Matrix Metalloproteinase 2 as a Potential Mediator of Vascular Smooth Muscle Cell Migration and Chronic Vascular Remodeling in Hypertension

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Key Words

Matrix metalloproteinase 2 · Vascular smooth muscle cells · Migration · Hypertension · Vascular remodeling · Extracellular matrix

Abstract

For vascular remodeling in hypertension, it is essential that vascular smooth muscle cells (VSMCs) reshape in order to proliferate and migrate. The extracellular matrix (ECM) needs to be degraded to favor VSMC migration. Many proteases, including matrix metalloproteinases (MMPs), contribute to ECM proteolysis and VSMC migration. Bioactive peptides, hemodynamic forces and reactive oxygen-nitrogen species regulate MMP-2 expression and activity. Increased MMP-2 activity contributes to hypertension-induced maladaptive arterial changes and sustained hypertension. New ECM is synthesized to supply VSMCs with bioactive mediators, which stimulate hypertrophy. MMP-2 stimulates the interaction of VSMCs with newly formed ECM, which triggers intracellular signaling via integrins to induce a phenotypic switch and persistent migration. VSMCs switch from a contractile to a synthetic phenotype in order to migrate and contribute to vascular remodeling in hypertension. MMPs also disrupt growth factors bound to ECM, thus contributing to their ca-

capacity to regulate VSMC migration. This review sheds light on the proteolytic effects of MMP-2 on ECM and non-ECM substrates in the vasculature and how these effects contribute to VSMC migration in hypertension. The inhibition of MMP activity as a therapeutic target may make it possible to reduce arterial maladaptation caused by hypertension and prevent the resulting fatal cardiovascular events.

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Introduction

Hypertension is a multifactorial, worldwide health problem that involves genetic and epigenetic factors, unhealthy diets, lifestyle factors and excess weight [1–3]. Initially, the vascular remodeling caused by increasing blood pressure is beneficial as it allows vessels to adapt to transient hemodynamic changes [4]. However, a significant and persistent increase in blood pressure contributes to chronic maladaptive remodeling and vascular dysfunction, which induces alterations in the extracellular matrix (ECM) and a switch in the phenotype of vascular smooth muscle cells (VSMCs) [4–6]. The ECM plays an important role during vascular remodeling as its proteolysis contributes to detaching VSMCs from the matrix, thus

facilitating migration and proliferation, endothelial cell invasion and inflammatory cells to infiltrate into the arterial wall [4, 7–9].

Chronic and maladaptive remodeling significantly differs according to the location in the vascular tree. Eutrophic remodeling, which occurs in resistance arteries, is characterized by reduced lumen and external diameter with normal media thickness, and an enhanced media-to-lumen ratio. The VSMCs rearrange themselves around the vessel lumen and no cell hypertrophy is observed in either the early or moderate stages of hypertension [10–13]. When hypertension persists and becomes severe, the eutrophic remodeling is usually replaced by hypertrophic remodeling. Hypertrophic remodeling, which mainly occurs in the large conduit arteries such as the aorta, leads to a significant increase in arterial wall thickness, cross-sectional area and media-to-lumen ratio [5, 12]. It is associated with increased arterial collagen deposition and elastin fragmentation, thus contributing significantly to arterial stiffness [12, 13]. Various proteases have been implicated in the pathophysiology of hypertension. Matrix metalloproteinases (MMPs) are key contributors to maladaptive vascular remodeling [5, 9].

Regulation of Transcription and Activity of MMP-2 in Hypertension

MMPs are zinc-dependent proteases that proteolyze ECM in many tissues and contribute to cell migration in normal development or during pathological conditions [8]. They are usually grouped according to substrate specificity as collagenases (MMP-1, MMP-8, MMP-13 and MMP-18), gelatinases (MMP-2 and MMP-9), stromelysins (MMP-3, MMP-10 and MMP-11), matrilysins (MMP-7 and MMP-26), membrane type (MMP-14–17, MMP-24 and MMP-25) and others (MMP-12, MMP-19–21, MMP-23, MMP-27 and MMP-28) [14]. In this review, we will focus on MMP-2, as it is significantly involved in chronic maladaptive cardiovascular remodeling in clinical and animal models of hypertension [15–24]. It is also an intracellular protease that degrades troponin I, myosin light chain and titin in cardiac myocytes and thus contributes to cardiac dysfunction associated with oxidative stress diseases [25–27].

