-}$ mice exhibit skeletal defects

with craniofacial abnormalities, osteopenia and angiogenesis (Holmbeck et al. 1999; Zhou et al. 2000). MT1-MMP not only acts as an interstitial collagenase, but is also the main activator of pro-MMP2 at the cell surface (Sato et al. 1994; Sounni et al. 2010b). Although MMP2 exhibits gelatinolytic activity, it does not cleave type I collagen in a similar manner than do the classical interstitial collagenases (Detry et al. 2012). Nevertheless, MMP2 contribution in interstitial collagen remodeling has been evidenced *in vivo*, by intercrossing *Col1a1r/r* mice with $Mmp2^{-/-}$ mice and generation of double transgenic $Col1a1r/r/Mmp2^{-/-}$ mice in FVBn strain. Intriguingly, these $Col1a1r/r/Mmp2^{-/-}$ mice display severe developmental defects resembling the skeletal defect syndromes found in *MMP2*-null patients with inactivating mutations in *Mmp2* gene (Egeblad et al. 2007; Martignetti et al. 2001). While $Mmp2^{-/-}$ mice have only mild aspects of these abnormalities, collagen metabolism perturbation in double transgenic $Col1a1r/r/Mmp2^{-/-}$ mice increases alteration phenotype of $Mmp2^{-/-}$ mice, suggesting that MMP2 is important in type I collagen remodelling through a mechanism different than that used by classical interstitial collagenases (MMP1, MMP8, MMP13 and MT1-MMP).

14.4 MMP-Mediated Proteolysis of Endothelial Cell-Cell Contact Molecules

The functional barrier properties of blood vessels are not only dependent on endothelial cell interactions with underlying basement membrane, but also on the resistance and cohesive features of endothelial cells. Cell-cell cohesion involves the adherent complex vascular endothelial-cadherin (VE-cadherin), the inter-endothelial cell tight junction proteins (TJPs) and junctional adhesion molecules (JAMs). TJPs consist of three major families of transmembrane proteins, zonula occludens-1 (ZO-1), claudins and occludins (Matter and Balda 2003). MMP contribution to endothelial cell-cell contact regulation is well documented in several experimental model of cerebral ischemia (Hawkins et al. 2007; Yang et al. 2007b). For instances, MMP activity has been correlated with the breakdown of tight junctions leading to increased blood-brain barrier (BBB) permeability, ischemia, diabetic retinopathy, vericosis and atherosclerosis (Fujimoto et al. 2008; Hu et al. 2007; Navaratna et al. 2007; Yang et al. 2007a). There is direct evidence that MMP2, MMP9 and MT1-MMP activities induce changes in TJPs (claudin-5 and occludin) leading to BBB disruption of rat brain (Yang et al. 2007b). Moreover, MMP-9 gene deletion reduced ZO-1 degradation associated with attenuation of BBB leakage (Asahi et al. 2001). Accordingly, TIMP-1 gene deletion accelerates ZO-1 degradation through increased MMP-9 activity in cerebral ischemia (Fujimoto et al. 2008). Another report supports also the role of MMP2, MMP3 and MMP9 in TNF alpha-induced alteration of the blood cerebrospinal fluid barrier *in vitro* (Zeni et al. 2007).

The role of MMPs in the maintenance of systemic vessel integrity and remodeling in diabetic retinopathy has been linked to the breakdown of occludin (Giebel et al. 2005) and VE-cadherin (Navaratna et al. 2007). Beside MMPs, a number of recent findings point out to the role of ADAMs (a disintegrin and metalloproteinase with thrombospondin motif) in endothelial adherent junction. For instance, proteolytic activity of ADAM10 induces removal and shedding of VE-cadherin from endothelial cell surface, which in turn regulates vascular permeability and inflammation process associated with atherosclerosis (Schulz et al. 2008). ADAM-10 effect on endothelial cell permeability and T cell transmigration involve VEcadherin ectodomain cleavage generating a soluble fragment, while the remaining carboxyterminal membrane bound portion is further cleaved by γ-secretase. ADAM-10-mediated VEcadherin cleavage is induced by thrombin activation of endothelial cells, Ca^{2+} influx, as well as induction of apoptosis by staurosporine treatment. Inhibition of ADAM-10 by GI254023X decreased endothelial cell permeability and transmigration of T cells.

Tight junction proteins such as JAM-A, JAM-B, and JAM-C regulate leukocyte-endothelial cell interaction through their ability to undergo heterophilic binding with leukocyte integrins LFA-1, VLA-4, and Mac1, respectively (Ebnet et al. 2004; Keiper et al. 2005). In addition, their junctional localization in endothelial cells regulates endothelial barrier permeability through the control of actomyosin-dependent contractility and VE-catherin-mediated cell-cell contact in a Rap1-dependent manner (Orlova et al. 2006). A recent study suggests that MMPs could be involved in the generation of a soluble JMA-C form (sJMA-C) appearing as a potent proangiogenic mediator of pathological angiogenesis (Rabquer et al. 2010). However, the individual MMP or ADAM involved in this process remains to be identified and it is not clear whether this process could affect vascular leakage and permeability in tumors.

In addition to these effects on vascular permeability, MMP contribution to vascular contraction is well documented. For instance, MMPs affect membrane Ca^{2+} and/or K^+ channel activity, likely through an interaction with αvβ3 integrin (Miyazaki et al. 2011). MMP inhibitors block Ca^{2+} entry and vascular contraction (Chew et al. 2004). During varicose vein formation, MMP2 induces venous dilation *via* hyperpolarization and activation of K^+ channels (Raffetto et al. 2007). MMP2 also regulates Ca^{2+} entry into smooth muscle (VSM) which in turn causes hyperpolarization and relaxation of venous segments (Raffetto et al. 2010).

