Published in final edited form as:

Hypertension. 2015 April ; 65(4): 698–703. doi:10.1161/HYPERTENSIONAHA.114.03618.

Matrix Metalloproteinases Promote Arterial Remodeling in Aging, Hypertension, and Atherosclerosis

Mingyi Wang*, Soo Hyuk Kim, Robert E. Monticone, and Edward G. Lakatta*

Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, Biomedical Research Center (BRC), 251 Bayview Blvd, Baltimore, MD 21224

Introduction

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases, which are highly activated by inflammatory signaling, including that of angiotensin II (Ang II) (see Figure for reviews)^{1, 2}. Activated MMPs are able to degrade collagen, elastin, and other extracellular molecules², likely resulting in aging, hypertension, and atherosclerotic effects within the arterial wall (for reviews)^{1, 2}. The modified extracellular matrix (ECM) and its context of vasoconstrictors and vasodilators via cleavage by MMPs creates a proinflammatory microenvironment that shifts the phenotypes of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) (for reviews)^{1, 2}. These phenotypic shifts in which cells become secretory, migratory, proliferative and senescent facilitate arterial remodeling such as intimal-medial thickening (IMT), fibrosis, calcification, and aneurysms that are associated with a decrease in endothelial-dependent vasodilation and an increase in stiffness (for reviews)^{1, 2}. Impressively, MMP inhibition effectively retards/alleviates arterial structural remodeling, decreases stiffness, and improves vascular endothelial function in animal models^{3–8}, providing a rationale for the translation of MMP actions to therapeutic approaches in aging humans to curb the epidemic of cardiovascular disease.

1. Role of MMP activation in arterial remodeling

MMP activation facilitates arterial remodeling during aging (Figure & Table).

1.1. Endothelial inflammation

Increased MMP activity facilitates endothelial inflammation such as EC senescence/apoptosis/necrosis, thrombosis, and dysfunction (Figure & Table). MMP-1 enhances EC senescence via p53 activation⁹. MMP-2 cleaves the intercellular and cell matrix junctions including VE-cadherin and β and γ -catenin, which initiates EC apoptosis or necrosis mediated by activated caspase 3, contributing to increased permeability^{10,11}. Activated local MMP-2 also promotes platelet aggregation and thrombus formation, while loss of MMP-2 in

*Corresponding authors: Mingyi Wang, MD, PhD, Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, BRC, 251 Bayview Blvd, Baltimore, MD 21224, Phone: 410-558-8112, mingyi.wang@grc.nia.nih.gov or Edward G. Lakatta MD, Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, BRC, 251 Bayview Blvd, Baltimore, MD 21224, Phone: 410-558-8208, lakatta@grc.nia.nih.gov.

Conflicts of interest

None

platelets reduces arterial injury-associated thrombosis¹², suggesting that MMP-2 is causally associated with formation of thrombi. In addition, exposure of ECs to MMP-2 diminishes nitric oxide production, due to degradation of the heat shock protein 90, an endothelial nitric synthase (eNOS) cofactor, and disturbs vasodilation⁶.

1.2. Intimal-medial thickening

The MMP-associated invasion and proliferation of de-differentiated VSMCs is an essential molecular and cellular event of diffuse IMT (Figure & Table). Intracellular activated MMP-2 markedly cleaves VSMC calponin-1, a differentiation marker, shifting the phenotype of these cells to a de-differentiated state¹³. Extracellular-activated MMPs cleave collagen and basement membranes (BM) to release resident VSMCs from a non-permissive quiescent status to a permissive proliferation state (for review)¹⁴. Activated MMP-1/-2/-9 treatment increases the release of soluble platelet-derived growth factor (PDGF) and milk fat globule-EGF 8 (MFG-E8)¹⁵, potent mitogens to VSMCs (for reviews)^{1, 2}. MMP-2 increases phosphorylation of ERK-1/-2 (p-ERK-1/-2) and CDK-2/-4, promoting the proliferation of VSMCs^{16, 17}. In addition, the noncanonical MMP-1-protease-activated receptor-1-signaling cascade also triggers VSMC de-differentiation and proliferation¹⁸. Notably, MMP-8 also directly promotes VSMC proliferation¹⁹. The exogenous broad spectrum MMP inhibitor, Batimastat, suppresses p-ERK-1/-2¹⁶, and overexpression of the endogenous MMP inhibitor TIMP3 reduces the proliferation of VSMCs²⁰. These findings suggest that activated MMPs function as “growth factors” of VSMCs *in vitro* and MMP-mediated VSMC proliferation *in vivo* contribute to arterial IMT^{18, 19, 21}.

The invasive property of VSMCs induced by MMPs is another essential cellular event of IMT. Ang II signaling cascade molecules, Ang II per se, monocyte chemoattractant protein-1 (MCP-1), MFG-E8, transforming growth factor beta 1 (TGF-β1), and intracellular calcium-dependent, calpain-1 all trigger the activation of MMP-2 in VSMCs (for reviews)^{1, 2, 22}. MMP-2 cleaves the BM and enables VSMC invasion, which is prevented by the MMP inhibitor GM6001 (for reviews)^{1, 2}. VSMCs isolated from both MMP-2 and MMP-9 knockout mice with reduced intimal hyperplasia lose their invasiveness *in vitro*⁵.

1.3. Elastin fiber network destruction

MMP activation plays a causal role in the elastogenesis (production) and elastolysis (degradation) in the arterial wall (Figure & Table). Elastin fibers are effectively digested by activated MMP-2/-9²³. An MMP activation inhibitor PD166739 markedly blunts elastin fiber degradation³. In addition, MMP activation triggers phosphorylation of ERK-1/-2, which retards tropoelastin production in VSMCs *in vitro* and elastogenesis in the rat aorta *in vivo*^{16, 24}. These findings suggest that proliferation in which p-ERK-1/-2 is involved is coupled to the elastogenesis in VSMCs.