One domain common to all MMPs is the catalytic site, containing zinc which is responsible for the proteolysis of many substrates. MMPs are synthesized in an inactive form (also called zymogen), with an autoinhibitory hydrophobic propeptide that is bound to zinc by a cysteine

thiol to prevent autolysis [28]. Many MMPs contain a hemopexin-like C-terminal domain which makes them capable of recognizing and adhering to the ECM. In addition, this domain helps in initiating MMP activation and proteolytic activity [28, 29]. The only exception is the group of matrilysins, which lacks the hinge and the hemopexin domain. Membrane-type MMPs also contain transmembrane and cytosolic domains and a furin cleavage site at the end of the propeptide, making them active at the cell membrane. MMP-2 and MMP-9 contain three fibronectin type II-like domains at the catalytic site, which confers specificity to interact and degrade type IV and denatured collagen [28].

MMPs are regulated at multiple levels including gene transcription, posttranslational modification and interaction with tissue inhibitors of matrix metalloproteinases (TIMPs). The activation of 72-kDa MMP-2 can occur by the proteolytic removal of its propeptide, which is performed by either membrane-type MMPs or serine proteases. This disrupts the binding between the thiol moiety of a cysteine sulfhydryl residue in the MMP-2 propeptide and zinc at the catalytic site, and results in a 64-kDa enzyme [28, 30]. Nonproteolytic agents such as detergents and oxidants also contribute to MMP-2 activation by disrupting the cysteine thiol and zinc [28]. Although MMP-2 is expressed under physiological conditions and is found in almost all cell types, stimuli such as bioactive peptides, hemodynamic forces, cytokines, reactive oxygen-nitrogen species (RONS) and growth factors may regulate its expression and activity [31]. The 72-kDa MMP-2 may also be activated by S-glutathiolation and peroxynitrite (ONOO⁻). Figure 1 illustrates a link between bioactive mediators and transcription factors with MMP-2 expression in endothelial cells and VSMCs.

Hypertension contributes to MMP-2 activation and vascular remodeling by inducing mechanical stress [32, 33]. Arteries submitted to increased transmural pressure showed increased MMP-2 activity and elastin proteolysis [32]. Mechanical stress increased MMP-2 in VSMCs by activating the platelet-derived growth factor mechanoreceptor (PDGF-R) and protein kinase B/Akt signaling pathways [34] (fig. 1b). In endothelial cells, static stretch increases MMP-2 expression via c-Jun N-terminal kinase (JNK; fig. 1a) [35]. Moreover, inhibition of nuclear factor kappa B (NF-κB), but not extracellular-signal-regulated kinase (ERK), blocked MMP-2 activation in aorta cultured at 150 mm Hg, thus suggesting that NF-κB also participates in mechanical stress and pressure-induced vascular remodeling [4, 36].