14.5 MMP-Mediated Vessel Maturation Through Pericyte Recruitment

During the process of angiogenesis, vascular mural cells (VSMCs or pericytes) are recruited to the newly formed blood vessels where they contribute to vessel maturation. Pericytes, the mural cells of microvessels, extend long cytoplasmic processes on the abluminal surface of the endothelial cells, making tight contacts

that are important for blood vessel stabilization. They are important in the formation and/or remodeling of perivascular ECM including the vascular basement membrane, and they regulate vessel function (Armulik et al. 2005; Diaz-Flores et al. 2009; von Tell et al. 2006). Pericytes control vessel permeability through their contractile properties and regulate blood flow in vessels, and consequently they could influence delivery of drug to tumors (Feron 2004; Raza et al. 2010). Pericytes are recruited in newly formed vessels through several molecular axis including PDGFB/PDGFR-β, S1P/endothelial differentiation gene-1 (EDG-1), Ang1/Tie2 and TGF-β/activine-like kinase receptor (ALK5) (Gerhardt and Semb 2008; Jain 2003; Park et al. 2009). For instance, double deletion of PDGFB and PDGFR-β in mice lead to lethal microhaemorages due to lack of vessel coverage by pericytes (Lindahl et al. 1997). Increasing evidences demonstrate that MMPs affect vessel coverage through different mechanisms. MMPs induce pericytes migration through ECM degradation, but also regulate their differentiation and recruitment from bone marrow through the release of angiogenic factors sequestered in the ECM (Chantrain et al. 2006; Sounni and Noel 2005). MMP inhibition in different experimental tumor models of melanoma and neuroblastoma reduced pericyte recruitment and decreased tumor vessel perfusion (Chantrain et al. 2004; Noel et al. 2008; Spurbeck et al. 2002). Indeed, MMP3 and MMP7 promote pericyte recruitment and vessel maturation through shedding of membrane bound HB-EGF and signaling *in vivo* (Suzuki et al. 1997). If inflammatory cell-derived MMP9 promotes tumor angiogenesis by releasing ECMbound VEGF (Bergers et al. 2000; Huang et al. 2002), pericyte coverage along tumor microvessels is directly affected in MMP9 deficient mice xenotransplanted with human neuroblastoma. Interestingly, bone marrow transfer from wild type mice to $MMP9^{-/-}$ mice completely restores tumor vessels maturation (Chantrain et al. 2004). These data suggest that MMP9 is an important regulator of pericyte recruitment from bone marrow.

A number of studies demonstrated that TGFβ promotes investment and differentiation of peri-vascular cells leading to vessel stabilization. TGFβ has been implicated as a regulator of vascular integrity (Gleizes and Rifkin 1999; Pepper 1997; Tuxhorn et al. 2002), vasculogenic and angiogenic processes (Dickson et al. 1995; Pepper 1997), endothelial and mural cell proliferation and/or differentiation (Sato 1995; Vinals and Pouyssegur 2001; Yan and Sage 1998). Moreover, vascular abnormalities have been described in TGFβ null mice (Dickson et al. 1995). In VSMCs, TGFβ can bind to ALK5 and activate SMADs 2 and 3 to promote cell differentiation, increase contractility and ECM synthesis (Chan et al. 2010; Kano et al. 2007). Alternatively, TGFβ may also promote vascular stability by increasing the expression of factors such as Ang-1 that stabilizes vasculature by acting on adjacent endothelial cells (Thurston et al. 1999). Moreover TGFβ-induced fibroblast or smooth muscle cell (SMC) contractility could increase tension on ECM leading to increased interstitial fluid pressure to further restrict capillary outflow (Heldin et al. 2004). The control of TGFβ bioavailability is a post-translational pathway subject to regulation by MMP activity. MMP2, -3, -7 induce *in vitro* the release of TGFβ1 from decorin, a proteoglycan that sequester TGFβ in the ECM (Imai et al. 1997). Furthermore, studies on MT1-MMP revealed its

important role in the activation of proTGFβ *in vivo* and control of vascular homeostasis (Sounni et al. 2010a; Tatti et al. 2008).

14.6 MT1-MMP: A Key Regulator of Vessel Function and Physiology

MT1-MMP is likely the most important MMP regulating endothelial cell functions. Among all the MMPs knockout mice generated, *Mt1-mmp* mice only showed impaired angiogenesis leading to delayed ossification and consequently a severe skeletal defect (Sounni and Noel 2005; Zhou et al. 2000). Beside its role in ECM remodeling, MT1-MMP promotes endothelial cell migration, lumen formation and vascular guidance tunnels in collagen matrices (Stratman et al. 2009). It stimulates angiogenesis in fibrin gel more efficiently than other proteases (Collen et al. 2003; Hiraoka et al. 1998; Hotary et al. 2002). MT1-MMP proangiogenic capacities in both physiological and pathological conditions are related to several mechanisms including: (1) ECM remodeling (Hotary et al. 2003), (2) transcriptional and post-translational control of VEGF expression and biodisponibility (Deryugina et al. 2002; Eisenach et al. 2010; Sounni et al. 2002, 2004), (3) interaction with cell surface molecules, such as CD44 (Kajita et al. 2001) and sphingosine 1-phosphate (S1P) (Langlois et al. 2004), (4) hematopoietic progenitor cells mobilization (Vagima et al. 2009), or (5) degradation of anti-angiogenic factors such as decorin in cornea (Mimura et al. 2009). Furthermore, a number of recent reports have shed light of the role of MT1-MMP in TGFβ signaling during angiogenesis and vessel maturation (Hawinkels et al. 2010; Sounni et al. 2011; Tatti et al. 2008).

Spatial and temporal MT1-MMP expression during angiogenesis has been recently followed in the transgenic *Mt1-mmp+/LacZ mice* (Yana et al. 2007). MT1-MMP expression at leading edges of newly developed vessels is a result of coordinated crosstalk between endothelial cells and VSMCs during vascular maturation step of angiogenesis. Works by Lehti and colleagues (Lehti et al. 2005) showed that MT1-MMP is important for PDGFR-β processing and propagating signaling in VSMCs and promoting cell migration. The vascular network of *Mt1-mmp*$^{-/-}$ mice brain have a sever reduction in mural cell density and abnormal vessel morphology, due to impaired PDGFB/PDGFR-β signaling in VSMCs. Moreover, MT1-MMP induces VSMC dedifferentiation and acquisition of migratory and invasive phenotype during vascular injury through low density lipoprotein (LDL) receptor-related protein (LRP) proteolysis that promotes signaling through PDGFB/PDGFR-β axis (Lehti et al. 2009). In addition, MT1-MMP regulates signaling in vascular cells through several mechanisms. MT1-MMP cooperates with platelet-derived S1P to induce endothelial cell migration and morphogenic differentiation (Langlois et al. 2004). It regulates signaling of the advanced glycation end products (AGE)/a receptor for AGE (RAGE) axis in vascular disorders associated with diabetic (Kamioka et al. 2011). Furthermore, a recent

