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Vascular Extracellular Matrix Remodeling and Hypertension

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Abstract

Significance: The vascular extracellular matrix (ECM) not only provides mechanical stability but also manipulates vascular cell behaviors, which are crucial for vascular function and homeostasis. ECM remodeling, which alters vascular wall mechanical properties and exposes vascular cells to bioactive molecules, is involved in the development and progression of hypertension.

Recent Advances: This brief review summarized the dynamic changes in ECM components and their modification and degradation during hypertension and after antihypertensive treatment. We also discussed how alterations in the ECM amount, assembly, mechanical properties, and degradation fragment generation provide input into the pathological process of hypertension.

Critical Issues: Although the relevance between ECM remodeling and hypertension has been recognized, the underlying mechanism by which ECM remodeling initiates the development of hypertension remains unclear. Therefore, the modulation of ECM remodeling on arterial stiffness and hypertension in genetically modified rodent models is summarized in this review. The circulating biomarkers based on ECM metabolism and therapeutic strategies targeting ECM disorders in hypertension are also introduced.

Future Directions: Further research will provide more comprehensive understanding of ECM remodeling in hypertension by the application of matridomic and degradomic approaches. The better understanding of mechanisms underlying vascular ECM remodeling may provide novel potential therapeutic strategies for preventing and treating hypertension. *Antioxid. Redox Signal.* 34, 765–783.

Keywords: hypertension, extracellular matrix, stiffness, remodeling, vascular smooth muscle cell

Introduction

THE RISK FACTORS FOR HYPERTENSION include aging, obesity, smoking, alcoholism, cold stress, potassium intake deficiency, a high-salt diet, *etc.* (12, 53, 84, 87, 117, 119, 182). Long-term hypertension results in the elevated pressures on vascular walls and cardiac chambers, systemic vascular remodeling, atherothrombosis, and atherosclerosis, *etc.*, thereby damaging target organs such as the heart, brain, and kidneys (118). A number of reviews have summarized the process and characteristics of vascular remodeling during hypertension (92). In brief, increased peripheral resistance is related to structural alterations in resistance vessels, mainly characterized by vascular smooth muscle cell (VSMC) proliferation and hypertrophy, stenosis of the lumen, and an increase in the media/lumen ratio. In

addition, the large arteries exhibit increased stiffness and loss of compliance, which is monitored by the pulse wave velocity (PWV). These characteristics of vascular remodeling in hypertension are typically associated with an imbalance in the renin–angiotensin–aldosterone system, endothelial cell (EC) dysfunction, and contractile properties and phenotypic switching of VSMCs, as well as with extracellular matrix (ECM) reorganization and inflammation throughout the entire vessel wall.

The vascular ECM is well known for its ability to form an intricate three-dimensional network that provides mechanical support for various cell types and maintains vascular wall integrity. The ECM also actively integrates extracellular signals and influences resident cell physiology. In addition, the mechanical characteristics of the ECM, including its elasticity, strength, and deformability, provide inputs into

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cell behaviors (160). During vascular remodeling in hypertension, the ECM undergoes profound alterations characterized mainly by elastic fiber fragmentation and excessive collagen deposition as well as the rearrangement of matricellular proteins and proteoglycans (PGs) (14). Recent studies have also concluded that not only the quantity but also the quality of the ECM, including correct assembly, appropriate crosslinking, and the synthesis/degradation balance, plays a pivotal role in hypertension-associated vascular remodeling (3).

ECM Components and Homeostasis in the Vascular Wall

ECM proteins are the major noncellular components in the vascular wall (62). Identification of vascular ECM components is essential for revealing the dynamic structural and functional characterization under physiological and pathological conditions. Matridomics is defined as a proteomics approach to catalog the ECM components present in tissues, and provide comprehensive information about the quantity and quality of ECM proteins (31). This approach includes extraction of decellularized ECM fraction, solubilization and deglycosylation of ECM proteins, and analysis by liquid chromatography tandem mass spectrometry (5, 35). The Mayr laboratory has utilized the matridomics approach and identified 103 different ECM proteins in the human aorta, mainly elastin, collagens, glycoproteins, and PGs, as well as proteases and their inhibitors (35).

The composition of ECM components varies in distinct layers of the vascular wall. Type IV collagen, along with type XV collagen, type XVIII collagen, laminin, nidogen, perlecan, agrin, and fibronectin, are assembled into a mesh-like structure named the basement membrane (BM), which provides an anchoring site for ECs in the tunica intima (83). Elastin contributes to the formation of the internal elastic lamina (IEL), which separates the tunica intima from the tunica media. In the middle layer, elastin is deposited on the microfibril scaffold, which is composed of fibrillins and proteins involved in fiber formation, including microfibril-associated glycoproteins (MAGPs), microfibrillar-associated proteins (MFAPs), and fibulins. Elastin is crosslinked by lysyl oxidase (LOX) to form the three-dimensional lamellar network. The contractile smooth muscle cells and elastic fibers are arranged into concentric circles, constituting a recoiling functional unit of the vascular wall, and endowing arteries with elasticity to expand and retract during the cardiac cycle (3, 97). Type I, III, V, and VI collagen fibers, fibronectin, laminin, PGs, and glycoproteins are also interposed between fenestrated lamellar layers (134, 177). The major ECM components in the tunica adventitia are type I and III fibrillar collagens, chondroitin sulfate, and dermatan sulfate PGs, fibronectin, and many other ECM proteins produced by adventitial fibroblasts (177). Fibrillar collagens secreted into the tunica media and tunica adventitia aggregate into quarter-staggered fibrils and are crosslinked by LOX, limiting excessive vasodilation and endowing arteries with strength. The vascular ECM also contains nonstructural matricellular proteins—including thrombospondins (TSPs), tenascin C (TNC), osteopontin (OPN), secreted protein, acidic and rich in cysteine (SPARC), *etc.*—

that regulate cell adhesion, migration, proliferation, and cytokine-related responses (Fig. 1).