Angiotensin II also increases MMP-2 expression and activity to contribute to hypertension. In endothelial cells and VSMCs, an angiotensin II-induced increase in MMP-2 expression was dependent on the angiotensin II type 1 (AT₁) receptor [37]. The two-kidney one-clip (2K-1C) model of hypertension in rats, in which angiotensin II is increased, also showed augmented expression and activity of aortic MMP-2 and its protease activator, MMP-14, which contributed to hypertension-induced hypertrophic remodeling [15, 16, 19]. The arterial levels of TIMP-1, -2, -3 and -4 had no significant changes in the 2K-1C rats [16, 19] or in the presence of angiotensin II in VSMCs [38]. However, angiotensin II increased the activity of NADPH oxidase and RONS levels in the aorta of 2K-1C, which may have contributed to MMP-2 activation. Treating hypertensive rats with tempol, a superoxide scavenger, or apocynin, significantly reduced MMP-2 activity [17]. The downstream signaling that usually follows AT₁ receptor activation is mediated by kinases and transcription factors. In VSMCs, angiotensin II increases MMP-2 expression by transactivating the epidermal growth factor receptor (EGF-R) and by activating the Janus kinase/signal transducers and activators of transcription (JAK2/STAT)-3 pathways (fig. 1b) [37]. In human umbilical vein endothelial cells, angiotensin II increases MMP-2 activation via Src-family tyrosine kinase and phosphatidylinositol-3-kinase (PI3K)-dependent mechanisms as well as via phosphorylation of focal adhesion kinase (FAK) and JNK (fig. 1a) [37, 39]. The JNK pathway also mediates the activation of the transcription factor activator protein-1 (AP-1) [37]. The AP-1 site is present in the promoter region of MMP-2 and contains Fos and Jun elements, which rapidly respond to a variety of signals, such as RONS [40, 41]. NF- κ B is an oxidative-sensitive transcription factor that regulates the expression of MMP-2 and many other genes involved in inflammation and remodeling [42]. NF- κ B inhibition downregulates MMP-2 in the vasculature of different models of hypertension and ameliorates vascular dysfunction and remodeling [42, 43].

Oxidative stress is also an important stimulus that modulates MMP-2. Increased RONS production in the vasculature contributes to MMP-2 activation and hypertension-induced chronic cardiovascular alterations [44, 45]. Grote et al. [46] showed that the knockdown of p47phox in VSMCs submitted to cyclic mechanical stretch led to significantly reduced RONS and a down-regulation of MMP-2 mRNA. Our group also showed that tempol diminishes RONS and MMP-2 activity in the aorta and heart of 2K-1C hypertensive rats and ameliorates hypertension-induced vascular and left ventricular

Fig. 1. Hypertension and bioactive agents increase MMP-2 expression in endothelial cells and VSMCs by triggering transcription factors. Diverse transcription factors that are activated by bioactive peptides, hemodynamic forces, cytokines and RONS to increase MMP-2 expression in endothelial cells (a) and VSMCs (b). In endothelial cells, Ang II increases MMP-2 gene expression through the AT₁ receptor, which activates Src-family tyrosine kinases, PI3K and FAK pathways. Ang II and mechanical stress also phosphorylate JNK and lead to AP-1 activation. Ang II-induced MMP-2 signaling in VSMCs initiates the transactivation of EGF-R and then JAK2/STAT3 activation. Ang II or mechanical stress activates NADPH oxidase and increases ROS production. ROS increase MMP-2 expression by themselves or by triggering transcription factors such as NF- κ B and AP-1. Ang II = Angiotensin II; PKB/Akt = protein kinase B/Akt; Src = Src-family tyrosine kinases.

remodeling [17, 47]. RONS may increase MMP-2 expression by activating NF- κ B and AP-1 in many cardiovascular diseases including hypertension [48, 49] (fig. 1b).

At the posttranslational level, ONOO⁻, a short-lived and harmful pro-oxidant species, activates MMP-2 without the conventional cleavage of the inhibitory propeptide. Micromolar concentrations of ONOO⁻ react with intracellular levels of S-glutathione to produce a stable disulfide S-oxide (GSNO₂) that induces the S-glutathiolation of the cysteine sulfhydryl residue of the MMP-2 propeptide domain [50, 51]. This posttranslational effect uncovers the catalytic domain of MMP-2 and results in its intracellular activation in several cardiovascular diseases associated with enhanced oxidative stress [52].

