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Review Article

Hypertension, Mechanical Force, and Renal Disease

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Abstract

Hypertension or high blood pressure is a major public health problem and a leading cause of disability and death in the world. Mechanical forces generated from blood pressure and blood flow are responsible for cell metabolism, growth, proliferation, migration, differentiation, and morphology, but also lead cell detachment, injury, and apoptosis. Mechanical force-induced apoptosis could damage various organs including the heart, kidneys, lungs, brain and other vasculatures, and cause different pathogenesis such as premature vascular, renal and cardiovascular mortalities. One-quarter of the world's adult population has hypertension, and the increasing economic burden of hypertension has been attributed to economic progress lagging in the developing countries and quality of life in the developed countries. In this review, we summarize the recent progresses in understanding the molecular mechanisms of hypertension and renal pathogenesis, and exploring the regulation of signaling network in mechanical force stimulation. These advances have significantly increased our understanding of the connection between hypertension-mechanotransduction and mechanical stress-pathogenesis, and lead us to search for novel potential targets and strategies in the treatment of hypertension and other related diseases.

ABBREVIATIONS

AII: Angiotensin II; AT_1: AII receptor type 1; AP-1: Activator Protein-1; CNP: c-type Natriuretic Peptide; COX: Cyclooxygenase; ECM: Extracellular Matrix; Egr-1: Early growth response gene-1; ENaC: Epithelial Sodium Channel; ERK: Extracellular Signal-regulated Kinase; ET-1: Endothelin-1; FAK: Focal Adhesion Kinase; G: G protein; GADD 153: Growth Arrest and DNA Damage-inducible gene 153; GEF: Guanine nucleotide Exchange Factor; GFs: Growth Factors; GPCRs: G Protein Coupled Receptors; HIF: Hypoxia-inducible Factor; ICAM: Intercellular Adhesion Molecule; IGF: Insulin-like Growth Factor; IL: Interleukin; JNK: c-Jun N-terminal protein Kinase; MAPK: Mitogen-activated Protein Kinase; MCP: Monocyte Chemotactic Protein; MMP: Matrix Metalloproteinase; MS: Mechanical Sensitive; mTOR: Mammalian Target of Rapamycin; NOS: Nitric Oxide Synthase; PCNA: Proliferation Cell Nuclear Antigen; PI-3K: Phosphatidylinositol-3 Kinase; PKA: Protein Kinase A; PKB: Protein Kinase B; PKC: Protein Kinase C; PLA_2: Phospholipase A_2; PLC: Phospholipase C; PLD: Phospholipase D; PTKs: Protein Tyrosine Kinases; REB: Response Element-Binding Protein; RGS: Regulator of G protein Signaling; RTK: Receptor Tyrosine Kinase; SGK: Serum-Glucocorticoid-induced protein Kinase; SM22: Smooth Muscle cell specific protein; SOD: Superoxide Dismutase; THA2: Thromboxane Synthase A2; TLR: Toll Like Receptor; TNF: Tumor Necrosis Factor; T-PA: Tissue Plasminogen Activator; TRAAK: TWIK-Related Arachidonic Acid-stimulated K^+ channel; TREK: TWIK-Related K+ channel; TRP: Transient Receptor Potential; VCAM: Vascular Cell Adhesion Molecule.

INTRODUCTION

Hypertension or high blood pressure is a chronic medical condition characterized by a sustained increase in vasoconstriction and attenuated vasodilation in the face of elevated mechanical stress in the blood vessel wall [1]. This requires the heart to work harder than normal to circulate blood through the blood vessel, and generates more mechanical force pushing against the blood vessel wall. Mechanical forces are responsible for the modulation of blood vessel size and morphology in the development and for the regulation of cell signaling network in cell metabolism, growth, proliferation, migration, differentiation, detachment, injury, and apoptosis [2-4]. Hypertension is a progressive cardiovascular syndrome that can damage various organs including the heart, kidneys, lungs, brain and other vasculatures, and lead to premature morbidity and death [1-6]. The relationship between hypertension and chronic kidney disease remains enigmatic and a matter of considerable clinical and academic interest with evidence supporting that hypertension is both a cause and a consequence of chronic kidney disease [3-7]. On the one hand, high blood pressure predicts end-stage renal disease in diabetic and nondiabetic patients [5-7]. On the other hand, renal malfunction predicts later onset of hypertension [7,8]. In this brief review, we discuss how mechanical forces generated by high blood pressure

and fast blood flow in hypertensive condition regulate signaling networks to modulate cellular function, and lead to chronic kidney disease.