Most ECM components in the vascular wall are not static but rather highly dynamic, constantly undergoing production, degradation, and organization to maintain vascular homeostasis. Proteases that hydrolyze ECM proteins include matrix metalloproteinases (MMPs), members of the disintegrin and metalloproteinase (ADAM) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) families, serine proteases (*e.g.*, plasmin, neutrophil-elastase, and cathepsin G), cysteine proteases (*e.g.*, cathepsin B, L, and S), and aspartyl proteases (cathepsin D) (70). In vascular tissues, elastic fibers can be degraded by MMP-2, MMP-7, MMP-9, and MMP-12, and collagens are mainly degraded by MMP-1, MMP-8, MMP-13, and MMP-18 (80, 137). The activity of MMPs is inhibited by endogenous tissue inhibitors of metalloproteinases (TIMPs). Vascular ECM turnover is regulated by MMP and TIMP equilibrium, and dysregulation of the MMP/TIMP ratio leads to impaired ECM homeostasis. Degradomics is defined as the genomic and proteomic approaches to reveal the proteases and their inhibitors, substrates, and interactors. Degradomics requires high-throughput, high-content techniques such as terminal amine isotopic labeling of substrates (TAILS) and combined fractional diagonal chromatography that allow the identification and quantification of proteases and the proteolytic-cleavage fragments (40, 103). The Mayr laboratory has identified substrates for MMP-3, MMP-9, MMP-12, and MMP-14 in human vasculature by using degradomics (36, 153). However, more comprehensive analyses of the substrates for proteases beyond the commonly studied MMPs using degradomics are needed.

Vascular ECM Alterations in Hypertension and Hypertension-Associated Vascular Remodeling

Alterations in ECM production, degradation, and organization in arterial layers are important features of hypertensive vascular remodeling (Fig. 1). Changes in ECM components can be triggered by increased circumferential wall stress, growth factors, inflammatory cytokines, chemokines, oxidative stress, and other pathological processes (95).

Alterations in ECM components

Elastin is the most predominant ECM constituent in the middle layer of large elastic arteries and determines the mechanical properties of the vascular wall (166). Elastin fibers are prone to fragmentation and rupture in age-related arterial stiffness and hypertension. Pathogenic factors related to aging, such as mechanical fracture, calcification, exposure to glycation/carbamylation products, and peroxidation, facilitate the susceptibility of elastin to degradation by serine and cysteine proteases and MMPs (43). Reduced elastin amounts were observed in stroke-prone spontaneously hypertensive rats (SHR-SP) (78). Since the elastases mentioned above are partially produced by inflammatory cells such as polymorphonuclear neutrophils and macrophages, the activated immune and inflammatory reactions in arterial walls may contribute to increased elastolysis and subsequent elastin degradation (114, 170). In contrast to the above observations, augmented elastin production in response to mechanical stress was observed at the very early stage of

FIG. 1. ECM composition in normal and hypertensive vascular walls. *Left*, ECM composition in distinct layers of the normal vascular wall. *Right*, the currently reported alterations of vascular ECM component during hypertension. BM, basement membrane; EC, endothelial cell; ECM, extracellular matrix; EEL, external elastic lamina; FB, fibroblast; IEL, internal elastic lamina; VSMC, vascular smooth muscle cell. Color images are available online.

hypertension in deoxycorticosterone acetate (DOCA)-salt, renal clipped, Dahl/salt-sensitive rats (86). However, this newly synthesized tropoelastin cannot be assembled into mature elastin fibers and fails to provide entropic elasticity (3, 90, 161).

Collagen is another basic structural element in vascular walls that limits excessive vasodilation. Increased deposition of collagen I, III, and IV in the vascular wall has been reported in both conduit and resistance arteries from patients with essential hypertension (75) as well as in experimental murine models of hypertension (15, 164). Accumulating evidence has shown the prohypertensive factors and the downstream signaling pathways involved in excessive production of collagens. Examples include transforming growth factor- β (TGF- β)-stimulated Smad2/3 and mitogen-activated protein kinase (MAPK) pathways; angiotensin II (Ang II)-activated activator protein-1 (AP-1), protein kinase C (PKC), and p38MAPK signaling; and cyclic stretch-triggered c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) 1/2, and nuclear factor- κ B (NF- κ B) pathways in VSMCs and fibroblasts (64, 95). Recently, Wu *et al.* performed a cell sorting and lineage tracing study to explore the cellular origin of matrix production during hypertension. They showed that adventitial collagen production is not attributable only to resident fibroblasts; adventitial Sca-1⁺ progenitor cells also acquire a fibroblast-like phenotype and are able to produce collagen. Bone marrow-derived cells account for ~60% of the matrix-producing Sca-1⁺ cells, whereas the EC lineage accounts for 24% and the VSMC lineage does not contribute to this population (175).

In addition to the notable alterations in structural components, changes in some nonstructural proteins, including glycosaminoglycans, PGs, and matricellular proteins, occur during hypertensive vascular remodeling. Fibronectin (9) and its alternatively spliced forms (159), OPN (168), large chondroitin sulfate PG, large heparan sulfate PG, biglycan (PGI), and decorin (PGII) are upregulated in the arteries of spontaneously hypertensive rat (SHR) (167). TNC expression is markedly elevated in DOCA-salt-induced hypertensive mice and SHR (42, 74, 111). In L-N^G-nitro arginine methyl ester (L-NAME)-induced hypertensive rats, similar upregulation of TNC is found in the aorta, but the level of TNC is decreased in small mesenteric arteries (11). Clinical studies also showed increased serum levels of both B and C domain-containing TNC in patients with arterial hypertension (54).