MMP-2 Induces Chronic Maladaptive Vascular Remodeling in Hypertension

Clinical and animal models of hypertension show that MMP-2 significantly contributes to hypertension-induced arterial remodeling and dysfunction [15–20]. The contribution of MMP-2 activity to vascular remodeling starts during the early and adaptive phase of hypertension [19, 53] and persists until its chronic and maladaptive phase. In fact, MMP knockout mice treated with angiotensin II were more hypertensive than their wild-type counterparts, which may be a result of less collagen proteolysis and therefore reduced arterial compliance [53]. Increased MMP-2 levels in the aortas of 2K-1C rats were observed at 2–10 weeks of hypertension, and this was accompanied by increased deposition of collagen and elastin [19]. Increased MMP-2 levels were also observed in aortas of deoxycorticosterone acetate (DOCA)-salt hypertensive rats, in which MMP-2 is seen in all layers of the aortic wall [54].

Many MMP inhibitors have been extensively used to determine the involvement of MMPs in hypertension-induced cardiovascular alterations. Doxycycline at a subantimicrobial dosage is already useful as a broad MMP inhibitor as it chelates the zinc ion in the catalytic site of MMPs. Important articles from Golub et al. [55] and Lee et al. [56] showed the beneficial actions of doxycycline as an MMP inhibitor in many clinical and experimental conditions such as periodontitis. Administration of doxycycline at 30 mg/kg/day inhibited MMP-2-induced chronic vascular remodeling, reduced collagen and elastin deposition in aortas and ameliorated hypertension in 2K-1C rats [15, 18, 20] (fig. 2). In addition,

doxycycline reduced endothelial dysfunction in 2K-1C rats by restoring acetylcholine-induced relaxation in isolated aortas [15]. Similarly, 30 mg/kg/day of doxycycline reduced MMP-2 activity in both the large and small arteries of N-nitro-L-arginine methyl ester-treated rats. It prevented hypertension-induced hypertrophic remodeling in the aortas, but not eutrophic remodeling in the small arteries [57]. Doxycycline also reduced MMP-9 and MMP-14 levels in the aortas of 2K-1C hypertensive rats [16]. On the other hand, it was found that inhibition of MMPs with GM6001 or reducing RONS levels with tempol prevented the norepinephrine- and angiotensin II-induced inward remodeling of rat cremaster arterioles. Interestingly, RONS inhibition reduced the arteriolar activity of MMP-2, whereas MMP inhibition did not affect RONS production, indicating that RONS are upstream of MMP activation during inward remodeling [58]. Inhibition of MMP and transforming growth factor (TGF)- β signaling also prevented warfarin-induced elastocalcinosis, elastin proteolysis, arterial stiffness and hypertension in rats [59].

Contribution of MMP-2 in VSMC Migration

VSMC migration and proliferation are possible mechanisms induced by MMP-2 to remodel arteries in hypertension [4, 5]. Cultured VSMCs incubated with PDGF showed increased MMP-2 activity, accompanied by an enhanced capacity to migrate and proliferate. Incubating the cells with an MMP-2 antibody inhibited both the mitogenic effect and migration induced by PDGF [60]. Furthermore, cultured VSMCs from MMP-2 knockout mice showed reduced PDGF-induced migration in addition to a reduced amount of intimal hyperplasia in vivo following carotid artery ligation [61]. Similarly, cultured VSMCs from human saphenous veins transfected with small inhibitory MMP-2 RNA lost their capacity to invade a matrigel barrier in vitro [62]. Interleukin-1 β , a pro-inflammatory cytokine, also enhanced MMP-2 synthesis and activity in cultured rat aortas to contribute to VSMC migration. GM6001 significantly inhibited interleukin-1 β -induced VSMC migration, suggesting that MMP-2 may mediate neointima formation following injury [63].

MMP-2 disrupts the ECM and contributes to VSMC migration and rearrangement in the vascular lumen in many cardiovascular diseases. MMP-2 may further process growth factors bound to the ECM, thus contributing to their capacity to regulate VSMC migration [4, 7]. We illustrate some of these MMP-2-related mechanisms that may increase VSMC migration and maladaptive changes in hypertension (fig. 3).