report shows that MT1-MMP activity at endothelial cell surface mediates Tie-2 shedding and regulates angiopoietin1 (Ang1)/Tie-2-associated signaling pathways (Onimaru et al. 2010). It is generally accepted that Ang1-mediated activation of Tie-2 promotes vascular stabilization and quiescence, whereas Ang2 acts in opposition to Ang1 to facilitate VEGF mediated angiogenesis (Gale and Yancopoulos 1999). MT1-MMP interference with Ang1-Tie2 reinforces its role in vessel activation a well known process widely attributed to VEGF (Findley et al. 2007).

Recently, we provided evidence for MT1-MMP activity in perivascular stroma *in vivo* and regulation of vascular stability and permeability (Sounni et al. 2010a). By assessing the effect of MMP deletion on vessel permeability and leakage applied to the skin of *Mmp2*$^{-/-}$, *Mmp9*$^{-/-}$, *Mmp8*$^{-/-}$, *Mmp13*$^{-/-}$ and Mt1-*mmp*$^{-/-}$ mice, we found that except Mt1-*mmp*$^{-/-}$ mice, both induced and steady state leakage were not affected in these mice, whereas and Mt1-*mmp*$^{-/-}$ mice have a higher steady-state vascular leakage. Moreover, treatment of wild-type mice with broad spectrum MMP inhibitor GM6001 (Ilomasta, Galardin) significantly increases vascular leakage *in vivo*. These data indicate that MMP inhibition renders vessels more susceptible to induced acute leakage and implies a link between basal MMP activity and vessel function. A link between MT1-MMP and TGFβ pathway in vascular homeostasis maintenance has been demonstrated by our finding on MT1-MMP-mediated control of TGFβ bioavailability and signaling through the TGF-beta receptor type-1 ALK5 in vascular wall *in vivo* (Sounni et al. 2010a). Interestingly, ALK5 inhibitor increased *in vivo* vascular leakage and enhanced macromolecule delivery and biodistribution in two syngenic model of skin carcinoma (K14-HPV16 transgenic mice) and mammary adenocarcinoma (MMTV-PyMT mice). These data shed light on MT1-MMP contribution to the TGFβ-controlled vascular homeostasis and remodeling. They further indicate that TGFβ and/or MT1-MMP-selective antagonists may enhance vascular leakage and therapeutic delivery to tissues where hemodynamic limits efficient drug delivery. Recently, MT1-MMP-dependent shedding of endoglin from endothelial cell surface has been documented and associated to angiogenesis inhibition *in vitro*. This study correlates a decrease of circulating endoglin with colorectal cancer and suggests that the release of soluble endoglin by MT1-MMP could likely act as decoy for TGFβ, blocks downstream signaling in endothelial cells and inhibits tumor angiogenesis (Hawinkels et al. 2010). However, MT1-MMP levels in these samples were not correlated with the level of soluble endoglin and further studies are required to support the controversial anti-angiogenic effect of MT1-MMP *in vivo*. This effect of MT1-MMP interaction with TGFβ signaling on angiogenesis *in vivo*, appears therefore as a complex regulatory mechanism that depends on its spatial distribution either in perivascular stroma or endothelial cell compartment. A direct shedding of endoglin from endothelial cell surface inhibits angiogenesis (Hawinkels et al. 2010), whereas the cleavage of LTBP-1 (Dallas et al. 2002; Tatti et al. 2008) or LAP-TGFβ from the stroma in fibrotic tissue increases TGFβ availability which in turn activates TGFβ signaling in vascular cells (Sato 1995; Sounni et al. 2010a). An additional level of complexity comes from the regulation

of MT1-MMP/TGFβ signaling axis by type I collagen. Type I collagen induces MT1-MMP expression which in turn regulates TGFβ signaling in stromal and cancer cells (Gilles et al. 1997; Noel et al. 2001; Ottaviano et al. 2006; Shields et al. 2011). Altogether these observations highlight the multifunctional feature of MT1-MMP. MT1-MMP emerged recently as a key angiomodulator enzyme that controls vessel maturation and/or regression both in normal and pathological conditions.

14.7 Concluding Remarks and Therapeutic Potentials

The ECM in vessel wall is no longer seen as a simple scaffold for vascular cells, but is now viewed as a dynamic actor in vascular cell signaling and physiology control. Deregulation of the balance between ECM synthesis and degradation contributes to vascular pathologies and tumor angiogenesis. Recent progresses have highlighted the role of MMPs in vascular biology and underlined the multiple functions of these proteases in the regulation of vessel functions. MMPs are now recognized as key modulators of angiogenesis in different diseases such as cancer (Lafleur et al. 2003; Lopez-Otin and Matrisian 2007), AMD (Noel et al. 2007), psoriasis (Suomela et al. 2001), diabetic retinopathy (Giebel et al. 2005) and pulmonary oedema (Davey et al. 2011). ECM disruption on the arterial wall is likely a main factor in the pathogenesis of vascular system (Raffetto and Khalil 2008), as a decrease in structural matrix proteins has been demonstrated in atherosclerotic lesions, abdominal and intracranial aneurysms, and vascular dilatation (Ruigrok et al. 2006; Wagsater et al. 2011). It is well accepted that increased macrophage and SMC-derived MMP activities have deleterious effects on atherosclerotic plaque stability leading finally to plaque rupture (Johnson 2007). MMP12 overexpressed in ruptured plaque tissues (Jormsjo et al. 2000) appears as a key target that led to the generation of selective MMP inhibitors with the aim to inhibit plaque rupture of advanced atherosclerosis lesion (Fic et al. 2011).