Hypertension and mechanical force

The vascular wall is an integrated functional component of the circulatory system. Hypertension leads to a chronic increased mechanical force on the vessel wall due to high blood pressure and fast blood flow [1,2]. To adapt to increased mechanical forces, vascular endothelial cells, vascular smooth muscle cells, and the surrounding environment undergo structural and functional changes known as vascular remodeling. Multiple mechanisms underlie the remodeling process, including increased expression of humoral factors and their receptors, adhesion molecules, integrins and their receptors, and many enzymes as well as related proteins [9,10]. The remodeling process appears to collaborate and interact in the response to pressure elevation. The most relevant mechanical forces that influence vessel size and morphology are shear stress, circumferential stress, and axial stress [11,12].

Shear stress is the tangential force that a fluid (blood) exerts parallel to the vessel surface due to friction of the blood against the vessel wall. Circumferential stress describes the perpendicular force that the intraluminal pressure applies on the vessel wall. Axial stress in blood vessels is defined by the exerted longitudinal force, vessel radius, and wall thickness and governs length adaptations. Many commercially available devices have been used *in vitro* cell models to study the effect of different mechanical forces on cell responses. Exposure of cells cultured as a monolayer to these instruments (Flexercell strain unit with a uniaxial circular well device, a linear stretching tub, biaxial cyclic cell strain devices, aparallel-plate flow channel and perfused transcapillary co-culture system) provides different patterns of mechanical forces.

Upon long-term exposure to blood pressure and blood flow, the structural and functional properties of vessels are modified to accommodate these changes in pressure by vascular remodeling [10,13]. This remodeling encompasses increased cell growth, proliferation, migration, differentiation and apoptosis, as well as alteration of the extracellular matrix (ECM) and vessel wall shape and composition [10-13]. This remodeling also enables arteries to withstand the increased pressure load. Consequently, arteries become more rigid and have a reduced compliance than in their native state, which decreases their ability to dampen the cyclic changes in blood pressure [10]. The progressive stiffening ultimately results in altered gene expression, signal transduction and cell functions, and causes various clinical complications [4-14]. A raised peripheral resistance due to harder and more rigid arteries leads to more severe hypertension and hypertension-induced changes in different levels.

The kidneys are one of the key organs affected by mechanical forces in hypertension patients. The glomerulus is a highly specialized structure that is the site of plasma ultrafiltration and urine production. The glomerular capillary wall, composed of glomerular endothelial cells, glomerular basement membrane, and glomerular epithelial cells (podocytes), is exposed to mechanical forces *in vivo* arising from capillary blood pressure and blood flow. Podocytes, consisting of a cell body, major processes and foot processes interlinked by slit diaphragms, may experience lateral stretch as a capillary dilates, force perpendicular to the plane of the basement membrane (vertical traction) as they balloon in response to increased filtrate flow, or shear force from increased filtrate flow [15,16]. In mechanically stressed podocytes, the processes of podocytes become thinner and more elongated, whereas the cell body size decreases. Through an actin-based contractile apparatus, podocytes counterbalance pressure within the underlying capillary to prevent outward ballooning of the vessel and to preserve the normal architecture of the cells [15-18]. How do the mechanosensitive cells convert physical stimuli to biochemical signals?

Mechanical force regulates signaling network

As blood flows, cells on the vascular wall are constantly subjected to mechanical forces that appear to activate the same signaling pathways that are activated by hormones, growth factors, and inflammatory mediators. Mechanical stimuli can cause many important physiological responses which regulate cell functions in the chronic remodeling and development of organs. Changes in blood pressure and flow rate, such as hypertension, generate altered haemodynamic forces, and have been strongly implicated in the pathogenesis of cardiovascular disease and many other diseases [1,2]. Mechanical forces are sensed at the cell surface by sensors such as receptors, receptor tyrosine kinase (RTK), ion channels, and ECM-integrin complex, transduced through the cell by different signaling cascades, and activated different kinases or other enzymes that ultimately result in altered cell function (Figure 1) [19-23]. Although the molecular identity of the sensors has long remained elusive, it is clear that an increasing number of signaling pathways are involved in the responses to mechanical force.