1.4. Arterial fibrosis

MMP-associated activation of TGF-β1 facilitates arterial fibrosis (Figure & Table). MMP cleavage of the elastin network releases fibrillin-1 bound latent TGF beta binding protein-1 (LTBP-1) (for reviews)^{1, 2}. Also, MMP-2 cleaves the LTBP-1 stepwise, leading to the activation of TGF-β1, enhancing increased VSMC production of collagen I, II, and III, and

fibronectin (for reviews)^{1, 2}. These data indicate that elastolysis and fibrosis may be two separate faces of the same coin. Activation of calpain-1 leads to MMP-2 activation, TGF- β 1 activation and collagen production in VSMCs²⁵. MMP-2/-9 is also closely associated with collagen accumulation in hypertensive arterial walls²⁶. MMP-8/-13, in contrast, is associated with collagen degradation in arterial wall plaques²⁷.

1.5. Calcification

MMP activation is associated with arterial calcification (Figure & Table). The overexpression of calpain-1 reduces the calcification inhibitors osteonectin and osteopontin and induces alkaline phosphatase activity (ALP) via MMP-2 activation²⁵. Collagenase pre-treatment induces VSMC senescence²⁸. Senescent VSMCs are phenotypically shifted into a secretory procalcification status in which calcification-related genes and proteins, including ALP, runt-related transcription factor 2 (RUNX2), and bone morphogenic protein-1 (BMP-1) become overexpressed (for review)²⁹. MMP-2/-9 deficiency retards the development of aortic calcification^{8, 23}.

1.6. Adventitial expansion

Activation of MMPs is associated with adventitial expansion and alterations to its properties (Figure & Table). MMP-2/-9 and their downstream target molecule, TGF- β 1, activate adventitial (myo) fibroblasts, facilitating collagen production that contributes to adventitial fibroplasia^{30, 31}. An increased infiltration of monocytes/macrophages and mast cells into the adventitia accompanied by activation of MMP-2/-9 promotes the destruction of the arterial wall^{32, 33}.

2. Arterial wall MMP activation during aging, and in hypertension or atherosclerosis

The arterial remodeling mediated via MMP activation is the histopathological signature of arterial aging, hypertension, and atherosclerosis (Figure).

2.1. Arterial aging

Aging is the result of interactive genetic and epigenetic events within different cell types and tissues throughout a lifetime, and is characterized by a chronic low-grade arterial wall inflammation (proinflammation), stiffness, and a blood pressure (BP) increase (for reviews)^{1, 2}. Proinflammation is not instigated by “professional” immunological cells such as leukocytes, but rather by phenotypically shifted arterial wall cells, including ECs, VSMCs, and fibroblasts (for reviews) (Figure)^{1, 2}. Proinflammation-associated arterial stiffening and BP increase are mainly determined by VSMC phenotypic shift or ECM modifications, or their combination³⁴. Intrinsic stiffening of VSMCs increases with age, which is likely linked to activity of serum response factor (SRF)^{34, 35}. SRF gene inactivation reduces vasoconstriction and increases intrinsic elasticity in the carotid artery in the absence of a significant change in ECM³⁴. Alteration of arterial stiffness in SRF-invalidated mice results from the downregulation of contractile protein genes, cytoskeletal organization, and in cell-matrix interactions³⁴.

Aging enhances MMP-2/-7/-9/-14 activity in the aortic walls of rodents, nonhuman primates and humans (for reviews)^{1, 2}. Increased MMP activity is associated with increases in Ang II signaling, proinflammation, fibrosis, and elastin fragmentation (for reviews)^{1, 2}. Ang II infusion to young rats increases MMP-2 activation, IMT, and fibrosis in the arterial wall, similar to that of untreated old control rats (for review)^{1, 2}. Importantly, an MMP inhibitor, PD166739, markedly blunts the age-associated increases in aortic MMP-2 and interstitial collagenase activity, and reduces the elastin fiber degeneration, collagen deposition, and BP increase³. Thus, Ang II /MMP-2 signaling is a driver of arterial wall matrix remodeling with aging, stiffening, and BP increase.

2.2. Hypertension

Aging increases the prevalence of hypertension (for reviews) (Figure)^{1, 2}. Hypertension is not only a disease characterized by increased BP but also characterized by proinflammation in the arterial wall. An increase in MMP proteolytic processes is one of the underlying mechanisms in hypertension^{4, 26, 36–40}. *In situ* zymography demonstrates gradients in localization of activated MMP-2/-9, in particular in the diffusely thickened intima of hypertensive rats^{4, 26, 39}.

Arterial MMP activation induction by Ang II plays a central role in the pathogenesis of hypertension. Exposure of carotid arterial rings to Ang II significantly increases MMP-2 activation, which is abolished by an AT1 antagonist Losartan³⁹. MMP-2 activation is a constituent of Ang II-mediated BP elevation, which is dependent upon the transcriptional control of MMP-7³⁷. Knockdown of the MMP-7 gene attenuates both MMP-2 activation and BP elevation³⁷, and as expected, MMP-2 inhibition by gene knockdown or pharmacological inhibition prevents a rise in BP in Ang II-induced hypertensive mice³⁷.