MT-MMPs effects on vessel wall function and integrity is of great interest for the delivery of therapeutics *in vivo*. MT-MMPs are able to modify the tumor physiology and to affect vessel permeability *in vivo*. At this end, understanding the cellular and molecular mechanisms of MTMMPs and their interaction with ECM and non ECM molecules, permeability and interstitial fluid pressure of tumor (Sounni et al. 2011) will open new targeting opportunities to enhance vascular leakage and delivery of therapeutics to tissues where hemodynamics limit efficient drug delivery. However, therapeutic benefits derived from ECM degrading enzyme inhibition may lead to vessel stabilization in cancer and in hyper active tissues. Particularly, this approach may be beneficial if combined with other target pathway inhibitors or cytoxic drugs for cancer treatment. In addition, increased understanding of regulation and function of cryptic fragments within ECM and their role in the control of vascular cell physiology will likely lead to more effective strategies for therapy. The complexity of targeting proteolytic enzymes due to their pro- and antiangiogenic function in cancer or vascular diseases (Lopez-Otin and Matrisian 2007), renders targeting cryptic collagen sites a highly selective approach for

regulating angiogenesis. Further investigations are required to understand how basement membrane molecules regulate vessel permeability and leakage in cancer and vascular diseases processes.

Acknowledgments This work was supported by grants from the Action de Recherche Concertée (ARC) de l'Université de Liège, Belgium, the FP7-HEALTH-2007-A Proposal No. 201279 "MICROENVIMET", the Fonds de la Recherche Scientifique-FNRS (F.R.S.-FNRS, Belgium), the Foundation against Cancer (foundation of public interest, Belgium), the Centre Anticancéreux près l'Université de Liège, the Fonds Léon Fredericq (University of Liège), the Direction Générale Opérationnelle de l'Economie, de l'Emploi et de la Recherche from the S.P.W. (Région Wallonne, Belgium), the Interuniversity Attraction Poles Programme—Belgian Science Policy (Brussels, Belgium).

References

Armulik A, Abramsson A, Betsholtz C (2005) Endothelial/pericyte interactions. Circ Res 97:512–523

Arteaga-Solis E, Gayraud B, Ramirez F (2000) Elastic and collagenous networks in vascular diseases. Cell Struct Funct 25:69–72

Asahi M, Wang X, Mori T, Sumii T, Jung JC, Moskowitz MA, Fini ME, Lo EH (2001) Effects of matrix metalloproteinase-9 gene knock-out on the proteolysis of bloodbrain barrier and white matter components after cerebral ischemia. J Neurosci 21:7724–7732

Bergers G, Benjamin LE (2003) Angiogenesis: tumorigenesis and the angiogenic switch. Nat Rev Cancer 3:401–410

Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, Tanzawa K, Thorpe P, Itohara S, Werb Z, Hanahan D (2000) Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol 2:737–744

Berk BC, Fujiwara K, Lehoux S (2007) ECM remodeling in hypertensive heart disease. J Clin Invest 117:568–575

Bhutto IA, Kim SY, McLeod DS, Merges C, Fukai N, Olsen BR, Lutty GA (2004) Localization of collagen XVIII and the endostatin portion of collagen XVIII in aged human control eyes and eyes with age-related macular degeneration. Invest Ophthalmol Vis Sci 45:1544–1552

Boudreau NJ, Jones PL (1999) Extracellular matrix and integrin signalling: the shape of things to come. Biochem J 339:481–488

Butler GS, Overall CM (2009) Proteomic identification of multitasking proteins in unexpected locations complicates drug targeting. Nat Rev Drug Discov 8:935–948

Chan MC, Hilyard AC, Wu C, Davis BN, Hill NS, Lal A, Lieberman J, Lagna G, Hata A (2010) Molecular basis for antagonism between PDGF and the TGFbeta family of signalling pathways by control of miR-24 expression. EMBO J 29:559–573

Chantrain C, Shimada H, Jodele S, Groshen S, Ye W, Shalinsky D, Werb Z, Coussens LM, DeClerck YA (2004) Stromal matrix metalloproteinase-9 regulates the vascular architecture in neuroblastoma by promoting pericyte recruitment. Cancer Res 64:1675–1686

Chantrain CF, Henriet P, Jodele S, Emonard H, Feron O, Courtoy PJ, DeClerck YA, Marbaix E (2006) Mechanisms of pericyte recruitment in tumour angiogenesis: a new role for metalloproteinases. Eur J Cancer 42:310–318

Chernov AV, Sounni NE, Remacle AG, Strongin AY (2009) Epigenetic control of the invasion-promoting MT1-MMP/MMP-2/TIMP-2 axis in cancer cells. J Biol Chem 284:12727–12734

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

Collen A, Hanemaaijer R, Lupu F, Quax PH, Van Lent N, Grimbergen J, Peters E, Koolwijk P, Van Hinsbergh VW (2003) Membrane-type matrix metalloproteinasemediated angiogenesis in a fibrin-collagen matrix. Blood 101:1810–1817

Cretu A, Roth JM, Caunt M, Akalu A, Policarpio D, Formenti S, Gagne P, Liebes L, Brooks PC (2007) Disruption of endothelial cell interactions with the novel HU177 cryptic collagen epitope inhibits angiogenesis. Clin Cancer Res 13:3068–3078

Dallas SL, Rosser JL, Mundy GR, Bonewald LF (2002) Proteolysis of latent transforming growth factor-beta (TGF-beta)- binding protein-1 by osteoclasts. A cellular mechanism for release of TGF-beta from bone matrix. J Biol Chem 277:21352–21360

Davey A, McAuley DF, O'Kane CM (2011) Matrix metalloproteinases in acute lung injury: mediators of injury and drivers of repair. Eur Respir J 38(4):959–970

Davis GE, Senger DR (2008) Extracellular matrix mediates a molecular balance between vascular morphogenesis and regression. Curr Opin Hematol 15:197–203

Deryugina EI, Soroceanu L, Strongin AY (2002) Up-regulation of vascular endothelial growth factor by membrane-type 1 matrix metalloproteinase stimulates human glioma xenograft growth and angiogenesis. Cancer Res 62:580–588

Detry B, Erpicum C, Paupert J, Blacher S, Maillard C, Bruyere F, Pendeville H, Remacle T, Lambert V, Balsat C, Ormenese S, Lamaye F, Janssens E, Moons L, Cataldo D, Kridelka F, Carmeliet P, Thiry M, Foidart JM, Struman I, Noel A (2012) Matrix metalloproteinase-2 governs lymphatic vessel formation as an interstitial collagenase. Blood 119:5048–5056