In the past decade, proteomic approaches have provided comprehensive information on molecular features in cardiovascular diseases and advanced the understanding of ECM components involved in the fibrotic process (32). Proteomic studies have been increasingly applied in hypertension patients and experimental models, and several differentially expressed proteins have been identified (23, 32, 51, 109). A quantitative serum proteomic analysis using the isobaric tags for relative and absolute quantification method identified 101 differentially expressed proteins between the essential hypertension group and the healthy control group. Only 3% of the differentially expressed proteins were ECM proteins in the serum, and the changes included decreased expression of cartilage oligomeric matrix protein (COMP) and increased expression of fibulin-5 (178). Recently, a proteomic study on left mammary artery samples from patients with elevated PWV quantitated 38 ECM molecules. Compared with the

normal PWV group, the high PWV group exhibited upregulation of collagen type VIII α 1, collagen type VIII α 2, and collagen type IV α 1. In addition, three members of the small leucine-rich proteoglycan (SLRP) family, including prolargin, asporin, and mimecan, which serve as regulators of collagen deposition and arrangement, were downregulated in the high PWV group (109). Proteomic analysis of aortic walls in SHR showed a decreased protein level of mimecan after 6 weeks of load-free swimming training (51). However, current proteomic data on vascular ECM alterations are primarily based on the analysis of total protein extracted from artery samples. Extraction of decellularized vascular ECM combined with matrix proteomic studies is expected to provide unprecedented insights into ECM remodeling in hypertension (Table 1).

Alterations in the ECM topological arrangement

Not only the biochemical composition but also the topological arrangement of the ECM is altered in response to hypertensive stimuli. Chow *et al.* described the organization, realignment, and recruitment of elastin and collagen in response to mechanical loading by using a multiphoton imaging method. Medial collagen fibers display a wavy configuration in the static state, and exhibit engagement and circumferential distribution throughout the stretching process. Adventitial collagen, originally existing as larger wavy bundles of fibers, begins to strengthen at >20% strain. Realignment of collagen fibers toward the major direction of loading occurs in both the medial and adventitial layers in response to unequal biaxial loading. Medial elastin fibers start to straighten at the onset of loading but plateau at >20% strain (29). Another study also revealed the dimensional structural alterations in elastin and collagen fibers in the thoracic aorta during pressurization. Increased intraluminal pressure in the mouse aorta leads to reduced waviness of collagen fibers. The collagen fibers in smooth muscle-rich layers are more likely to strengthen than those in the elastic lamina (158). Therefore, pressurization-induced topological alterations are multifaceted due to the heterogeneity of vascular layers and the different mechanical properties of collagen and elastin.

The construction of the vascular topological structure depends on the biological behavior of VSMCs as well as the elaborate regulation of the ECM constituent assembly. Hays *et al.* found that collagen cultured with VSMCs from the Wistar-koyto rat thoracic aorta displays a parallel alignment, whereas collagen cultured with VSMCs from SHR exhibits shorter fragments, disorganization with greater alignment angles, and a multidirectional orientation (65). Matrix fibronectin controls the organization and assembly of other matrix proteins, and removal of polymerized fibronectin from decellularized ECM markedly reduces the deposition of collagen I and TNC. Fibronectin accumulation is observed in the large arteries of hypertensive rats (9), thus providing a scaffold to facilitate the excessive assembly and deposition of collagens I and IV, laminin, and TNC (67). LOX regulates the crosslinking of both elastin and collagen during fiber assembly; thus, dysregulation of LOX expression and activity alters the topological structure and mechanical properties of the vascular ECM. An increase in vascular LOX activity has been reported in SHR and Ang II-infused hypertensive mice, resulting in an increase in crosslinked elastin and collagen fibers (46, 113). Treatment with the LOX inhibitor

TABLE 1. VASCULAR EXTRACELLULAR MATRIX ALTERATIONS IN HYPERTENSION

<i>Classification</i>	<i>ECM proteins</i>	<i>Detection method</i>	<i>Alterations</i>	<i>References</i>
Elastic fiber	Elastin	Isolation of insoluble elastin	Decreased elastin content and increased elastase-like enzyme activity in 20-week-old SHR	(78)
		Isolation of insoluble elastin	Augmented elastin production at the early stage of hypertension in DOCA salt-induced hypertensive rats	(86)
	Fibullin-5	Proteomics	Increase in serum from patients with essential hypertension	(178)
	LOX	Western blot	Increase in SHR and Ang II-induced hypertensive mice	(46, 113)
Collagens	Collagen	Electron microscopy	Increased density of collagen in resistance arteries from patients with essential hypertension	(75)
		Picrosirius red staining Western blot	Increased total collagen content and the ratio of collagen I/III in resistance arteries from ouabain-induced hypertensive rats	(15)
		Confocal microscopy	Increased collagen deposition in mesenteric arteries from Ang II-infused hypertensive mice	(164)
GPs	Collagen IV, collagen VIII	Proteomics	Increase in left mammary artery from patients with elevated PWV	(109)
	Fibronectin	Immunohistochemistry	Increase in SHR aorta	(9)
		Northern blot	Increased alternative spliced forms in aorta from DOCA-salt-induced hypertensive rats and SHR	(159)
Proteoglycans	Large chondroitin sulfate PG, large heparan sulfate PG, biglycan, decorin	DEAE anion-exchange chromatography and SDS-PAGE	Increase in SHR arteries <i>in vitro</i>	(167)
PG	Prolargin, asporin, mimecan	Proteomics	Decrease in left mammary artery from patients with elevated PWV	(78)
	Mimiecan	Proteomics	Decrease in aortic wall from SHR after 6-week swimming training	(86)
Matricellular proteins	TSP-1	Quantitative sandwich enzyme immunoassays	Decreased plasma levels in patients with hypertension and restored after treatment	(19)
	TSP-4	Western blot, mRNA microarray, real-time PCR	Increase in mesenteric arteries from SHR	(130)
	COMP	Proteomics	Decrease in serum from patients with essential hypertension	(178)
	OPN	Immunoenzymatic assay	Increase in plasma from patients with hypertension	(155)
		Immunohistochemistry, Western blot, ELISA	Increase in plasma and aorta from SHR and Ang II- or L-NAME-induced hypertensive mice	(145)
	SPARC	Immunohistochemistry, <i>in situ</i> hybridization	Increase in blood vessels from Ang II-infused rats	(133)
	TNC	Immunohistochemistry	Increase in artery from DOCA-salt-induced hypertensive mice and SHR	(42, 111)

Ang II, angiotensin II; COMP, cartilage oligomeric matrix protein; DOCA, deoxycorticosterone acetate; ECM, extracellular matrix; ELISA, enzyme-linked immunosorbent assay; GP, glycoprotein; L-NAME, L-N^G-Nitro arginine methyl ester; LOX, lysyl oxidase; mRNA, messenger RNA; OPN, osteopontin; PCR, polymerase chain reaction; PG, proteoglycan; PWV, pulse wave velocity; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; SHR, spontaneously hypertensive rat; SPARC, secreted protein, acidic and rich in cysteine; TNC, tenascin C; TSP, thrombospondin.