Beyond Ang II stimulus, a mechanical and dietary sodium overload also increases the activation of arterial and circulating MMP-2/-9 gene and protein and its attendant hypertension^{41, 42}. Ex vivo data show that an increase in stress and disturbed blood flow in the arterial walls results in marked increases of MMP-2/-9 activity⁴³. The BP-associated increases in arterial MMP-1/-2/-3/-9/-12 likely results from activation of the proinflammatory transcriptional factors NF- κ B and Ets-1^{3, 44}. In addition, in renal hypertension, the activation of MMP-2/-9 is dependent upon increased BP, which contributes to increases in reactive oxygen species (ROS) and decreases in NO bioavailability as well as to eventual endothelial dysfunction⁴.

Importantly, the micro-processing of extracellular bioactive molecules via MMP activation reinforces the progression of hypertension (Table). Activated MMP-2 contributes to an increase in BP by both increasing the bioavailability of vasoconstrictors such as big ET-1 and decreasing vasodilators such as adventitial calcitonin gene-related peptide (CGRP) and eNOS^{4, 6, 45, 46}. MMP-1/-2/-7/-9 reduces the density of beta (2) adrenergic receptor ($\beta(2)$ -AR) in arterioles and enhances the arteriolar tone, which also contributes to an increase in BP^{36, 38}.

2.3. Atherosclerosis

Age-associated arterial wall remodeling provides fertile soil for the acceleration of atherogenesis (for reviews) (Figure)^{1, 2}. The MMPs, including MMP-2/-7/-8/-9/-13, are involved in the various stages of atherosclerosis, which are potentially associated with an increase in miR-21 and a decrease in miR-24, unique signatures of plaque instability^{27, 47–50}. miR-21 is an immunomiR, which is markedly increased in atherosclerosis and regulates the associated immunoresponses^{51, 52}. Downregulation of miR-24 promotes an invasive macrophage subset⁵⁰.

Strong evidence indicates that the MMP activation catalyzes atherosclerosis progression from a benign phenotype to fibroatheroma, characterized by a large and soft lipid-rich necrotic core and neovessel covered by a thin and inflamed fibrous cap (see review)⁵³. Increased uptake of glucose measured by positron emission tomography (PET) predicts MMP-9 activation, which is associated with high-risk lipid-rich, hemorrhage, or inflamed plaques⁵⁴. Activated MMP-2/-7/-8/-9 promotes the angiogenesis, growth, and vulnerability of atherosclerotic plaques^{47, 55, 56}. Importantly, the AT1 blocker Losartan inhibits MMP-2/-9 activation, neovascularization, and the vulnerability of atherosclerotic plaques⁵⁵.

2.4. Arterial aneurysm/dissection

Age-associated hypertensive or atherosclerotic remodeling sets the stage for inflammatory catastrophes: aortic dissection and rupture (Figure). In humans, activation of MMP-9 is higher in dissected arterial than in control tissue⁵⁷; and is closely associated with the progression of aneurysm^{57, 58}. In mice, optical imaging of MMP activity accurately predicts the growth rate of abdominal aortic aneurysm (AAA)⁵⁹. These findings suggest that inflammatory MMP signaling pathways play a central role in the pathogenesis of aortic aneurysm/dissection.

The Ang II antagonist Ang 1–7, AT1 antagonist Losartan, and TGF receptor mutant potentially prevent the formation and progression of aneurysm in various mouse models and alleviate activation of MMP (protein and gene)^{31, 60–67}. MMPs, downstream molecules of both Ang II and TGF- β (for reviews)^{1, 2}, play causal roles in the development of the aortic aneurysm^{59, 68, 69}. MMP-2/-9 activation is able to erode the arterial wall, a histological foundation of the aortic aneurysm development^{59, 68}. Further, MMP-2/-9 activation signaling also promotes a loss of VSMCs and facilitates aortic dilation⁷⁰. Impressively, MMP-2 regulates a TGF- β 1/ERK-1/-2 noncanonical pathway in VSMCs and facilitates vascular wall dilatation in a fibrillin-1 mutation Marfan syndrome animal model⁶⁹.

Emerging evidence indicates that the miRs are strong modulators of the Ang II, TGF- β 1, MMP- mediated cascade and promote aneurysm formation. Notably, an age-associated increase in miR-29b upregulates the activity of MMP-2/-9 gene and protein, activates TGF- β 1, and promotes aortic dilation in both elastase infusion and Ang II infusion aneurysmal models^{6, 64}. Additionally, miR-21 is implicated as a modulator of proliferation and apoptosis of VSMCs and MMP-2 gene expression during development of AAA in ApoE $^{-/-}$ mice induced by Ang II⁶⁷. A reduction of miR-195 in AAA is associated with the

upregulation of MMP-2/-9 gene and protein, promoting the AAA development in an ApoE^{-/-} – infused Ang II model⁶⁶.

Analysis of proteins extracted from aortic media detected an amyloid protein called medin, a 5.5 kDa fragment of milk fat globule protein E8, a downstream molecule of Ang II, which becomes deposited in the aortic medium in almost 100% of the Caucasian population over 50 years of age (for reviews) ^{1, 2, 22}. Importantly, the medin precursor of MFG-E8 is also involved with the progression of both atherosclerosis and hypertension such as arterial stiffening (for reviews) ^{2, 22}. The medin fragment derives from the C2-like domain of MFG-E8 and is co-localized with elastin fibers of arteries and is associated with the development of aortic aneurysm/dissection (for reviews) ^{1, 2, 22}. In an *in vitro* model, aggregated medin induces death of VSMCs and increased the production of metalloproteinase-2, likely promoting the destruction of the arterial wall in vivo (for reviews) ^{1, 2, 22}. In addition, an increase in BP through upregulation of NF-κB and Ets-1 and activation of MMP-2/-3/-9/-12 accelerates AAA in rats induced by an elastase perfusion^{3, 44}.