Di Lullo G, Sweeney S, Korkko J, Ala-Kokkor L, San Antonio J (2002) Mapping the ligandbinding sites and disease-associated mutations on the most abundant protein in the human-type I collagen. J Biol Chem 277:4223–4231

Diaz-Flores L, Gutierrez R, Madrid JF, Varela H, Valladares F, Acosta E, Martin- Vasallo P, Diaz-Flores L Jr (2009) Pericytes. Morphofunction, interactions and pathology in a quiescent and activated mesenchymal cell niche. Histol Histopathol 24:909–969

Dickson MC, Martin JS, Cousins FM, Kulkarni AB, Karlsson S, Akhurst RJ (1995) Defective haematopoiesis and vasculogenesis in transforming growth factor-beta 1 knock out mice. Development 121:1845–1854

Diez J (2007) Arterial stiffness and extracellular matrix. Adv Cardiol 44:76–95

Ebnet K, Suzuki A, Ohno S, Vestweber D (2004) Junctional adhesion molecules (JAMs): more molecules with dual functions? J Cell Sci 117:19–29

Egeblad M, Werb Z (2002) New functions for the matrix metalloproteinases in cancer progression. Nat Rev Cancer 2:161–174

Egeblad M, Shen HC, Behonick DJ, Wilmes L, Eichten A, Korets LV, Kheradmand F, Werb Z, Coussens LM (2007) Type I collagen is a genetic modifier of matrix metalloproteinase 2 in murine skeletal development. Dev Dyn 236:1683–1693

Eisenach PA, Roghi C, Fogarasi M, Murphy G, English WR (2010) MT1-MMP regulates VEGF-A expression through a complex with VEGFR-2 and Src. J Cell Sci 123:4182–4193

Feron O (2004) Targeting the tumor vascular compartment to improve conventional cancer therapy. Trends Pharmacol Sci 25:536–542

Ferreras M, Felbor U, Lenhard T, Olsen BR, Delaisse J (2000) Generation and degradation of human endostatin proteins by various proteinases. FEBS Lett 486:247–251

Fic P, Zakrocka I, Kurzepa J, Stepulak A (2011) Matrix metalloproteinases and atherosclerosis. Postepy Hig Med Dosw (Online) 65:16–27

Findley CM, Cudmore MJ, Ahmed A, Kontos CD (2007) VEGF induces Tie2 shedding via a phosphoinositide 3-kinase/Akt dependent pathway to modulate Tie2 signaling. Arterioscler Thromb Vasc Biol 27:2619–2626

Fujimoto M, Takagi Y, Aoki T, Hayase M, Marumo T, Gomi M, Nishimura M, Kataoka H, Hashimoto N, Nozaki K (2008) Tissue inhibitor of metalloproteinases protect bloodbrain barrier disruption in focal cerebral ischemia. J Cereb Blood Flow Metab 28:1674–1685

Gale NW, Yancopoulos GD (1999) Growth factors acting via endothelial cell-specific receptor tyrosine kinases: VEGFs, angiopoietins, and ephrins in vascular development. Genes Dev 13:1055–1066

Gerhardt H, Semb H (2008) Pericytes: gatekeepers in tumour cell metastasis? J Mol Med 86:135–144

Giebel SJ, Menicucci G, McGuire PG, Das A (2005) Matrix metalloproteinases in early diabetic retinopathy and their role in alteration of the blood-retinal barrier. Lab Invest 85:597–607

Gilles C, Polette M, Seiki M, Birembaut P, Thompson EW (1997) Implication of collagen type I-induced membrane-type 1-matrix metalloproteinase expression and matrix metalloproteinase-2 activation in the metastatic progression of breast carcinoma. Lab Invest 76:651–660

Gleizes PE, Rifkin DB (1999) Activation of latent TGF-beta. A required mechanism for vascular integrity. Pathol Biol (Paris) 47:322–329

Gocheva V, Zeng W, Ke D, Klimstra D, Reinheckel T, Peters C, Hanahan D, Joyce JA (2006) Distinct roles for cysteine cathepsin genes in multistage tumorigenesis. Genes Dev 20:543–556

Hawinkels LJ, Kuiper P, Wiercinska E, Verspaget HW, Liu Z, Pardali E, Sier CF, ten Dijke P (2010) Matrix metalloproteinase-14 (MT1-MMP)-mediated endoglin shedding inhibits tumor angiogenesis. Cancer Res 70:4141–4150

Hawkins BT, Lundeen TF, Norwood KM, Brooks HL, Egleton RD (2007) Increased blood-brain barrier permeability and altered tight junctions in experimental diabetes in the rat: contribution of hyperglycaemia and matrix metalloproteinases. Diabetologia 50:202–211

Heldin CH, Rubin K, Pietras K, Ostman A (2004) High interstitial fluid pressure – an obstacle in cancer therapy. Nat Rev Cancer 4:806–813

Hiraoka N, Allen E, Apel IJ, Gyetko MR, Weiss SJ (1998) Matrix metalloproteinases regulate neovascularization by acting as pericellular fibrinolysins. Cell 95:365–377

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

Hotary KB, Yana I, Sabeh F, Li XY, Holmbeck K, Birkedal-Hansen H, Allen ED, Hiraoka N, Weiss SJ (2002) Matrix metalloproteinases (MMPs) regulate fibrininvasive activity via MT1-MMP-dependent and -independent processes. J Exp Med 195:295–308

Hotary KB, Allen ED, Brooks PC, Datta NS, Long MW, Weiss SJ (2003) Membrane type I matrix metalloproteinase usurps tumor growth control imposed by the threedimensional extracellular matrix. Cell 114:33–45

Hu J, Van den Steen PE, Sang QX, Opdenakker G (2007) Matrix metalloproteinase inhibitors as therapy for inflammatory and vascular diseases. Nat Rev Drug Discov 6:480–498

Huang S, Van Arsdall M, Tedjarati S, McCarty M, Wu W, Langley R, Fidler IJ (2002) Contributions of stromal metalloproteinase-9 to angiogenesis and growth of human ovarian carcinoma in mice. J Natl Cancer Inst 94:1134–1142