β -aminopropionitrile (BAPN) ameliorates the development of hypertension (79). Another collagen crosslinking enzyme named transglutaminase 2 (TG2) can be activated by the increased production of TGF- β and decreased production of nitric oxide (NO), thereby promoting additional collagen crosslinking (156).

Imbalance between proteases and their inhibitors

Accelerated turnover and deposition of extracellular collagens is observed in essential hypertension. Procollagen type I C-terminal propeptide (PICP) and carboxy-terminal telopeptide of type I collagen (ICTP) are considered markers

for type I collagen synthesis and degradation, respectively. The PICP/ICTP ratio is increased in the serum of SHR compared with that of control rats, supporting the increased synthesis/degradation ratio of type I collagen in hypertension (38). Abnormally high serum concentrations of PICP are also observed in patients with essential hypertension (39). Previous studies reported that excessive arterial collagen deposition in hypertension may be facilitated by diminished MMP activity.

Decreased serum MMP-1 levels together with increased TIMP-1 concentrations were observed in patients with hypertension (93). Activity of MMP-1 and MMP-9 and expression of the MMP inducer and activator proteins in internal mammary artery are downregulated in hypertensive patients undergoing coronary artery bypass grafting surgery (48). MMP-3 activity in resistance arteries of SHR was also decreased, thus facilitating the accumulation of fibronectin and PGs (24). However, accumulating data indicate the increased MMP expression and activity in the development of hypertension. In patients with isolated systolic hypertension, serum levels of MMP-2 and MMP-9 are increased, and MMP-9 levels positively correlate with aortic stiffness (184). Niemirska *et al.* found that plasma MMP-9 and TIMP-1 concentrations and the MMP-9/TIMP-1 ratio are significantly elevated in children with untreated primary hypertension, and that there are significant positive correlations between arterial stiffness and the TIMP-1 concentration (123). Odenbach *et al.* reported that MMP-2 activity in the aorta is upregulated in Ang II-infused mice and is involved in the maintenance of agonist-induced arterial constriction (125). The discrepancy in changes of MMPs in hypertension may attribute to the following aspects. Plasma levels of

MMPs may vary with different stages, the severity of hypertension, and the occurrence of hypertension-related complications. Examples are the decreased MMP activity in young SHR-SP vessels, whereas increased vascular MMP activity in the older hypertensive rats (76, 151); the higher pro-MMP2 activity in hypertensive patients with heart failure (HF) than in those without HF (56). Furthermore, plasma or serum levels of MMPs represent their global expression, and the changes of MMPs in specific vasculature need to be evaluated additionally.

ADAMTS-1, a PG-degrading enzyme, is upregulated by Ang II and proinflammatory factors in ECs and VSMCs and by vascular endothelial growth factor (VEGF) in ECs. These stimuli strongly implicated in vascular remodeling enhance the binding of nuclear factor of activated T-cells (NFAT) or CCAAT-enhancer-binding protein β (C/EBP β) to the *ADAMTS-1* promoter (126). Cathepsin L/V protein levels are upregulated in the mesenteric arteries and serum of patients with hypertension, and their activity is augmented in Ang II-induced hypertensive mice. Ang II stimulation induces the release of lysosomal cathepsin B in THP-1 cells, which leads to NOD, LRR, and pyrin domain-containing protein 3 (NLRP3) inflammasome activation, decreased NO release, and macrophage digestion dysfunction. Inhibition of cathepsin B abrogates Ang II-induced NLRP3 inflammasome activation and macrophage dysfunction, thus revealing the involvement of cathepsin B in the sterile inflammatory response to Ang II (100). Plasma cathepsin D levels were inversely associated with endothelial-dependent vasodilation in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (102) (Table 2).

TABLE 2. VASCULAR PROTEASE ALTERATIONS IN HYPERTENSION

Classification	Protease	Substrates	Alterations	References
MMPs	MMP-9	Collagen, gelatin, elastin, fibronectin	Decreased plasma levels in patients with essential hypertension and restored after treatment; increased gelatinase activity in Ang II-infused mice; positively related with human aortic PWV	(52, 127, 184, 188)
	MMP-2	Collagen, gelatin, elastin, fibronectin	Decreased plasma levels in patients with essential hypertension; increased gelatinase activity in Ang II-infused mice and DOCA-salt-induced hypertensive rats	(52, 174, 184)
	MMP-1	Collagen, entactin, PGs, ovostatin, MMP-2, MMP-9, pro-MMP-9	Decreased serum levels in patients with hypertension and restored after lisinopril treatment	(93)
	MMP-7	Collagen, gelatin, fibronectin, laminin, elastin, transferrin, casein	Increased in PE-, Ang II-, and L-NAME-induced hypertensive rats	(171)
ADAMs	ADAM-17/TACE	Collagen, GPs, Notch1, vasorin, APP, <i>etc.</i>	Increase in SHR and Ang II-treated VSMCs	(124, 172, 192)
Cathepsins	Cathepsin D		Elevated gradually with increasing BP in SHR	(180)
	Cathepsin L/V		Increased in the mesenteric arteries and serum from patients with hypertension; augmented activity in Ang II-induced hypertensive mice	(82)

ADAM, a disintegrin and metalloproteinase; APP, amyloid precursor protein; BP, blood pressure; MMP, matrix metalloproteinase; PE, phenylephrine; TACE, tumor necrosis factor- α -converting enzyme; VSMC, vascular smooth muscle cell.

Vascular ECM Remodeling Is Involved in Hypertension

Changes in constituents and topology in the vascular wall ECM have been implicated in the pathogenesis of hypertension. Gene mutations in populations and genetically modified rodent models provide evidence that the ECM is involved in mediating arterial stiffness, vascular cell function and behavior, and inflammatory and oxidative events.