Cellular specific inflammatory changes also promote the formation of aortic aneurysm/dissection. EC-specific Nox-2 associated ROS production increases MMP activation and susceptibility to aortic dissection⁷¹. Adventitial mast cells directly augment MMP-9 activity produced by monocytes/macrophages, contributing to the progression of AAA in the ApoE^{-/-} mice³². Pharmacological inhibition with Tranilast, an inhibitor of mast cell degranulation, attenuates AAA development in these rodents³².

Importantly, ERK-1/-2 deficiency reduces MMP-2/-9 activation and prevents AAA induced by elastase infusion⁷². Cathepsin S deficiency decreases MMP-2 activation and retards the pathogenesis of aneurysm⁷³. Chronic treatment with a broad-spectrum MMP inhibitor, doxycycline, prevents the development of spontaneous aortic aneurysm lesions⁶⁸.

Concluding remarks and perspective views

A chronic increase in MMP activation is central to age-associated arterial structural remodeling (Figure). Furthermore, the quintessential vascular diseases such as hypertension and atherosclerosis could be viewed as accelerated arterial aging and are also linked to increased MMP activation (Figure). The pathophysiological vascular, cellular and molecular events of aging, hypertension, atherosclerosis, and their complications are recapitulated in experimental animals with over-activation of MMPs (Table). In contrast, MMP inhibition attenuates age-associated pathophysiologic arterial remodeling in animal models of hypertension and atherosclerosis ^{4–8, 68}. Thus, appreciation of the MMP involvement in arterial wall aging and age-associated arterial diseases and the ability to detect its involvement in arterial wall inflammation, vulnerable plaques and the progression of aneurysm/dissection will impact on future translational research to delay arterial remodeling that accompanies aging and its participation in these age-associated arterial diseases.

Acknowledgments

Funding sources

This research was supported by the Intramural Research Program of the National Institute on Aging, National Institutes of Health.

References

1. Wang M, Jiang L, Monticone RE, Lakatta EG. Proinflammation: The key to arterial aging. *Trends in endocrinology and metabolism*. 2014; 25:72–79. [PubMed: 24365513]
2. Lakatta EG. The reality of aging viewed from the arterial wall. *Artery Res*. 2013; 7:73–80. [PubMed: 23667404]
3. Wang M, Zhang J, Telljohann R, Jiang L, Wu J, Monticone RE, Kapoor K, Talan M, Lakatta EG. Chronic matrix metalloproteinase inhibition retards age-associated arterial proinflammation and increase in blood pressure. *Hypertension*. 2012; 60:459–466. [PubMed: 22689745]
4. Castro MM, Rizzi E, Ceron CS, Guimaraes DA, Rodrigues GJ, Bendhack LM, Gerlach RF, Tanus-Santos JE. Doxycycline ameliorates 2k-1c hypertension-induced vascular dysfunction in rats by attenuating oxidative stress and improving nitric oxide bioavailability. *Nitric oxide : biology and chemistry / official journal of the Nitric Oxide Society*. 2012; 26:162–168. [PubMed: 22327038]
5. Kuzuya M, Kanda S, Sasaki T, Tamaya-Mori N, Cheng XW, Itoh T, Itoharu S, Iguchi A. Deficiency of gelatinase a suppresses smooth muscle cell invasion and development of experimental intimal hyperplasia. *Circulation*. 2003; 108:1375–1381. [PubMed: 12939223]
6. Nagareddy PR, Rajput PS, Vasudevan H, McClure B, Kumar U, Macleod KM, McNeill JH. Inhibition of matrix metalloproteinase-2 improves endothelial function and prevents hypertension in insulin-resistant rats. *British journal of pharmacology*. 2012; 165:705–715. [PubMed: 21740410]
7. Pires PW, Rogers CT, McClain JL, Garver HS, Fink GD, Dorrance AM. Doxycycline, a matrix metalloprotease inhibitor, reduces vascular remodeling and damage after cerebral ischemia in stroke-prone spontaneously hypertensive rats. *American journal of physiology. Heart and circulatory physiology*. 2011; 301:H87–97. [PubMed: 21551278]
8. Sasaki T, Nakamura K, Sasada K, Okada S, Cheng XW, Suzuki T, Murohara T, Sato K, Kuzuya M. Matrix metalloproteinase-2 deficiency impairs aortic atherosclerotic calcification in apoe-deficient mice. *Atherosclerosis*. 2013; 227:43–50. [PubMed: 23312504]
9. Struwing IT, Durham SN, Barnett CD, Mao CD. Enhanced endothelial cell senescence by lithium-induced matrix metalloproteinase-1 expression. *The Journal of biological chemistry*. 2009; 284:17595–17606. [PubMed: 19407340]
10. Wu WB, Huang TF. Activation of mmp-2, cleavage of matrix proteins, and adherens junctions during a snake venom metalloproteinase-induced endothelial cell apoptosis. *Experimental cell research*. 2003; 288:143–157. [PubMed: 12878166]
11. Shapiro S, Khodalev O, Bitterman H, Auslender R, Lahat N. Different activation forms of mmp-2 oppositely affect the fate of endothelial cells. *American journal of physiology. Cell physiology*. 2010; 298:C942–951. [PubMed: 20071690]
12. Momi S, Falcinelli E, Giannini S, Ruggeri L, Cecchetti L, Corazzi T, Libert C, Gesele P. Loss of matrix metalloproteinase 2 in platelets reduces arterial thrombosis in vivo. *The Journal of experimental medicine*. 2009; 206:2365–2379. [PubMed: 19808257]
13. Castro MM, Cena J, Cho WJ, Walsh MP, Schulz R. Matrix metalloproteinase-2 proteolysis of calponin-1 contributes to vascular hypocontractility in endotoxemic rats. *Arteriosclerosis, thrombosis, and vascular biology*. 2012; 32:662–668.
14. Johnson JL. Matrix metalloproteinases: Influence on smooth muscle cells and atherosclerotic plaque stability. *Expert review of cardiovascular therapy*. 2007; 5:265–282. [PubMed: 17338671]
15. Stegemann C, Didangelos A, Barallobre-Barreiro J, Langley SR, Mandal K, Jahangiri M, Mayr M. Proteomic identification of matrix metalloproteinase substrates in the human vasculature. *Circulation. Cardiovascular genetics*. 2013; 6:106–117. [PubMed: 23255316]
16. Lovdahl C, Thyberg J, Hultgardh-Nilsson A. The synthetic metalloproteinase inhibitor batimastat suppresses injury-induced phosphorylation of map kinase erk1/erk2 and phenotypic modification of arterial smooth muscle cells in vitro. *Journal of vascular research*. 2000; 37:345–354. [PubMed: 11025397]