Memebrane-mechanosensors

Mechanoreceptors: Cells are equipped with numerous receptors that allow them to detect and respond to micro-environment changes such as mechanical forces generated by blood pressure and blood flow. Exposure of vascular endothelial cells and smooth muscle cells to mechanical forces increase the synthesis of endothelin-1 (ET-1) and expression of ET receptor type B (ET_B receptor) [23]. In podocytes, mechanical forces induce angiotensin II (AII) secretion and AII type 1 (AT_1) receptor expression [24,25]. Both ET-1 and AII act through G protein coupled receptors (GPCR) to stimulate their downstream effectors. The regulation of blood pressure within the normal range requires precise kinetic control of GPCR signaling [26].

Many studies demonstrated that the levels of some growth factors and inflammatory mediators are also significantly increased when cells are exposed to mechanical forces [9,12-14]. Fluid shear stress differentially modulates the expression of genes encoding basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF) B chain in vascular endothelium and smooth muscle cells, and stimulates extracellular signal-regulated kinases (ERK) signaling pathway [27,28]. In human periodontal ligament cells mechanical stress induces immune response genes expression: cytokines (TNF-α, IL-1β), chemokines (IL-8, CCL-20), human β-defensin-2 and-3, and Toll-

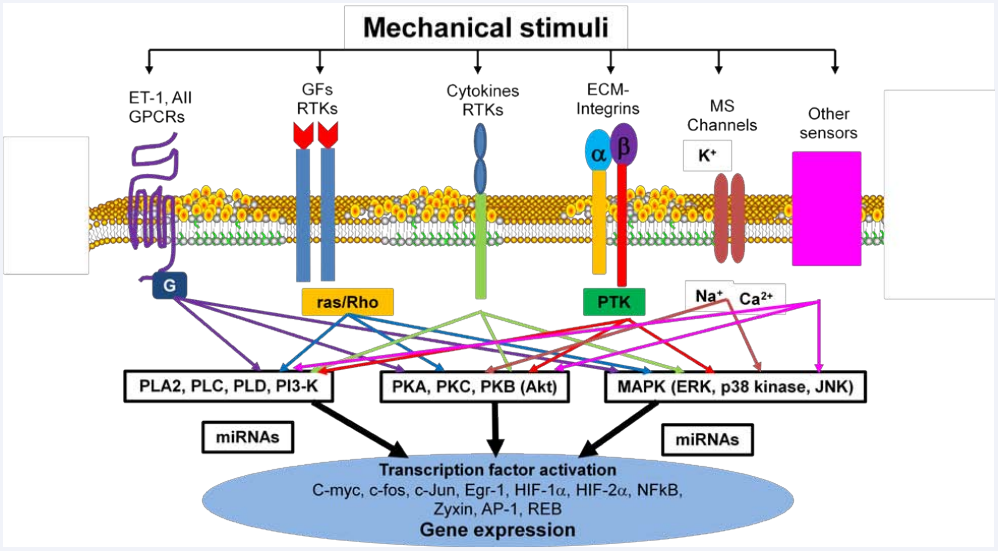

Figure 1 Schematic representation of cell mechanotransduction. Mechanical forces induce the activation of mechanical sensors on the plasma membrane which can convert physical stimuli to biochemical signals. As a result, these signals further activate different signal pathways which lead to regulate gene expression and to modulate cellular function.

like receptors (TLR-2 and TLR-4) in a force- and time-dependent manner [29]. In mouse models, physical force regulates fibrosis through inflammatory focal adhesion kinase (FAK)-ERK-monocyte chemotactic protein-1 (MCP-1) pathways [30,31]. Through their receptors, these growth factors and inflammatory mediators regulate cell growth, proliferation, differentiation and apoptosis via many different signaling pathways. Now, increasing evidence indicates that the activation of growth factor receptors and inflammatory mediator receptors in response to increased mechanical stress plays a critical role in cell signaling regulation of hypertension [32].