Genetically modified animal models

Mutation and modification of genes related to elastin and related fibrillar proteins (fibulin, fibrillin, emilin1), collagens, proteases and their inhibitors, and matricellular proteins have revealed phenotypic changes in the arterial wall architecture and blood pressure (BP) fluctuations (Table 3).

ECM remodeling and vascular stiffness

Arterial stiffness develops with aging and other pathological states, and is primarily caused by ECM remodeling, smooth muscle cell adhesion and stiffness, calcification of the elastic lamellae, and elevated transmural distending pressure (143). In recent years, the increased stiffness of large elastic arteries in hypertension has received increasing attention and is recognized as a risk factor for cardiovascular disease morbidity and mortality, which can be reflected by the PWV (116). During hypertension, increased arterial stiffness can be detected at the very early stage, predicting the subsequent process of BP elevation and target organ damage in hypertension (120).

The stiffness of large arteries is mainly determined by collagen and elastin, the two most abundant ECM components in vascular walls. Mutations in the collagen III gene (COL3A1) lead to Ehlers-Danlos syndrome, which is characterized by vascular dilation and aortic rupture (21). In contrast, excessive collagen deposition is deleterious to the vascular wall and increases stiffness. Stakos *et al.* reported that patients with hypertension have increased levels of procollagen type I N-terminal propeptide (PINP)/collagen type I carboxy-terminal telopeptide (CITP), which indicates increased collagen synthesis and is positively associated with PWV (152). In addition, You *et al.* revealed a positive correlation of PWV with the relative content of collagen and a negative correlation with the relative content of elastin in ascending aorta specimens from hypertension patients (185). Elastin haploinsufficiency is sufficient to reduce arterial compliance and elevate BP in mice (50). Martinez-Revelles *et al.* revealed the effect of improper crosslinking of elastin on arterial stiffness in a mouse model of LOX overexpression in VSMCs. Elevated LOX expression and activity lead to increased insoluble elastin deposition and increased elastin assembly with smaller fenestrae in the IEL, which in turn increases arterial stiffness (113).

Collagen and elastin are not the only ECM components determining arterial stiffness. Deposition of fibronectin, fibulin, glycosaminoglycan, and PGs also influences the mechanical properties of the arterial wall, including stiffness (191). Fibronectin polymerization occurs after its addition to cell-embedded collagen biogels, and induces increases in tensile strength and toughness (57). Although no changes in the collagen and elastin densities were observed in

aldosterone-salt hypertensive rats, aldosterone induced arterial fibronectin accumulation and increased the intrinsic carotid stiffness (122). Another study using sinoaortic denervated (SAD) rats showed that enhanced arterial thickness and stiffness are associated with increased VSMC attachment to the surrounding ECM *via* fibronectin and its $\alpha_5\beta_1$ integrin receptor (10). Hyaluronan transgenic (Tg) mice exhibit an increased aortic cross-sectional area, and enhanced arterial stiffness and strength. Excessive accumulation and cross-linking of hyaluronan in the tunica media leads to a shift in the smooth muscle cell (SMC) phenotype, showing increased proliferation and osteoprotegerin production (107). A recent study identified the association of aggrecan (ACAN) and fibulin-1 (FBLN-1) polymorphisms with the aortic PWV in young healthy adults. Both aggrecan and fibulin-1 are down-regulated in aortas from donors with high arterial stiffness and systolic BP, suggesting their reduced expression in facilitating age-related aortic stiffening (183).

ECM remodeling and VSMC biology

Multiple prohypertensive factors, such as mechanical stretching and exposure to growth factors, cytokines, and hormones, lead to a hypercontractile state of VSMCs and dedifferentiation to a proliferative and synthetic phenotype in both large and small arteries (16, 162). In larger conductive arteries, VSMCs primarily undergo hypertrophy, stiffening (144), and apoptosis (33, 147), and contribute to the increased intima-media thickness and arterial stiffness.

Vascular ECM remodeling during hypertension exerts effects on the functional and structural alterations in VSMCs. Several studies have shown that the mechanical properties of the extracellular environment, such as substrate stiffness, directly impact cell behaviors, including motility, proliferation, and differentiation. For example, an elevated substrate modulus increases VSMC contractility without inducing phenotype switching (157), whereas the increased nanoscale rigidity of collagen fibrils causes VSMCs to dedifferentiate into a proliferative phenotype (115). A recent study indicated that substrate stiffening induces a contractile-to-synthetic phenotypic transition in VSMCs, accompanied by down-regulation of DNA methyltransferase 1 (DNMT1), which leads to the loss of specific SMC markers and the acquisition of osteogenic markers, thereby facilitating the phenotypic transition induced by matrix stiffening (176). Increased ECM stiffness mechanically activates Yes-associated protein (YAP) and WW domain-containing transcription regulator protein 1 (TAZ); these proteins translocate to the nucleus, where they interact with TEAD and regulate the expression of several genes, including connective tissue growth factor (CTGF) and collagens. Activation of YAP/TAZ signaling increases VSMC proliferation and migration (66, 131). Increased ECM stiffness may also activate matrix binding receptor integrins and the subsequent intracellular signaling pathways, including phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), β -catenin, and RhoA/Rho-associated protein kinase (ROCK), which results in VSMC contraction, proliferation, and migration (27, 41, 91, 132) (Fig. 2).