17. Lee SJ, Kim WJ, Moon SK. Tnf-alpha regulates vascular smooth muscle cell responses in genetic hypertension. *International immunopharmacology*. 2009; 9:837–843. [PubMed: 19306950]
18. Austin KM, Nguyen N, Javid G, Covic L, Kuliopulos A. Noncanonical matrix metalloprotease-1-protease-activated receptor-1 signaling triggers vascular smooth muscle cell dedifferentiation and arterial stenosis. *The Journal of biological chemistry*. 2013; 288:23105–23115. [PubMed: 23814055]
19. Xiao Q, Zhang F, Grassia G, Hu Y, Zhang Z, Xing Q, Yin X, Maddaluno M, Drung B, Schmidt B, Maffia P, Ialenti A, Mayr M, Xu Q, Ye S. Matrix metalloproteinase-8 promotes vascular smooth muscle cell proliferation and neointima formation. *Arteriosclerosis, thrombosis, and vascular biology*. 2014; 34:90–98.
20. Baker AH, Zaltsman AB, George SJ, Newby AC. Divergent effects of tissue inhibitor of metalloproteinase-1, -2, or -3 overexpression on rat vascular smooth muscle cell invasion, proliferation, and death in vitro. Timp-3 promotes apoptosis. *The Journal of clinical investigation*. 1998; 101:1478–1487. [PubMed: 9502791]
21. Moe KT, Naylynn TM, Yin NO, Khairunnisa K, Allen JC, Wong MC, Chin-Dusting J, Wong P. Tumor necrosis factor-alpha induces aortic intima-media thickening via perivascular adipose tissue inflammation. *Journal of vascular research*. 2013; 50:228–237. [PubMed: 23711955]
22. Wang M, Wang HH, Lakatta EG. Milk fat globule epidermal growth factor viii signaling in arterial wall remodeling. *Current vascular pharmacology*. 2013; 11:768–776. [PubMed: 22272902]
23. Basalyga DM, Simionescu DT, Xiong W, Baxter BT, Starcher BC, Vyavahare NR. Elastin degradation and calcification in an abdominal aorta injury model: Role of matrix metalloproteinases. *Circulation*. 2004; 110:3480–3487. [PubMed: 15545515]
24. Lannoy M, Slove S, Louedec L, Choqueux C, Journe C, Michel JB, Jacob MP. Inhibition of erk1/2 phosphorylation: A new strategy to stimulate elastogenesis in the aorta. *Hypertension*. 2014; 64:423–430. [PubMed: 24866134]
25. Jiang L, Zhang J, Monticone RE, Telljohann R, Wu J, Wang M, Lakatta EG. Calpain-1 regulation of matrix metalloproteinase 2 activity in vascular smooth muscle cells facilitates age-associated aortic wall calcification and fibrosis. *Hypertension*. 2012; 60:1192–1199. [PubMed: 23006733]
26. Ceron CS, Rizzi E, Guimaraes DA, Martins-Oliveira A, Cau SB, Ramos J, Gerlach RF, Tanus-Santos JE. Time course involvement of matrix metalloproteinases in the vascular alterations of renovascular hypertension. *Matrix biology : journal of the International Society for Matrix Biology*. 2012; 31:261–270. [PubMed: 22342460]
27. Quillard T, Araujo HA, Franck G, Tesmenitsky Y, Libby P. Matrix metalloproteinase-13 predominates over matrix metalloproteinase-8 as the functional interstitial collagenase in mouse atheromata. *Arteriosclerosis, thrombosis, and vascular biology*. 2014; 34:1179–1186.
28. Riches K, Angelini TG, Mudhar GS, Kaye J, Clark E, Bailey MA, Sohrabi S, Korossis S, Walker PG, Scott DJ, Porter KE. Exploring smooth muscle phenotype and function in a bioreactor model of abdominal aortic aneurysm. *Journal of translational medicine*. 2013; 11:208. [PubMed: 24028184]
29. Burton DG, Matsubara H, Ikeda K. Pathophysiology of vascular calcification: Pivotal role of cellular senescence in vascular smooth muscle cells. *Experimental gerontology*. 2010; 45:819–824. [PubMed: 20647039]
30. Fleenor BS, Marshall KD, Durrant JR, Lesniewski LA, Seals DR. Arterial stiffening with ageing is associated with transforming growth factor-beta1-related changes in adventitial collagen: Reversal by aerobic exercise. *The Journal of physiology*. 2010; 588:3971–3982. [PubMed: 20807791]
31. Wang Z, Ren Z, Hu Z, Hu X, Zhang H, Wu H, Zhang M. Angiotensin-ii induces phosphorylation of erk1/2 and promotes aortic adventitial fibroblasts differentiating into myofibroblasts during aortic dissection formation. *Journal of molecular histology*. 2014; 45:401–412. [PubMed: 24343777]
32. Tsuruda T, Kato J, Hatakeyama K, Kojima K, Yano M, Yano Y, Nakamura K, Nakamura-Uchiyama F, Matsushima Y, Imamura T, Onitsuka T, Asada Y, Nawa Y, Eto T, Kitamura K. Adventitial mast cells contribute to pathogenesis in the progression of abdominal aortic aneurysm. *Circulation research*. 2008; 102:1368–1377. [PubMed: 18451339]