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

Jain RK (2003) Molecular regulation of vessel maturation. Nat Med 9:685–693

Johnson JL (2007) Matrix metalloproteinases: influence on smooth muscle cells and atherosclerotic plaque stability. Expert Rev Cardiovasc Ther 5:265–282

Jormsjo S, Ye S, Moritz J, Walter DH, Dimmeler S, Zeiher AM, Henney A, Hamsten A, Eriksson P (2000) Allele-specific regulation of matrix metalloproteinase-12 gene activity is associated with coronary artery luminal dimensions in diabetic patients with manifest coronary artery disease. Circ Res 86:998–1003

Kajita M, Itoh Y, Chiba T, Mori H, Okada A, Kinoh H, Seiki M (2001) Membrane-type 1 matrix metalloproteinase cleaves CD44 and promotes cell migration. J Cell Biol 153:893–904

Kamioka M, Ishibashi T, Ohkawara H, Eguchi R, Sugimoto K, Uekita H, Matsui T, Yamagishi SI, Ando K, Sakamoto T, Sakamoto N, Takuwa Y, Wada I, Shiomi M, Maruyama Y, Takeishi Y (2011) Involvement of membrane type 1-matrix metalloproteinase (MT1-MMP) in rage activation signaling pathways. J Cell Physiol 226(6):1554–1563

Kano MR, Bae Y, Iwata C, Morishita Y, Yashiro M, Oka M, Fujii T, Komuro A, Kiyono K, Kaminishi M, Hirakawa K, Ouchi Y, Nishiyama N, Kataoka K, Miyazono K (2007) Improvement of cancer-targeting therapy, using nanocarriers for intractable solid tumors by inhibition of TGF-beta signaling. Proc Natl Acad Sci U S A 104:3460–3465

Keiper T, Santoso S, Nawroth PP, Orlova V, Chavakis T (2005) The role of junctional adhesion molecules in cell-cell interactions. Histol Histopathol 20:197–203

Kessenbrock K, Plaks V, Werb Z (2010) Matrix metalloproteinases: regulators of the tumor microenvironment. Cell 141:52–67

Kojima T, Azar DT, Chang JH (2008) Neostatin-7 regulates bFGF-induced corneal lymphangiogenesis. FEBS Lett 582:2515–2520

Lafleur MA, Handsley MM, Edwards DR (2003) Metalloproteinases and their inhibitors in angiogenesis. Expert Rev Mol Med 5:1–39

Langlois S, Gingras D, Beliveau R (2004) Membrane type 1-matrix metalloproteinase (MT1-MMP) cooperates with sphingosine 1-phosphate to induce endothelial cell migration and morphogenic differentiation. Blood 103:3020–3028

Lehti K, Allen E, Birkedal-Hansen H, Holmbeck K, Miyake Y, Chun TH, Weiss SJ (2005) An MT1-MMP-PDGF receptor-beta axis regulates mural cell investment of the microvasculature. Genes Dev 19:979–991

Lehti K, Rose NF, Valavaara S, Weiss SJ, Keski-Oja J (2009) MT1-MMP promotes vascular smooth muscle dedifferentiation through LRP1 processing. J Cell Sci 122:126–135

Lindahl P, Johansson BR, Leveen P, Betsholtz C (1997) Pericyte loss and microaneurysm formation in PDGF-B-deficient mice. Science 277:242–245

Liu X, Wu H, Byrne M, Jeffrey J, Krane S, Jaenisch R (1995) A targeted mutation at the known collagenase cleavage site in mouse type I collagen impairs tissue remodeling. J Cell Biol 130:227–237

Liu MC, Choong DY, Hooi CS, Williams LH, Campbell IG (2007) Genetic and epigenetic analysis of the TIMP-3 gene in ovarian cancer. Cancer Lett 247:91–97

Lopez-Otin C, Matrisian LM (2007) Emerging roles of proteases in tumour suppression. Nat Rev Cancer 7:800–808

Lopez-Otin C, Overall CM (2002) Protease degradomics: a new challenge for proteomics. Nat Rev Mol Cell Biol 3:509–519

Marneros AG, She H, Zambarakji H, Hashizume H, Connolly EJ, Kim I, Gragoudas ES, Miller JW, Olsen BR (2007) Endogenous endostatin inhibits choroidal neovascularization. FASEB J 21:3809–3818

Martignetti JA, Aqeel AA, Sewairi WA, Boumah CE, Kambouris M, Mayouf SA, Sheth KV, Eid WA, Dowling O, Harris J, Glucksman MJ, Bahabri S, Meyer BF, Desnick RJ (2001) Mutation of the matrix metalloproteinase 2 gene (MMP2) causes a multicentric osteolysis and arthritis syndrome. Nat Genet 28:261–265

Matter K, Balda MS (2003) Signalling to and from tight junctions. Nat Rev Mol Cell Biol 4:225–236

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

Miyazaki D, Nakamura A, Fukushima K, Yoshida K, Takeda S, Ikeda S (2011) Matrix metalloproteinase-2 ablation in dystrophin-deficient mdx muscles reduces angiogenesis resulting in impaired growth of regenerated muscle fibers. Hum Mol Genet 20:1787–1799

Morwood SR, Nicholson LB (2006) Modulation of the immune response by extracellular matrix proteins. Arch Immunol Ther Exp (Warsz) 54:367–374

Mott JD, Werb Z (2004) Regulation of matrix biology by matrix metalloproteinases. Curr Opin Cell Biol 16:558–564

Nagase H, Visse R, Murphy G (2006) Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res 69:562–573

Navaratna D, McGuire PG, Menicucci G, Das A (2007) Proteolytic degradation of VEcadherin alters the blood-retinal barrier in diabetes. Diabetes 56:2380–2387

Neptune ER, Frischmeyer PA, Arking DE, Myers L, Bunton TE, Gayraud B, Ramirez F, Sakai LY, Dietz HC (2003) Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. Nat Genet 33:407–411

Noel A, Albert V, Bajou K, Bisson C, Devy L, Frankenne F, Maquoi E, Masson V, Sounni NE, Foidart JM (2001) New functions of stromal proteases and their inhibitors in tumor progression. Surg Oncol Clin N Am 10:417–432, x–xi