Integrin-extracellular matrix: Integrins exist as αβ pairings that interact with ECM components including fibronectin (ligand for α5β1and αvβ3), vitronectin (ligand for αvβ3), and laminin (ligand for α6β1). Many these components sense mechanical forces and their responses depend on specific integrin-ECM interactions [33-36]. Mechanical forces cause direct stretching of cell surface integrin binding sites. Force-induced conformational changes in the ECM may alter integrin structure and lead to activation of several signaling pathways within the cell [36]. Integrins connect the ECM to the cytoskeleton, and provide cells with mechanical anchorages and signaling platforms. Activation of these signaling pathways leads to altered regulation of genes that synthesize several enzymes and catabolize ECM proteins [9,10,13,14]. On the other hand, these pathways are also involved the deformation of gap junctions to alter cell-to-cell communications [37]. The increased intracellular Ca^{2+} concentration is associated with mechanical stimulation in the cell membrane and intercellular gap junctions [38].

Mechanosensitive ion channels: Mechanical forces cause a change in membrane potential of the cell resulting from the opening of mechanosensitive ion channels [39,40]. As mechano-electrical molecular switches, these channels convert mechanical forces exerted on the cell membrane into electrical or biochemical signals in physiological processes. Mechanosensitive ion channels exist in all cells, and respond to mechanical forces along the plane of the cell membrane. These channels can be either non-selective depolarizing, permeable to Na^+, K^+ and Ca^{2+}, or hyperpolarizing channels selective for K^+ [41]. For instance, recent work has identified and electrophysiologically characterized two members of a new family of two-pore-domain, weakly inward-rectifying K^+ channels: TWIK-Related K^+ channel (TREK) and TWIK-Related Arachidonic Acid (AA)-stimulated K^+ channel (TRAAK) [42]. TREK channels are polymodal K^+ channels (i.e. gated by a variety of chemical and physical stimuli) expressed in a variety of tissues, but are particularly abundant in the brain and heart. TRAAK is similar to TREK in that it can be activated by membrane tension and arachidonic acid. TRAAK is widely expressed in the brain, spinal cord, and retina, which indicates that it has a function wider than mechanotransduction in neuronal excitability [43]. The epithelial sodium channel (ENaC) belongs to the superfamily of amiloride-sensitive Na^+ channels of the transporting epithelia and degenerins (MEC/DEG channels), many of which are suspected to be directly gated by mechanical stimuli [44,45]. The MEC/DEG subfamily of degenerins is responsible for swelling-induced neuronal degeneration in nematodes. The subfamily includes the MEC-4, MEC-6 and MEC-10 proteins, which are thought to function as subunits of a mechanosensetive ion channel that might have a role in touch sensitivity [46,47]. Transient receptor potential (TRP) proteins constitute a large non-voltage-gated cation channel superfamily, activated polymodally by various physicochemical stimuli, and are implicated in a variety of cellular functions [48]. In mammals many TRP family members such as TRPC1, TRPC3, TRPC6, TRPM4, TRPM7, TRPN1, TRPA1, TRPY1, TRPP1, TRPP2, and notably, TRPV1, TPRV2 and TRPV4, have been reported to be involved in mechanotransduction [49]. TRPs are up-regulated in animal models of congestive heart failure or hypertension models [50]. TRPC6, TRPM6, and TRPP2 have been implicated in hereditary focal segmental glomerulosclerosis, hypomagnesemia with secondary hypocalcemia, and polycystic kidney disease, respectively [51]. In addition, TRPV5 contributes

to several acquired mineral dysregulations, such as diabetes mellitus, acid-base disorders, diuretics, immunosuppressant agents, and vitamin D analogues-associated Ca^{2+} imbalance, whereas TRPV4 may function as an osmoreceptor in the kidneys and participate in the regulation of sodium and water balance [52].

Intracellular transducers and effectors

G protein, Rho and GEF: Mechanical forces increase the levels of AII in podocytes [24,53] and ET-1 in vascular smooth muscle cells [23] and endothelial cells [54]. These hormones bind to their receptor to activate heterotrimeric G protein and to promote their signaling pathways. Mechanical stimuli also induce conformational changes of mechanosensitive proteins. Instead of mechanical-induced AII release, Zou et al. [53] demonstrated that mechanical stress activates AT_1 receptor without the involvement of AII in cardiomyocytes. The role of G protein in hypertension is also demonstrated by genetic studies. A genetic ablation of $G\alpha_q$ in mice has been shown to result in a cardiac malformation and craniofacial defects [55], whereas an overstimulation of the $G\alpha_q$ pathway in mice has been shown to result in the development of hypertrophic cardiomyopathy [56-58]. Regulator of G protein signaling 2 (RGS2) can selectivity attenuate $G\alpha_q$ signaling [59]. RGS2 knockout mice (RGS2+/- and RGS2-/-) exhibit a strong hypertensive phenotype, renovascular abnormalities, persistent constriction of the resistant vasculature, and prolong response of the vasculature to vasoconstrictors *in vivo* [60,61]. Many current pharmacological therapies of hypertension focus on the regulation of vascular resistance by blocking hormones such as catecholamines and AII to activate their receptors and G protein signaling.