33. Zhou J, Tang PC, Qin L, Gayed PM, Li W, Skokos EA, Kyriakides TR, Pober JS, Tellides G. Cxcr3-dependent accumulation and activation of perivascular macrophages is necessary for homeostatic arterial remodeling to hemodynamic stresses. *The Journal of experimental medicine*. 2010; 207:1951–1966. [PubMed: 20733031]
34. Galmiche G, Labat C, Mericskay M, Aissa KA, Blanc J, Retailleau K, Bourhim M, Coletti D, Loufrani L, Gao-Li J, Feil R, Challande P, Henrion D, Decaux JF, Regnault V, Lacolley P, Li Z. Inactivation of serum response factor contributes to decrease vascular muscular tone and arterial stiffness in mice. *Circulation research*. 2013; 112:1035–1045. [PubMed: 23426017]
35. Qiu H, Zhu Y, Sun Z, Trzeciakowski JP, Gansner M, Depre C, Resuello RR, Natividad FF, Hunter WC, Genin GM, Elson EL, Vatner DE, Meininger GA, Vatner SF. Short communication: Vascular smooth muscle cell stiffness as a mechanism for increased aortic stiffness with aging. *Circulation research*. 2010; 107:615–619. [PubMed: 20634486]
36. Kalogeris TJ, Korthuis RJ. Vascular receptors as new substrates for matrix metalloproteinases in hypertension and other inflammatory states. *American journal of physiology. Heart and circulatory physiology*. 2010; 299:H13–15. [PubMed: 20400684]
37. Odenbach J, Wang X, Cooper S, Chow FL, Oka T, Lopaschuk G, Kassiri Z, Fernandez-Patron C. Mmp-2 mediates angiotensin ii-induced hypertension under the transcriptional control of mmp-7 and tace. *Hypertension*. 2011; 57:123–130. [PubMed: 21079048]
38. Rodrigues SF, Tran ED, Fortes ZB, Schmid-Schonbein GW. Matrix metalloproteinases cleave the beta2-adrenergic receptor in spontaneously hypertensive rats. *American journal of physiology. Heart and circulatory physiology*. 2010; 299:H25–35. [PubMed: 20382857]
39. Wang M, Zhang J, Spinetti G, Jiang LQ, Monticone R, Zhao D, Cheng L, Krawczyk M, Talan M, Pintus G, Lakatta EG. Angiotensin ii activates matrix metalloproteinase type ii and mimics age-associated carotid arterial remodeling in young rats. *The American journal of pathology*. 2005; 167:1429–1442. [PubMed: 16251426]
40. Wu KI, Schmid-Schonbein GW. Nuclear factor kappa b and matrix metalloproteinase induced receptor cleavage in the spontaneously hypertensive rat. *Hypertension*. 2011; 57:261–268. [PubMed: 21220710]
41. Ferreira-Sae MC, Cipolli JA, Cornelio ME, Matos-Souza JR, Fernandes MN, Schreiber R, Costa FO, Franchini KG, Rodrigues RC, Gallani MC, Nadruz W Jr. Sodium intake is associated with carotid a000rtery structure alterations and plasma matrix metalloproteinase-9 upregulation in hypertensive adults. *The Journal of nutrition*. 2011; 141:877–882. [PubMed: 21430243]
42. Ruddy JM, Jones JA, Stroud RE, Mukherjee R, Spinale FG, Ikonomidis JS. Differential effects of mechanical and biological stimuli on matrix metalloproteinase promoter activation in the thoracic aorta. *Circulation*. 2009; 120:S262–268. [PubMed: 19752377]
43. Monson KL, Matsumoto MM, Young WL, Manley GT, Hashimoto T. Abrupt increase in rat carotid blood flow induces rapid alteration of artery mechanical properties. *Journal of the mechanical behavior of biomedical materials*. 2011; 4:9–15. [PubMed: 21094476]
44. Shiraya S, Miwa K, Aoki M, Miyake T, Oishi M, Kataoka K, Ohgi S, Ogihara T, Kaneda Y, Morishita R. Hypertension accelerated experimental abdominal aortic aneurysm through upregulation of nuclear factor kappab and ets. *Hypertension*. 2006; 48:628–636. [PubMed: 16940214]
45. Abdalvand A, Morton JS, Bourque SL, Quon AL, Davidge ST. Matrix metalloproteinase enhances big-endothelin-1 constriction in mesenteric vessels of pregnant rats with reduced uterine blood flow. *Hypertension*. 2013; 61:488–493. [PubMed: 23297376]
46. Fernandez-Patron C, Stewart KG, Zhang Y, Koivunen E, Radomski MW, Davidge ST. Vascular matrix metalloproteinase-2-dependent cleavage of calcitonin gene-related peptide promotes vasoconstriction. *Circulation research*. 2000; 87:670–676. [PubMed: 11029402]
47. Abbas A, Aukrust P, Russell D, Krohg-Sorensen K, Almas T, Bundgaard D, Bjerkeli V, Sagen EL, Michelsen OAE, Dahl TB, Holm S, Ueland T, Skjelland M, Halvorsen B. Matrix metalloproteinase 7 is associated with symptomatic lesions and adverse events in patients with carotid atherosclerosis. *PloS one*. 2014; 9:e84935. [PubMed: 24400123]
48. Fan X, Wang E, Wang X, Cong X, Chen X. Microrna-21 is a unique signature associated with coronary plaque instability in humans by regulating matrix metalloproteinase-9 via reversion-