Fig. 2. MMP inhibitor reduces chronic maladaptive vascular remodeling in hypertension. Doxycycline at 30 mg/kg/day reduces gelatinase activity and deposition of collagen and elastin in aortas of 10-week-old 2K-1C rats. **a** Results of in situ zymography photomicrographs of frozen sections of aortas incubated in the pres-

ence of Dq gelatin, a fluorogenic substrate that is cleaved by gelatinases. **b, c** Photomicrographs of aortas stained for collagen and elastin with Sirius red and Orceine, respectively. The techniques are described in [107] and [15]. Doxy = Doxycycline.

MMP-2 Contributes to VSMC Migration by Degrading ECM

Link between Basement Membrane, Collagen and Integrin

MMP-2 significantly degrades type IV collagen and laminin in the basement membrane of VSMCs. It helps to detach VSMCs from the matrix and allows them to migrate to the vessel lumen or rearrange themselves in the medial layer [64]. A study using cultured human saphenous veins removed from patients undergoing coronary artery bypass grafting showed that MMPs mediated type IV collagen proteolysis and contributed to increased VSMC migration. This effect was abolished if TIMP-1 or TIMP-3 was overexpressed using an adenovirus, also maintaining an intact basement membrane [65]. Proteolysis of type IV collagen may also contribute to the up-regulation of type I collagen, elastin, tenascin and the

adhesive receptor integrin in VSMCs [66]. In an in vivo model of intimal hyperplasia after injury, MMP-2 and MMP-9 seemed to be indispensable for rearranging and organizing the resynthesized type I collagen in the VSMC matrix [61]. Collagen is a very stiff protein which maintains the VSMC scaffold, but, in excess, it leads to arterial rigidity. Hypertension significantly contributes to increased MMP activity and collagen deposition in the conduit and resistance arteries, which leads to severe arterial stiffness [67–70].

MMP-2-mediated type IV collagen proteolysis also contributes to the attachment of newly resynthesized ECM with integrins, which then stimulates migratory and hypertrophic signals in VSMCs [66]. In fact, type I collagen cleavage products increase PDGF-mediated VSMC migration through $\alpha v \beta_3$ integrin more than native collagen [71]. Integrins are linked to MAP kinases and FAK, which contribute to VSMC motility and hypertrophy by

Fig. 3. MMPs contribute to hypertension-induced VSMC migration. Increased MMP activity in hypertension degrades collagen, elastin and basement membrane to favor VSMC migration and rearrangement in the aorta. MMP may also disrupt cadherins be-

tween VSMCs and process latent TGF- β to facilitate VSMC migration. MMPs may contribute to the VSMC phenotype switch and contribute to chronic vascular remodeling in hypertension.

mediating changes in the structure of the VSMC cytoskeleton. Overexpression of FAK-related non-kinase (an inhibitor of FAK activity) in cultured rat VSMCs exposed to PDGF inhibit FAK-induced VSMC migration and proliferation [72]. Angiotensin II, in the presence of PDGF, also increases VSMC migration through mechanisms dependent upon FAK, ERK and proline-rich tyrosine kinase 2 [73]. These effects may be related to angiotensin II-induced hypertrophic or eutrophic arterial remodeling in hypertension [53]. As MMP-2 activity is increased in the vasculature during hypertension and significantly degrades type IV collagen in the basement membrane, MMP-2 may indirectly trigger the ECM-integrin pathway to mediate VSMC migration. Interestingly, in rats with a balloon injury of the carotid artery, it was found that a loss of $\alpha_8\beta_1$ integrin also increased the capacity of VSMC to migrate and form neointima because it switched their phenotype from contractile to synthetic [74, 75].