Collagen not only determines vascular ECM stiffness but also affects VSMC biological characteristics under physiological and pathological conditions. VSMCs cultured on monomeric collagen I exhibit elevated expression of vascular

TABLE 3. PHENOTYPE OF HUMAN AND ANIMALS WITH GENE MUTATION OR MODIFICATION OF VASCULAR EXTRACELLULAR MATRIX COMPONENT

<i>Gene</i>	<i>Species</i>	<i>Mutation/ modification</i>	<i>BP</i>	<i>Phenotype</i>	<i>References</i>
<i>Eln</i>	Human	Loss of function mutation	Hypertension	SVAS, increased arterial stiffness	(98)
	Mouse	<i>Eln</i> ^{-/-}	Not detected	Died within a few days after birth, obstructive aortic occlusion	(97)
	Mouse	<i>Eln</i> ^{+/-}	Hypertension	Increased arterial stiffness, mild cardiac hypertrophy	(50, 165)
<i>Fibulin-4 (Fbln4)</i>	Mouse	<i>Fbln4</i> ^{-/-}	Not detected	Died at birth, ascending aortic aneurysm, increased artery stiffness	(71)
	Mouse	<i>Fbln4</i> ^{SMKO}	Not detected	Ascending aortic aneurysm and increased artery stiffness	(71)
	Mouse	<i>Fbln4</i> ^{E57K/E57K}	Hypertension	Elastic fiber fragmentation and increased stiffness in large artery	(61, 73)
<i>Fibulin-5 (Fbln5)</i>	Mouse	<i>Fbln5</i> ^{-/-}	Not detected	Increased artery stiffness, fragmented elastic fibers, decreased artery contractility	(181)
<i>Fbn1</i>	Human	Mutation	Normal	Marfan syndrome, thoracic aortic aneurysm, and dissection	(37)
	Mouse	<i>Fbn1</i> ^{mgR/mgR}	Increased pulse pressure	Fragmented arterial elastic fibers, increased aortic stiffness	(112)
<i>Emilin1</i>	Mouse	<i>Emilin1</i> ^{-/-}	Hypertension	Increased peripheral vascular resistance, activated TGF- β signaling	(186)
<i>Col1A1/Col1A2</i>	Human	Mutation	Not detected	Aortic dilatation, dissection and rupture, Ehler-Danlos syndrome	(21)
<i>Col1A1</i>	Mouse	Mutation	Not detected	Aortic dissection	(138)
<i>TSP-1</i>	Mouse	<i>Tsp-1</i> ^{-/-}	Increased central diastolic and mean arterial BP	Activity-associated increase in heart rate, a constant decrease in pulse pressure, attenuated hypertensive response to epinephrine	(77)
<i>TSP-4</i>	Mouse	<i>Tsp-4</i> ^{-/-}	A similar BP increase as WT mice after Ang II infusion	Alleviated dysfunction of endothelial-dependent relaxation	(129)
<i>COMP</i> <i>OPN</i>	Mouse	<i>Comp</i> ^{-/-}	Normal	Increased PWV and artery stiffness	(169)
	Mouse	<i>Opn</i> ^{-/-}	A similar BP increase as control mice after Ang II infusion	Decreased MMP-2 and MMP-9 activity	(17)
<i>MMP-2</i>	Mouse	<i>Mmp2</i> ^{-/-}	A similar BP increase as WT mice after Ang II infusion	Alleviation of Ang II-induced endothelial dysfunction and vascular stiffness	(6)
<i>MMP-9</i>	Mouse	<i>Mmp9</i> ^{-/-}	Elevated pulse pressure	Less collagen I breakdown products, reduced artery compliance, increased SBP in response to Ang II	(52)
<i>MMP-7</i>	Mouse	<i>Mmp7</i> ^{-/-}	Reduced BP in NE-induced hypertension	Attenuation of α 1-adrenergic contractile responses in isolated small mesenteric arteries	(171)
<i>TIMP-3</i>	Mouse	<i>Timp3</i> ^{-/-}	Decreased BP after L-NAME administration	Attenuated thickness and fibrosis in vascular walls	(68)
<i>Cathepsin A</i>	Mouse	<i>Cathepsin A</i> ^{-/-}	Hypertension	Abnormal elastic fiber formation and a reduced degradation rate of ET-1	(146)
<i>ADAMTS-16</i>	Rat	Loss of function mutation	Decreased BP in Dahl salt-sensitive rat	Decreased PWV and media thickness	(58)
<i>ADAMTS-18</i>	Mouse	<i>Adamts18</i> ^{-/-}	Hypertension	Early metabolic syndrome	(190)
<i>ADAM-17</i>	Mouse	<i>Adam17</i> ^{SMKO}	Transiently decreased BP in Ang II-induced hypertension	Alleviated cardiac hypertrophy and fibrosis	(148)

ADAMTS, a disintegrin and metalloproteinase with thrombospondin motif; Eln, elastin; ET-1, endothelin-1; Fbln, fibulin; Fbn, fibrillin; NE, norepinephrine; SBP, systolic blood pressure; SMKO, smooth muscle-specific knockout; SVAS, supravalvular aortic stenosis; TGF- β , transforming growth factor- β ; TIMP, tissue inhibitor of metalloproteinase; WT, wild type.

FIG. 2. Elevated ECM stiffness and vascular cell behaviors. Increased ECM stiffness activates YAP/TAZ signaling and integrins, which results in VSMC contraction, proliferation, and migration. YAP, Yes-associated protein. Color images are available online.

cell adhesion molecule-1 (VCAM-1) and undergo osteo-/chondrogenic phenotypic switching (128, 173), whereas polymerized type I collagen inhibits VSMC migration and proliferation *via* upregulating p27Kip1 and p21Cip1 (89). Another study further revealed that the degradation of polymerized collagen I by MMPs induces the release of collagen fragments that trigger SMC apoptosis through the activation of calpain and the subsequent proteolysis of antiapoptotic X-chromosome-linked inhibitor of apoptosis (xIAP) (104).