- inducing cysteine-rich protein with kazal motifs. *Experimental and molecular pathology*. 2014; 96:242–249. [PubMed: 24594117]
49. Wagsater D, Zhu C, Bjorkegren J, Skogsberg J, Eriksson P. Mmp-2 and mmp-9 are prominent matrix metalloproteinases during atherosclerosis development in the *ldlr*($-/-$)*apob*(100/100) mouse. *International journal of molecular medicine*. 2011; 28:247–253. [PubMed: 21567073]
 50. Di Gregoli K, Jenkins N, Salter R, White S, Newby AC, Johnson JL. MicroRNA-24 regulates macrophage behavior and retards atherosclerosis. *Arteriosclerosis, thrombosis, and vascular biology*. 2014; 34:1990–2000.
 51. Jiang Y, Wang HY, Cao HM, Wang CY, Zhang L, Wang H, Liu L, Li Y, Cai JH. Peripheral blood mirnas as a biomarker for chronic cardiovascular diseases. *Scientific reports*. 2014; 4:5026. [PubMed: 24848278]
 52. Kroesen BJ, Teteloshvili N, Smigielska-Czepiel K, Brouwer E, Boots AM, van den Berg A, Kluiver J. Immuno-mirs: Critical regulators of t-cell development, function and ageing. *Immunology*. 2015; 144:1–10. [PubMed: 25093579]
 53. Sakakura K, Nakano M, Otsuka F, Ladich E, Kolodgie FD, Virmani R. Pathophysiology of atherosclerosis plaque progression. *Heart, lung & circulation*. 2013; 22:399–411.
 54. Saito H, Kuroda S, Hirata K, Magota K, Shiga T, Tamaki N, Yoshida D, Terae S, Nakayama N, Houkin K. Validity of dual mri and f-fdg pet imaging in predicting vulnerable and inflamed carotid plaque. *Cerebrovascular diseases*. 2013; 35:370–377. [PubMed: 23635390]
 55. Cheng XW, Song H, Sasaki T, Hu L, Inoue A, Bando YK, Shi GP, Kuzuya M, Okumura K, Murohara T. Angiotensin type 1 receptor blocker reduces intimal neovascularization and plaque growth in apolipoprotein e-deficient mice. *Hypertension*. 2011; 57:981–989. [PubMed: 21464389]
 56. Fang C, Wen G, Zhang L, Lin L, Moore A, Wu S, Ye S, Xiao Q. An important role of matrix metalloproteinase-8 in angiogenesis in vitro and in vivo. *Cardiovascular research*. 2013; 99:146–155. [PubMed: 23512982]
 57. Zhang X, Wu D, Choi JC, Minard CG, Hou X, Coselli JS, Shen YH, LeMaire SA. Matrix metalloproteinase levels in chronic thoracic aortic dissection. *The Journal of surgical research*. 2014; 189:348–358. [PubMed: 24746253]
 58. Reeps C, Bundschuh RA, Pellisek J, Herz M, van Marwick S, Schwaiger M, Eckstein HH, Nekolla SG, Essler M. Quantitative assessment of glucose metabolism in the vessel wall of abdominal aortic aneurysms: Correlation with histology and role of partial volume correction. *The international journal of cardiovascular imaging*. 2013; 29:505–512. [PubMed: 22772434]
 59. Sheth RA, Maricevich M, Mahmood U. In vivo optical molecular imaging of matrix metalloproteinase activity in abdominal aortic aneurysms correlates with treatment effects on growth rate. *Atherosclerosis*. 2010; 212:181–187. [PubMed: 20542274]
 60. Boon RA, Seeger T, Heydt S, Fischer A, Hergenreider E, Horrevoets AJ, Vinciguerra M, Rosenthal N, Sciacca S, Pilato M, van Heijningen P, Essers J, Brandes RP, Zeiher AM, Dimmeler S. MicroRNA-29 in aortic dilation: Implications for aneurysm formation. *Circulation research*. 2011; 109:1115–1119. [PubMed: 21903938]
 61. Faugeron J, Nematalla H, Li W, Clement M, Robidel E, Frank M, Curis E, Ait-Oufella H, Caligiuri G, Nicoletti A, Hagege A, Messas E, Bruneval P, Jeunemaitre X, Bergaya S. Angiotensin ii promotes thoracic aortic dissections and ruptures in *col3a1* haploinsufficient mice. *Hypertension*. 2013; 62:203–208. [PubMed: 23630948]
 62. Gallo EM, Loch DC, Habashi JP, Calderon JF, Chen Y, Bedja D, van Erp C, Gerber EE, Parker SJ, Sauls K, Judge DP, Cooke SK, Lindsay ME, Rouf R, Myers L, ap Rhys CM, Kent KC, Norris RA, Huso DL, Dietz HC. Angiotensin ii-dependent tgfbeta signaling contributes to loeys-dietz syndrome vascular pathogenesis. *The Journal of clinical investigation*. 2014; 124:448–460. [PubMed: 24355923]
 63. Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, Myers L, Klein EC, Liu G, Calvi C, Podowski M, Neptune ER, Halushka MK, Bedja D, Gabrielson K, Rifkin DB, Carta L, Ramirez F, Huso DL, Dietz HC. Losartan, an at1 antagonist, prevents aortic aneurysm in a mouse model of marfan syndrome. *Science*. 2006; 312:117–121. [PubMed: 16601194]
 64. Merk DR, Chin JT, Dake BA, Maegdefessel L, Miller MO, Kimura N, Tsao PS, Iosef C, Berry GJ, Mohr FW, Spin JM, Alvira CM, Robbins RC, Fischbein MP. Mir-29b participates in early

aneurysm development in marfan syndrome. *Circulation research*. 2012; 110:312–324. [PubMed: 22116819]