Noel A, Jost M, Lambert V, Lecomte J, Rakic JM (2007) Anti-angiogenic therapy of exudative age-related macular degeneration: current progress and emerging concepts. Trends Mol Med 13:345–352

Noel A, Jost M, Maquoi E (2008) Matrix metalloproteinases at cancer tumor-host interface. Semin Cell Dev Biol 19:52–60

Nyberg P, Xie L, Kalluri R (2005) Endogenous inhibitors of angiogenesis. Cancer Res 65:3967–3979

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

Oliver G, Detmar M (2002) The rediscovery of the lymphatic system: old and new insights into the development and biological function of the lymphatic vasculature. Genes Dev 16:773–783

Onimaru M, Yonemitsu Y, Suzuki H, Fujii T, Sueishi K (2010) An autocrine linkage between matrix metalloproteinase-14 and Tie-2 via ectodomain shedding modulates angiopoietin-1-dependent function in endothelial cells. Arterioscler Thromb Vasc Biol 30:818–826

Orlova VV, Economopoulou M, Lupu F, Santoso S, Chavakis T (2006) Junctional adhesion molecule-C regulates vascular endothelial permeability by modulating VEcadherin- mediated cell-cell contacts. J Exp Med 203:2703–2714

Ottaviano AJ, Sun L, Ananthanarayanan V, Munshi HG (2006) Extracellular matrixmediated membrane-type 1 matrix metalloproteinase expression in pancreatic ductal cells is regulated by transforming growth factor-beta1. Cancer Res 66:7032–7040

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

Park JS, Seo J, Kim YO, Lee HS, Jo I (2009) Coordinated regulation of angiopoietin-1 and vascular endothelial growth factor by arsenite in human brain microvascular pericytes: implications of arsenite-induced vascular dysfunction. Toxicology 264:26–31

Pepper MS (1997) Transforming growth factor-beta: vasculogenesis, angiogenesis, and vessel wall integrity. Cytokine Growth Factor Rev 8:21–43

Pulukuri SM, Patibandla S, Patel J, Estes N, Rao JS (2007) Epigenetic inactivation of the tissue inhibitor of metalloproteinase-2 (TIMP-2) gene in human prostate tumors. Oncogene 26:5229–5237

Rabquer BJ, Amin MA, Teegala N, Shaheen MK, Tsou PS, Ruth JH, Lesch CA, Imhof BA, Koch AE (2010) Junctional adhesion molecule-C is a soluble mediator of angiogenesis. J Immunol 185:1777–1785

Radisky DC, Kenny PA, Bissell MJ (2007) Fibrosis and cancer: do myofibroblasts come also from epithelial cells via EMT? J Cell Biochem 101:830–839

Raffetto JD, Khalil RA (2008) Matrix metalloproteinases and their inhibitors in vascular remodeling and vascular disease. Biochem Pharmacol 75:346–359

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

Raffetto JD, Barros YV, Wells AK, Khalil RA (2010) MMP-2 induced vein relaxation via inhibition of [Ca2+]e-dependent mechanisms of venous smooth muscle contraction. Role of RGD peptides. J Surg Res 159:755–764

Raza A, Franklin MJ, Dudek AZ (2010) Pericytes and vessel maturation during tumor angiogenesis and metastasis. Am J Hematol 85:593–598

Rebustini IT, Myers C, Lassiter KS, Surmak A, Szabova L, Holmbeck K, Pedchenko V, Hudson BG, Hoffman MP (2009) MT2-MMP-dependent release of collagen IV NC1 domains regulates submandibular gland branching morphogenesis. Dev Cell 17:482–493

Ruigrok YM, Rinkel GJ, van't Slot R, Wolfs M, Tang S, Wijmenga C (2006) Evidence in favor of the contribution of genes involved in the maintenance of the extracellular matrix of the arterial wall to the development of intracranial aneurysms. Hum Mol Genet 15:3361–3368

Rundhaug JE (2005) Matrix metalloproteinases and angiogenesis. J Cell Mol Med 9:267–285

Sato Y (1995) Activation of latent TGF-beta at the vascular wall–roles of endothelial cells and mural pericytes or smooth muscle cells. J Atheroscler Thromb 2:24–29

Sato H, Takino T, Okada Y, Cao J, Shinagawa A, Yamamoto E, Seiki M (1994) A matrix metalloproteinase expressed on the surface of invasive tumour cells. Nature 370:61–65

Schulz B, Pruessmeyer J, Maretzky T, Ludwig A, Blobel CP, Saftig P, Reiss K (2008) ADAM10 regulates endothelial permeability and T-Cell transmigration by proteolysis of vascular endothelial cadherin. Circ Res 102:1192–1201

Shields MA, Dangi-Garimella S, Krantz SB, Bentrem DJ, Munshi HG (2011) Pancreatic cancer cells respond to Type I collagen by inducing snail expression to promote membrane Type 1 matrix metalloproteinase-dependent collagen invasion. J Biol Chem 286:10495–10504

Shoulders MD, Raines RT (2009) Collagen structure and stability. Annu Rev Biochem 78:929–958

Sohail A, Sun Q, Zhao H, Bernardo MM, Cho JA, Fridman R (2008) MT4-(MMP17) and MT6-MMP (MMP25), a unique set of membrane-anchored matrix metalloproteinases: properties and expression in cancer. Cancer Metastasis Rev 27:289–302

Sounni NE, Noel A (2005) Membrane type-matrix metalloproteinases and tumor progression. Biochimie 87:329–342

Sounni NE, Devy L, Hajitou A, Frankenne F, Munaut C, Gilles C, Deroanne C, Thompson EW, Foidart JM, Noel A (2002) MT1-MMP expression promotes tumor growth and angiogenesis through an up-regulation of vascular endothelial growth factor expression. FASEB J 16:555–564

Sounni NE, Roghi C, Chabottaux V, Janssen M, Munaut C, Maquoi E, Galvez BG, Gilles C, Frankenne F, Murphy G, Foidart JM, Noel A (2004) Up-regulation of vascular endothelial growth factor-A by active membrane-type 1 matrix metalloproteinase through activation of Src-tyrosine kinases. J Biol Chem 279:13564–13574