Elastin

Elastic fibers are responsible for conferring flexibility and adequate compliance to arteries. Hypertension significantly contributes to elastin breakdown, which, in turn, conveys its load-bearing role to collagen and contributes to arterial rigidity [7, 59, 76, 77]. Elastic fibers are also essential to provide a physical barrier between one VSMC and another, thus maintaining them in a contractile phenotype without migratory capacity [7]. Increased MMP-2 activity in rat arteries significantly degrades elastin and contributes to hypertension-induced arterial stiffness [59, 76]. This MMP-2-related effect may contribute to VSMC release and lead to hypertension-induced maladaptive remodeling. During remodeling, new elastin and collagen are resynthesized by VSMCs, which aggravates hypertension. Our group showed that treating 2K-1C hypertensive rats with doxycycline inhibited the MMP-2-induced increased aortic deposition of elastin

and collagen and maladaptive remodeling [15] (fig. 2). The resynthesis of elastin is not restricted to proliferative VSMCs, but is also produced by resident VSMCs [77, 78]. However, new elastin is frequently stiffer and less efficient, thus contributing to hypertension-induced vessel rigidity [77]. These effects are generally observed in both the conduit and resistance arteries of spontaneously hypertensive rats, in which the arterial internal elastic lamina contains several small fenestrae that are filled with abundant and rigid elastin trabeculae. The abnormal long-lasting elastin content and distribution in the arterial wall during hypertension may contribute to the resulting increased arterial stiffness [77, 79]. Elastin proteolysis also generates small soluble peptides, elastin-derived peptides, which bind to the elastin-laminin receptor in VSMCs and induce proliferation and migration through FAK activation [7, 77, 80]. The small soluble peptides may, in turn, contribute to even more MMP activation either by triggering MMP-dependent intracellular signals after binding to the elastin receptor or by stimulating leukocyte infiltration to the vascular wall, which may secrete MMPs [77]. MMP-induced elastin proteolysis may also activate latent TGF- β , which stimulates VSMC migration and proliferation [59]. It has also been suggested that emilin-1, an elastin microfibril interface-located protein, is important to stabilize molecular interactions between VSMCs and elastic fibers, which maintain arterial morphology and prevent VSMC migration [81]. Emilin-1 also inhibits TGF- β activation, thus maintaining adequate arterial myogenic response and the integrity of arterial wall [82].

MMP-2 Contributes to VSMC Migration by Degrading Non-ECM Components

Transforming Growth Factor- β

MMP-2 proteolyzes and then activates many non-ECM proteins, thus triggering intracellular pathways involved in VSMC migration and remodeling [52, 64]. TGF- β is a locally synthesized cytokine that, once activated [83, 84], triggers the SMAD pathway, protein kinases and integrin shedding, thereby significantly contributing to cell migration and tissue fibrosis [85]. TGF- β is also involved in VSMC phenotype switch after injury and stimulates vascular rigidity by increasing the synthesis of collagen and fibronectin [85]. MMP-2 activates latent TGF- β and then contributes to hypertension-mediated maladaptive vascular remodeling in rats [83, 86]. MMP-2 induced TGF- β activation in aortas of aged rats

and this effect contributed to SMAD signaling, synthesis of fibronectin and collagen and also arterial fibrosis [83]. TGF- β per se also increased MMP-2 activity in human VSMCs subjected to chronic cyclical mechanical strain [87]. Emilin-1 knockout mice developed hypertension followed by increased vascular resistance and reduced vessel diameter [88], thus showing the role of TGF- β in develop arterial maladaptive remodeling.

Cadherins

The cadherins are a family of proteins fundamental for conferring cell-cell adhesion and tissue integrity. The N- and T-cadherins are mostly found connecting VSMCs to each other, while E- and VE-cadherins are found connecting epithelial to epithelial and endothelial to endothelial cells. Both the cell-cell junctions and the cell-ECM-integrin similarly mediate changes in the VSMC cytoskeleton and contractile apparatus that contribute to migration [89]. Cadherins may also recruit vinculin, F-actin and myosin II to their adhesion site to mediate mechanotransduction [90]. N-cadherin contributes to maintain VSMCs in a quiescent phenotype without migratory capacity. Inhibition of N-cadherin by using a specific antibody decreased Ras homolog gene family member A activity and increased VSMC migration in cultured human aortic VSMCs [91]. Furthermore, loss of N-cadherin contributed to increasing β -catenin signaling and the migratory capacity of VSMCs either in vitro or during neointima formation after injury [91–94]. Both MMPs and calpains may cleave N-cadherin in the ectodomain and membrane domain to contribute to ischemia-induced acute renal failure and brain injury [93, 95, 96]. By cleaving N-cadherin, MMP-2 may disrupt the adherence junctions between VSMCs and then contribute to their migration and proliferation. Treatment of VSMCs from human saphenous veins with MMP inhibitors prevented N-cadherin proteolysis and beta-catenin translocation to the nucleus, which reduced PDGF-induced VSMC proliferation [92]. Treatment of DOCA-salt hypertensive rats with an MMP inhibitor prevented E-cadherin down-regulation and fibrosis progression in the kidney proximal tubule [97]. Furthermore, inhibition of N-cadherin with a synthetic cadherin inhibitory peptide reduced the intravascular pressure-induced myogenic constrictor response in rat cremaster arterioles [98].