Small GTPases such as the *ras* and Rho families are associated with actin-based cytoskeletal structure [62]. Rho proteins act as molecular switches to control cellular processes by cycling between an active GTP-bound state and an inactive GDP-bound state. Recent investigations have shown that shear stress mediates Rho-dependent cytoskeletal alignment and directional migration of the endothelial cells [63,64]. The inhibition of the Rho-associated kinase p160ROCK eliminates the shear-enhancement of migration speed [65]. We recently reported the role of Rho in mechanical force-activated renal epithelial phospholipase D [66]. All these data indicate that Rho, as a mechanosensitive motor, plays an important role in the regulation of cell function.

Some guanine nucleotide exchange factors (GEFs) specific for RhoA have been found to associate with the cytoskeleton and adhesions [67]. For example, vav2 was reported to be phosphorylated and activated in response to cyclic stretch in mesangial cells [68], and mechanical force activates RhoA through two GEFs, GEF-H1 and LARG in rat fibroblasts [69]. We recently found that mechanical force-activated phospholipase D is mediated by $G\alpha_{12/13}$-Rho [66]. It would be interesting to determine if p115RhoGEF activity is regulated by mechanical forces. Recent studies indicate that some RhoA GTPase activating proteins (GAPs) also play a role in the response to mechanical forces. In endothelial cells, shear stress regulates p190RhoGAP activity in a biphasic pattern [70].

Protein kinases: Cell mitogenic activities are stimulated by growth factors and other mitogens which are mediated through mitogen-activated protein kinases (MAPK) in the regulation of cell function. Exposure of cells to mechanical forces increases the release of several growth factors in the cells, and these growth factors further induce ERK activation [71,72]. Parallel to the ERK signaling pathway, mechanical forces also elevate the levels of endotoxin and cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL), and these stimuli activate p38 MAPK [73] and c-Jun NH_2-terminal protein kinases (JNK, also called stress-activated protein kinases) [74]. ERK activation enhances the phosphorylation of the transcription factor *Elk*1, the acetylation of core histone, and the expression of the *Elk*1 target gene, c-*fos* in the mediation of cell growth and proliferation, while JNK activation induces *c-Jun* phosphorylation in the regulation of cell programmed death.

A mechanical force-induced increase in cAMP content has been reported in fetal rabbit epithelial cells [75]. Increased cAMP concentration and induced protein kinase A (PKA) activation was also observed in lung tissues after partial pneumonectomy or mechanical ventilation [76]. Protein kinase B (PKB), also known as Akt, is a serine/threonine-specific protein kinase and a downstream effector of phosphatidylinositol-3 kinases (PI-3K). Mechanical stretch induces expression of insulin-like growth factor (IGF)-1 and its receptor, which activates IGF-1R/PI-3K/Akt in the regulation of proliferation of venous smooth muscle cells [77]. PI-3K/Akt pathway in mouse lung has significant protective effects in response to mechanical stress [78,79]. Protein kinase C (PKC) also controls the function of other proteins through the phosphorylation of their serine and threonine residues, and plays an important role in many of the pathologies of heart disease [80]. The activity of several major isozymes of PKC is regulated by the intracellular concentrations of free Ca^{2+} and diacylglycerol. Pulmonary arterial smooth muscle cells respond to mechanical force with a transient increase in inositol 1, 4, 5-trisphosphate and diacylglycerol leading to PKC activation [81]. PKCε induces dramatic alterations in muscle cell shape, leading to an overall increase in cell length, length-to-width ratio, and perimeter-to-area ratio [82,83].