Sounni NE, Dehne K, van Kempen L, Egeblad M, Affara NI, Cuevas I, Wiesen J, Junankar S, Korets L, Lee J, Shen J, Morrison CJ, Overall CM, Krane SM, Werb Z, Boudreau N, Coussens LM (2010a) Stromal regulation of vessel stability by MMP14 and TGFbeta. Dis Model Mech 3:317–332

Sounni NE, Rozanov DV, Remacle AG, Golubkov VS, Noel A, Strongin AY (2010b) Timp-2 binding with cellular MT1-MMP stimulates invasion-promoting MEK/ERK signaling in cancer cells. Int J Cancer 126:1067–1078

Sounni NE, Paye A, Host L, Noël A (2011) MT-MMPs as regulators of vessel stability associated with angiogenesis. Front Pharmacol 2:111

Spurbeck WW, Ng CY, Strom TS, Vanin EF, Davidoff AM (2002) Enforced expression of tissue inhibitor of matrix metalloproteinase-3 affects functional capillary morphogenesis and inhibits tumor growth in a murine tumor model. Blood 100:3361–3368

Stratman AN, Saunders WB, Sacharidou A, Koh W, Fisher KE, Zawieja DC, Davis MJ, Davis GE (2009) Endothelial cell lumen and vascular guidance tunnel formation requires MT1-MMP-dependent proteolysis in 3-dimensional collagen matrices. Blood 114:237–247

Strongin AY (2010) Proteolytic and non-proteolytic roles of membrane type-1 matrix metalloproteinase in malignancy. Biochim Biophys Acta 1803:133–141

Suomela S, Kariniemi AL, Snellman E, Saarialho-Kere U (2001) Metalloelastase (MMP- 12) and 92-kDa gelatinase (MMP-9) as well as their inhibitors, TIMP-1 and -3, are expressed in psoriatic lesions. Exp Dermatol 10:175–183

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

Tatti O, Vehvilainen P, Lehti K, Keski-Oja J (2008) MT1-MMP releases latent TGF-beta1 from endothelial cell extracellular matrix via proteolytic processing of LTBP-1. Exp Cell Res 314:2501–2514

Thurston G, Suri C, Smith K, McClain J, Sato TN, Yancopoulos GD, McDonald DM (1999) Leakage-resistant blood vessels in mice transgenically overexpressing angiopoietin-1. Science 286:2511–2514

Turley EA (2001) Extracellular matrix remodeling: multiple paradigms in vascular disease. Circ Res 88:2–4

Tuxhorn JA, McAlhany SJ, Yang F, Dang TD, Rowley DR (2002) Inhibition of transforming growth factor-beta activity decreases angiogenesis in a human prostate cancer-reactive stroma xenograft model. Cancer Res 62:6021–6025

Ucuzian AA, Greisler HP (2007) In vitro models of angiogenesis. World J Surg 31:654–663

Vagima Y, Avigdor A, Goichberg P, Shivtiel S, Tesio M, Kalinkovich A, Golan K, Dar A, Kollet O, Petit I, Perl O, Rosenthal E, Resnick I, Hardan I, Gellman YN, Naor D, Nagler A, Lapidot T (2009) MT1-MMP and RECK are involved in human CD34+ progenitor cell retention, egress, and mobilization. J Clin Invest 119:492–503

Vinals F, Pouyssegur J (2001) Transforming growth factor beta1 (TGF-beta1) promotes endothelial cell survival during in vitro angiogenesis via an autocrine mechanism implicating TGF-alpha signaling. Mol Cell Biol 21:7218–7230

von Tell D, Armulik A, Betsholtz C (2006) Pericytes and vascular stability. Exp Cell Res 312:623–629

Wagsater D, Zhu C, Bjorkegren J, Skogsberg J, Eriksson P (2011) MMP-2 and MMP-9 are prominent matrix metalloproteinases during atherosclerosis development in the Ldlr-/-Apob100/100 mouse. Int J Mol Med 28:247–253

Wiig H, Gyenge C, Iversen PO, Gullberg D, Tenstad O (2008) The role of the extracellular matrix in tissue distribution of macromolecules in normal and pathological tissues: potential therapeutic consequences. Microcirculation 15:283–296

Xu J, Rodriguez D, Petitclerc E, Kim JJ, Hangai M, Moon YS, Davis GE, Brooks PC, Yuen SM (2001) Proteolytic exposure of a cryptic site within collagen type IV is required for angiogenesis and tumor growth in vivo. J Cell Biol 154:1069–1079

Yan Q, Sage EH (1998) Transforming growth factor-beta1 induces apoptotic cell death in cultured retinal endothelial cells but not pericytes: association with decreased expression of p21waf1/cip1. J Cell Biochem 70:70–83

Yana I, Sagara H, Takaki S, Takatsu K, Nakamura K, Nakao K, Katsuki M, Taniguchi S, Aoki T, Sato H, Weiss SJ, Seiki M (2007) Crosstalk between neovessels and mural cells directs the site-specific expression of MT1-MMP to endothelial tip cells. J Cell Sci 120:1607–1614

Yang R, Liu H, Williams I, Chaqour B (2007a) Matrix metalloproteinase-2 expression and apoptogenic activity in retinal pericytes: implications in diabetic retinopathy. Ann NY Acad Sci 1103:196–201

Yang Y, Estrada EY, Thompson JF, Liu W, Rosenberg GA (2007b) Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat. J Cereb Blood Flow Metab 27:697–709

Zatterstrom UK, Felbor U, Fukai N, Olsen BR (2000) Collagen XVIII/endostatin structure and functional role in angiogenesis. Cell Struct Funct 25:97–101

Zeni P, Doepker E, Schulze-Topphoff U, Huewel S, Tenenbaum T, Galla HJ (2007) MMPs contribute to TNF-alpha-induced alteration of the blood-cerebrospinal fluid barrier in vitro. Am J Physiol Cell Physiol 293:C855–C864

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

Zucker S, Pei D, Cao J, Lopez-Otin C (2003) Membrane type-matrix metalloproteinases (MT-MMP). Curr Top Dev Biol 54:1–74