MMP-2 may also contribute to the proteolysis of tyrosine kinase receptors, cytokines, fibroblasts and insulin-like growth factors, thus contributing to VSMC migration in normal development [64, 99] or in the progression of inflammatory and cardiovascular diseases [8].

MMP-2 May Contribute to VSMC Migration by Inducing a Phenotype Switch

Contractile VSMCs are mainly located in the arterial tunica media. They are an essential cell phenotype that help to maintain adequate vessel tone and blood pressure. After vascular stretch or injury, VSMCs switch their phenotype from contractile (differentiated) to synthetic (dedifferentiated), which is characterized by myofibril disorganization and the downregulation of many contractile proteins, such as caldesmon and calponin. The synthetic phenotype is essential to allow VSMCs to undergo migration and proliferation, thus contributing to ECM resynthesis and hypertension-induced maladaptive vascular remodeling [100]. DOCA-salt rats show reduced levels of myocardin in VSMCs, which contributes to hypertension-induced increased proliferation and vascular remodeling [101]. Furthermore, hypertension resulting from aortic coarctation in minipigs shows that VSMC proliferation and ECM resynthesis may simultaneously occur with VSMC phenotype switch and a loss of cytoskeletal proteins [102]. It is probable that by degrading ECM, MMP-2 may contribute to the VSMC phenotype switch from contractile to synthetic, thus allowing cells to migrate and synthesize new ECM components [66]. MMP-2 is a key contributor to facilitating VSMC migration as it is more abundant in synthetic than contractile VSMCs [103]. A clinical study showed that injury induced by the surgical preparation of human saphenous veins increased MMP activity and reduced some cytoskeleton proteins, thus contributing to VSMC migration, intimal thickening and vein graft failure [104]. Furthermore, angiotensin II and age have been found to contribute to calpain-1-induced proteolysis of spectrin and vimentin in the cytoskeleton of VSMCs which also stimulates migration and remodeling [105].

Although it has been suggested that hypertension leads to significant arterial maladaptation and stiffness, several mechanisms including the activation of signaling pathways and proteases may be triggered before the onset of hypertension. By using a rat model of arterial elastocalcinosis induced by warfarin and vitamin K, a study showed that increased MMP activity contributed to the development of arterial stiffening and hypertension by degrading elastin and activating TGF- β signaling [59]. Furthermore, a diet-induced model of obesity in mice showed that the arterial stiffness, measured as pulse wave velocity, occurred 1 month after initiation of a diet and also preceded hypertension [106]. In this con-

text, angiotensin II or oxidative stress, by activating arterial MMP-2, may contribute to VSMC migration and arterial hypertrophy, which may also precede and cause hypertension.

Conclusion

The proteolytic effect of MMP-2 on ECM and non-ECM components and its contribution in VSMC reshaping and migration may lead to hypertension-induced maladaptive vascular remodeling. It may be the first step in the development of many other cardiovascular diseases including atherosclerosis, stroke, renal failure and cardiac failure. MMPs are thus considered to be promising as therapeutic targets, and their inhibition may prevent and ameliorate hypertension and its resulting fatal cardiovascular events.

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Disclosure Statement

There were no conflicts of interest.

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