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Abstract	MMPs constitute a family of endopeptidases implicated in numerous physiological and pathological tissue remodeling events. During development, MMPs are essential for organogenesis, vascular system development and maturation. Their expression is crucial for tissue repair during injury and plays an important role in vascular response to injuries or assaults. MMPs are mainly expressed by stromal cells including fibroblasts, inflammatory and endothelial cells. Their expression is highly correlated with endothelial tube formation and vessel maturation during development and tissue repair. However, aberrant extracellular and perivascular stroma remodeling mediated by these enzymes alters vessel function in vascular diseases. In this review, we will focus on mechanistic new insights on MMP action in tissue remodeling observed during vascular pathologies. Such alterations ~~are associated with cancer progression and vascular diseases leading~~ to vascular wall destabilization and dysfunctions in diabetic retinopathy, hypertension, aneurism rupture, ~~and~~ arthrosclerosis. As MMPs are major proteolytic pathway regulators in tissue remodeling, we will shed light on molecular and cellular events that are altered by their function in vascular wall.	

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

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2002). For instance, genetic studies show that mutations in *COL3A1* leads to Ehlers-Dahlos syndrome type IV 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

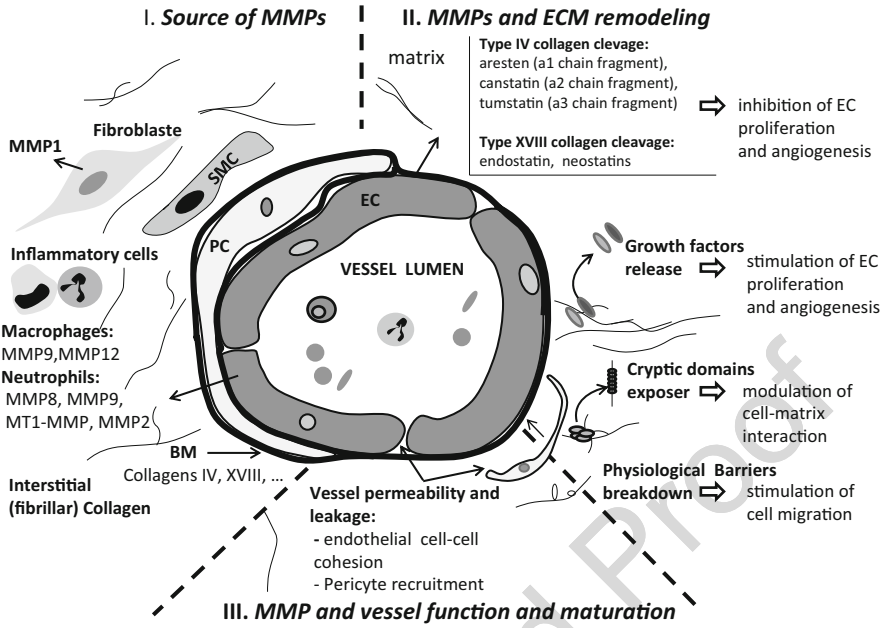

Fig. 14.1 MMP effects on vessel function and maturation. MMPs are produced in perivascular stroma by endothelial (EC), pericyte (PC) inflammatory cells, and fibroblasts (I). They regulate vessel function and maturation through different mechanisms which relay on their proteolytic activity. MMPs increase growth factor availability in perivascular stroma, unmask cryptic sites within extracellular matrix molecules and generate angiogenesis inhibitor form basement membrane (BM) 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 in 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. Nevertheless, MMP2 contribution in interstitial collagen remodeling has been evidence *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 ~~to~~ 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 ~~in~~ 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 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, Ca2+ 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 on vascular contraction is documented. MMPs affect membrane Ca2+ and/or K+ channel activity, likely through an interaction with αvβ3 integrin (Miyazaki et al. 2011). MMP inhibitors block Ca2+ 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 biodiponibility (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 propagating signaling ~~through~~ VSMCs and promoting cell migration. ~~Vasculature~~ 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. ~~It~~ 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

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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*−/− ~~and~~ *Mmp13*−/− and Mt1-*mmp*−/− mice, we found that except Mt1-*mmp*−/− mice, induced ~~or~~ steady state leakage were not affected in these mice and Mt1-*mmp*−/− mice have a higher steady-state vascular leakage. Moreover, ~~prior~~ 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 ALK5 ~~(TGFR-I)~~ 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 ~~in~~ 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*. ~~The~~ study correlates a decrease of circulating endoglin with colorectal cancer and suggests that released soluble endoglin by MT1-MMP could acts as decoy for TGFβ ~~that may~~ 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*. The 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; 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 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 ~~in MMP implication~~ in vascular biology ~~have~~ 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 ~~in~~ 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 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.

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