65. Moltzer E, te Riet L, Swagemakers SM, van Heijningen PM, Vermeij M, van Veghel R, Bouhuizen AM, van Esch JH, Lankhorst S, Ramnath NW, de Waard MC, Duncker DJ, van der Spek PJ, Rouwet EV, Danser AH, Essers J. Impaired vascular contractility and aortic wall degeneration in fibulin-4 deficient mice: Effect of angiotensin ii type 1 (at1) receptor blockade. *PloS one*. 2011; 6:e23411. [PubMed: 21858106]
66. Zampetaki A, Attia R, Mayr U, Gomes RS, Phinikaridou A, Yin X, Langley SR, Willeit P, Lu R, Fanshawe B, Fava M, Barallobre-Barreiro J, Molenaar C, So PW, Abbas A, Jahangiri M, Waltham M, Botnar R, Smith A, Mayr M. Role of mir-195 in aortic aneurysmal disease. *Circulation research*. 2014; 115:857–866. [PubMed: 25201911]
67. Maegdefessel L, Azuma J, Toh R, Deng A, Merk DR, Raiesdana A, Leeper NJ, Raaz U, Schoelmerich AM, McConnell MV, Dalman RL, Spin JM, Tsao PS. MicroRNA-21 blocks abdominal aortic aneurysm development and nicotine-augmented expansion. *Science translational medicine*. 2012; 4:122ra122.
68. Tae HJ, Marshall S, Zhang J, Wang M, Briest W, Talan MI. Chronic treatment with a broad-spectrum metalloproteinase inhibitor, doxycycline, prevents the development of spontaneous aortic lesions in a mouse model of vascular Ehlers-Danlos syndrome. *The Journal of pharmacology and experimental therapeutics*. 2012; 343:246–251. [PubMed: 22815532]
69. Xiong W, Meisinger T, Knispel R, Worth JM, Baxter BT. MMP-2 regulates ERK1/2 phosphorylation and aortic dilatation in Marfan syndrome. *Circulation research*. 2012; 110:e92–e101. [PubMed: 22550139]
70. Patel VB, Zhong JC, Fan D, Basu R, Morton JS, Parajuli N, McMurtry MS, Davidge ST, Kassiri Z, Oudit GY. Angiotensin-converting enzyme 2 is a critical determinant of angiotensin II-induced loss of vascular smooth muscle cells and adverse vascular remodeling. *Hypertension*. 2014; 64:157–164. [PubMed: 24799609]
71. Fan LM, Douglas G, Bendall JK, McNeill E, Crabtree MJ, Hale AB, Mai A, Li JM, McAteer MA, Schneider JE, Choudhury RP, Channon KM. Endothelial cell-specific reactive oxygen species production increases susceptibility to aortic dissection. *Circulation*. 2014; 129:2661–2672. [PubMed: 24807872]
72. Ghosh A, DiMusto PD, Ehrlichman LK, Sadiq O, McEvoy B, Futchko JS, Henke PK, Eliason JL, Upchurch GR Jr. The role of extracellular signal-related kinase during abdominal aortic aneurysm formation. *Journal of the American College of Surgeons*. 2012; 215:668–680. e661. [PubMed: 22917644]
73. Koole D, Zandvoort HJ, Schoneveld A, Vink A, Vos JA, van den Hoogen LL, de Vries JP, Pasterkamp G, Moll FL, van Herwaarden JA. Intraluminal abdominal aortic aneurysm thrombus is associated with disruption of wall integrity. *Journal of vascular surgery*. 2013; 57:77–83. [PubMed: 23127983]

MMP Activity, Arterial Aging, and Arterial Disease

Figure.

MMP activation plays a central role in arterial proinflammatory remodeling and stiffening, which is a structural and functional signature of aging, hypertension, and atherosclerosis.

Table

MMP activation is involved in arterial remodeling and functional changes

Arterial remodeling and functional change	MMP
Endothelial inflammation: EC apoptosis/senescence/death; and disruption of basement membrane	MMP-1/-2 ⁹⁻¹¹
Intimal-medial thickening-VSMCs: Proliferation/invasion/migration/apoptosis/senescence; and hypocontractility	MMP-1/-3 ⁵ , 13, 16, 17, 28, 39, 70
Elastolysis	MMP-2/-3/-9/-12 ²³ , 26, 44, 62, 68, 69, 71-73
Fibrosis: collagen deposition	MMP-2/-8/-9/-13 ²⁵ , 27, 30, 31
Calcification	MMP-2 ⁸ , 23, 25
Adventitial expansion: fibroblast transdifferentiation into myo fibroblasts; proliferation and inflammation; mast cell infiltration; and adipose tissue inflammation	MMP-2/-9/-12 ²¹ , 31-33
Vasoconstriction: degraded β 2-AR; eNOS; and CGRP as well as increased ET-1	MMP-1/-2/-9 ⁴ , 6, 38, 45, 46
Stiffening: tone	MMP-1/-7/-8/-9/-10/-12/-13/-15 ³⁰ , 31, 38, 41