Elastin governs VSMC proliferation, acts as a positive regulator of VSMC maturation, and modulates the VSMC phenotype toward a contractile state (140). A direct relationship between increased VSMC proliferation and decreased elastin levels has been reported in cultured VSMCs from supravalvular aortic stenosis and Williams-Beuren syndrome patients and elastin deficiency murine models (97, 136, 163). Li *et al.* found that loss of elastin leads to activation of mammalian target of rapamycin (mTOR) signaling, and that rapamycin inhibits VSMC proliferation and aortic obstruction in elastin-deficient mice (99). Supplementation of elastin-deficient VSMCs with tropoelastin increases the level of active RhoA and inhibits proliferation in a dose-dependent manner (85). The mechanism underlying the elastin-VSMC interaction may include interaction of the elastin C-terminal RKRK motif with integrin $\alpha_v\beta_3$ and the tropoelastin VGVAPG domain with G-protein coupled receptors (GPCRs) (47). In addition, elastin fibers sequester growth factors, such as latent TGF- β , and degradation of elastin fibers during hypertension releases fibrillin-1 from binding with latent TGF- β , thus enhancing the synthesis of collagen I, II, III, fibronectin, and CTGF *via* the activation of its downstream signaling effector Smad in VSMCs (Fig. 3). Recent studies have also elaborated on the roles of the elas-

tin degradation products, named elastin-derived peptides (EDPs), in hypertension. EDPs containing a GxxPG motif stabilize the type VIII β -turn conformation and exhibit bioactivity (13). EDPs bind to several cell surface receptors, including galectin-3 and integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$, but the most important signaling mediator is the elastin receptor complex (ERC), which consists of elastin binding protein (EBP), protective protein/cathepsin A (PPCA), and neuraminidase-1 (Neu-1) (8). EDPs bind to the ERC, promote VSMC proliferation through Gi activation, and amplify the elastin fragmentation effect (44, 121) (Fig. 3). Increased advanced glycation end products (AGEs) have been reported to promote proliferation of VSMCs *via* a reduction in cathepsin D and upregulation of Bcl2-associated athanogene 3 (BAG3) (96, 110). Proteases involved in ECM degradation also regulate VSMC proliferation and migration. Active MMP-2 cleaves calponin-1 in VSMCs to switch their phenotype to a dedifferentiated state and increases the phosphorylation of ERK1/2 to induce cell proliferation (26, 108).

The adhesive glycoprotein fibronectin builds connections between the ECM and VSMCs *via* $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrin receptors. VSMCs cultured on mechanical gradients coated with fibronectin undergo durotaxis toward stiffer regions (63). Fibronectin-splice variant containing extra domain A (Fn-EDA) drives integrin- and Toll-like receptor 4 (TLR4)-dependent VSMC proliferation and migration through activation of the focal adhesion kinase (FAK)/Src and Akt1/mTOR signaling pathways (81). Heparin, a major glycosaminoglycan component in the vascular ECM, maintains the contractile SMC phenotype and inhibits VSMC proliferation through blocking G1-to-S-phase transition *via* p27kip1-mediated inhibition of cyclin-dependent kinase 2 activity (49). Perlecan, a heparan sulfate PG expressed mainly in

FIG. 3. Elastin degradation and vascular cell behaviors. Degradation of elastin exposes VSMC to bioactive molecules including TGF- β and EDPs, contributing to the increased VSMC proliferation and ECM synthesis. EDP, elastin-derived peptides; ERC, elastin receptor complex; TGF- β , transforming growth factor- β . Color images are available online.

BMs, inhibits VSMC proliferation by sequestering fibroblast growth factor-2 (FGF-2) (106), whereas versican, a chondroitin sulfate PG, stimulates VSMC proliferation (72). TSP-1 induces VSMC migration and proliferation by modulating the function of miRNA-21, and enhances VSMC phenotypic switching (141, 154). OPN stimulates VSMC proliferation *via* epidermal growth factor receptor (EGFR)-mediated activation of the AP-1 and C/EBP β pathways (94). Cyr61/CTGF/NOV (CCN) proteins are a family of secreted matricellular proteins that control cell adhesion, growth, and differentiation. CCN1 stimulates VSMC adhesion and proliferation through interaction with $\alpha_6\beta_1$ integrin and heparin sulfate PGs (1), and CCN4 enhances the adhesion and migration of VSMCs *via* binding to integrin $\alpha_5\beta_1$ (105).

ECM remodeling, inflammation, and oxidative stress

Increased evidence has identified inflammation as a key mechanism underlying vascular cell dysfunction and arterial damage in hypertension (60). Studies have demonstrated increased plasma levels of C-reactive protein (CRP), interleukin (IL)-6, IL-1 β , and tumor necrosis factor- α (TNF- α) in hypertensive patients (7). Hypertension is associated with the infiltration of immune cells and the release of proinflammatory cytokines by activated T cells in vascular walls, which contribute to vascular remodeling (59). Xu *et al.* found collagen deposition and inflammatory cell infiltration at the early stage of hypertension in a two-kidney, one-clip rat hypertension model (179). During hypertension, MMPs degrade the ECM to facilitate the migration and recruitment of inflammatory cells and cleave cell surface receptors and other non-ECM molecules to mediate the adhesion, proliferation, and apoptosis of cells in the vessel wall; these events

are involved in the inflammatory process (170). Frolova *et al.* revealed that TSP-4 promotes the adhesion and migration of macrophages by activating ECs and interacting with macrophages in a β_2 and β_3 integrin-dependent manner (55). An *in vitro* study revealed that TNC enhances macrophage migration and activates the NF- κ B-related proinflammatory pathway *via* integrin $\alpha_v\beta_3$ (149). The N-terminal OPN fragment, a product of OPN proteolysis by thrombin and MMPs, correlates with increased inflammation severity in carotid plaques in patients with hypertension (2). The involvement of OPN in hypertension-related inflammation and remodeling is further evidenced by the finding that the early macrophage infiltration into the arterial wall in response to hypertension is blunted in OPN-deficient mice (22).

Oxidative stress refers to the excessive generation of reactive oxygen species (ROS), and its role in the pathogenesis of hypertension has been elucidated (139). Elevated expression and activity of LOX during hypertension have also been reported to incidentally enhance oxidative stress (113). TSP1 binding to CD47 leads to the phosphorylation of NADPH oxidase subunit p47 and the subsequent activation of Nox1, thus triggering the generation of superoxide and the impairment of arterial vasodilatation (30). CCN1 induces mitochondrial production of ROS through binding to $\alpha_v\beta_5$ and $\alpha_6\beta_1$ integrins and the heparin sulfate PG syndecan-4 during TNF- α -induced apoptosis in fibroblasts (28). Periostin inhibits glucose-induced ROS production by upregulating heme oxygenase-1 and preserving mitochondrial function in ECs (189). Although above evidence increasingly reveals the modulation of vascular ECM on ROS production, the interaction between ECM remodeling and oxidative stress in the pathogenesis of hypertension is still limited and needs to be further augmented.

Diagnostic and Therapeutic Relevance of the ECM in Hypertension

ECM alterations after antihypertensive treatment

Although the mechanisms of traditional antihypertensive medications, including angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), beta blockers, diuretics, *etc.*, are well clarified, their influence on vascular ECM remodeling is not fully understood. A series of studies revealed that treatment with ACEIs, ARBs, CCBs, and diuretics contributes to downregulation of MMP-2/9 in hypertension patients and rodent models (69). However, in some cases, plasma MMP-2 and MMP-9 levels are elevated by felodipine (CCB) and amlodipine (CCB) treatment, respectively (187, 188). Patients with essential hypertension who were treated with candesartan cilexetil (an ARB) show attenuated arterial stiffness, accompanied by a significant decrease in serum procollagen type III propeptide and an increase in serum MMP-3 levels (142). In addition, SHR treated with a combination of verapamil (CCB) and trandolapril (ACEI) showed a reduced collagen content, increased carotid artery fibronectin expression, and a significant increase in arterial distensibility (88). Notably, some ECM alterations are specific to certain treatments. For instance, serum TSP-1 levels in hypertensive patients are upregulated by treatment with perindopril (ACEI) but not other kinds of antihypertensive drugs, suggesting that TSP-1 could be a specific biomarker for ACEI efficacy (18, 19). Several nonclassical therapeutic strategies have also been used in preclinical studies. Cyclooxygenase (COX)-2 inhibitors, such as celecoxib or rofecoxib, showed protective effects in mice with Ang II-induced hypertension, and these effects were accompanied by reduced collagen deposition and an increase in the fenestrated area of the IEL (4). In addition, in SHR, upregulation of Fibulin-3 and MMP-2/9 is associated with hypertension and is inhibited by Xuezhikang, a traditional Chinese medicine extracted from red yeast rice (101). Treatment of brown Norway rats with the potassium channel openers minoxidil or diazoxide for 10 weeks elevated the elastic fiber content in the aortic media (150).

Targeting ECM for hypertension prediction and therapy

In a large multiethnic study, Duprez *et al.* found that the collagen biomarkers PIIINP and ICTP predicted the development of hypertension during a median time interval of ~10 years (45). Another study including 595 nonhypertensive Framingham Offspring Study participants demonstrated that increased serum concentrations of TIMP-1 and MMP-9 are associated with BP progression on follow-up (34). Studies on the role of ECM biomarkers in hypertension development and complications deserve more attention. Although current antihypertensive drugs are appropriately applied, their efficacy in some patients is not satisfactory. Thus, discovering new therapeutic strategies is of great importance. As shown in Table 3, altered ECM components could serve as pathogenic factors for vascular dysfunction and drivers of hypertension development or play an antihypertensive role, indicating that ECM proteins and proteases could be potential targets for antihypertensive treatment. Considering the complexity of the ECM, targeting a specific

ECM protein might be a biased and invalid approach. Thus, progress has been made toward ECM protease regulation in hypertension. In the 2K-1C hypertensive rat model, treatment with doxycycline, a nonselective MMP inhibitor, ameliorates hypertension, reverses impaired vasorelaxation, and prevents alterations in the vascular structure (25). In addition, MMP inhibition by GM6001 could reduce type I collagen deposition, and increase elastin in intrarenal vessels and attenuate adverse renovascular remodeling in hypertensive Dahl/SS rats (135).

Conclusions and Perspectives

Although exploration of the pathological mechanisms underlying hypertension has profoundly progressed in recent decades, knowledge on the dynamic alterations in the vascular ECM remains limited. It is unclear whether vascular ECM remodeling is a cause or result of hypertension, but evidence from human and animal studies, as discussed in this review, suggests that vascular ECM remodeling leads to the development of hypertension. In this review, we hypothesize that ECM remodeling in the component profiles, mechanical properties, degradation processes, and degraded fragment production leads to subsequent vascular wall structural and functional remodeling and results in hypertension. In further research, the application of matridomic and degradomic approaches may provide evidence for the identification of diverse ECM components. A better understanding of vascular matrix biology and the intricate mechanisms underlying hypertension may provide new insights into the development of antihypertensive strategies.

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Abbreviations Used

ACEIs = angiotensin-converting enzyme inhibitors
ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs
Ang II = angiotensin II
AP-1 = activator protein-1
ARBs = angiotensin receptor blockers
BM = basement membrane
BP = blood pressure
CCBs = calcium channel blockers
CCN = Cyr61/CTGF/NOV
C/EBP β = CCAAT-enhancer-binding protein β
CTGF = connective tissue growth factor
DOCA = deoxycorticosterone acetate
EC = endothelial cell
ECM = extracellular matrix
EDPs = elastin-derived peptides
ERC = elastin receptor complex
ERK1/2 = extracellular signal-regulated kinase 1/2
HF = heart failure

Abbreviations Used (Cont.)

ICTP = carboxy-terminal telopeptide of type I collagen
IEL = internal elastic lamina
IL = interleukin
LOX = lysyl oxidase
MAPK = mitogen-activated protein kinase
MMPs = matrix metalloproteinases
mTOR = mammalian target of rapamycin
NF- κ B = nuclear factor- κ B
NLRP3 = NOD, LRR, and pyrin domain-containing protein 3
NO = nitric oxide
OPN = osteopontin

PG = proteoglycan
PICP = procollagen type I C-terminal propeptide
PWV = pulse wave velocity
ROS = reactive oxygen species
SHR = spontaneously hypertensive rats
SHR-SP = stroke-prone spontaneously hypertensive rats
SMC = smooth muscle cell
TGF- β = transforming growth factor- β
TIMPs = tissue inhibitors of metalloproteinases
TNC = tenascin C
TNF- α = tumor necrosis factor- α
TSPs = thrombospondins
VSMC = vascular smooth muscle cell
YAP = Yes-associated protein