Protein tyrosine kinases (PTKs) are enzymes that catalyze the phosphorylation of tyrosyl residues. Two classes of PTKs are present in cells: the transmembrane receptor tyrosine kinases (RTKs) and the nonreceptor PTKs [84]. RTKs are induced by a large growth factor family, which enhance receptor catalytic activity or provide docking sites for downstream signaling proteins [85]. Many RTKs, including receptors for EGF, FGF, IGF and PDGF, have been proposed as mechanoreceptors in a variety of tissues [86,87]. Nonreceptor PTKs (e.g. FAK and c-Src) represent cellular enzymes that have intrinsic kinase activity but do not possess an extracellular domain. Both FAK and c-Src mediate cell migration by promoting membrane protrusion and focal adhesion turnover utilizing several signaling pathways. Desai et al. reported that mechanical stretch decreases FAK phosphorylation and reduces cell migration in airway epithelial cells [88]. We recently demonstrated that shear stress induces cell apoptosis via a c-Src in the cultured podocytes [89]. Shear stress also regulates endothelial nitric oxide synthase (NOS) expression through c-Src [90].

Other enzymes: Mechanical forces have been documented to stimulate phospholipase A_2 leading to lung inflammation and acute lung injury [91]. Exposure of rat lung cells to mechanical strain activates phospholipid turnover via phospholipase C, followed by PKC activation in the regulation of cell proliferation [92]. Mechanical stress stimulates phospholipase C activity and elevates intracellular calcium ion levels in neonatal rat cardiomyocytes [93]. Shear stress induces cell apoptosis via a c-Src-phospholipase D-mTOR signaling pathway in the cultured podocytes [89]. Mechanical stimulation of skeletal muscle induces phospholipase D activation, PA accumulation, and mTOR signaling [94]. Mechanical forces stimulate membrane phospholipid metabolism through different enzymes to generate several bioactive lipid molecules, which is the key step of the conversion of mechanical stimuli to biochemical signals in the cells [94,95]. Metabolism of the ECM and reorganization of the cytoskeleton are also responded to mechanical stimulation [9-14].

Nucleus where mechanical forces regulate gene expression

There are many studies supporting that mechanical forces provide an important context for cell growth and differentiation, tissue genesis and maintenance, and organ development and function. All these processes depend on the regulation of signaling networks in the cells [9-14,19-22]. At the molecular level, mechanical forces can regulate a variety of gene expression [9,14]. During development, mechanical forces cause changes in size, shape, number and position of cells by regulating cell growth, proliferation, differentiation, and polarity, and lead to organ development by coordinating cell-cell interactions, tissue spreading, compression, condensation, and self-organization [9-14,19-22,97]. These changes are therefore integral to any morphogenetic processes. The key in these processes is that mechanical forces modulate gene expression at the molecular level and regulate growth, proliferation, differentiation, migration and apoptosis at the cellular level.

The genes encoding for many proteins including vasoactive substances, growth factors, adhesion molecules, chemoattractant molecules, coagulation factors, antioxidant factors, and proto-oncogenes can respond to mechanical force stimulation by modulating mRNA levels during tissue morphogenesis and pathophysiology such as hypertension [9,14]. Although mechanical force induced gene expression has been studied for many years, significant progress has been made only due to microarray technology [28,29]. The technique enables simultaneous measurement of the transcriptional response of thousands of genes.

Exposing *in vitro* cultured cells to mechanical forces generated by different commercial available devices and analyzing the changes with microarray technology, we can profile gene expression in response to mechanical forces. Gene expression is modulated by specific transcription factors (e.g. *c-myc, c-fos, c-Jun*, Egr-1, AP-1, SP-1 and NF-κB/Rel) that bind to their target sequences in the promoter region of the gene. Using reporter systems, many laboratories have discovered mechanical force-inducible transcription factors, they are *c-fos, c-Jun,* HIF-1α and 2α, Egr-1, AP-1, SP-1, NF-κB/Rel, Zyxin, and REB [9,14,97,98], and these transcription factors are involved in force-induced gene expression. Mechanical forces increase the levels of AII, ET-1, different growth factors (EGF, FGF, PDGF, VEGF and TGF), nitric oxide, IL-6 and 8, CD44, TNF-α, and tissue factor [9,98]. As agonists, these products can stimulate different signaling pathways in the regulation of the cell signaling networks.

Mechanical forces also modulate the mRNA levels of different receptors (AT_1 receptor and ET-B receptor), ECM-integrin-cytoskeleton components (collagen, fibronectin, vitronectin, ICAM, VCAM, MCP, MMP, integrin, tensin, paxillin, actin, desmin, and calponin) and downstream effectors (COX-1, COX-2, SOD, FAK, catalase, SGK, NOS, and THA-2) as well as many other proteins (PCNA, GADD-153, SM22-a, CPR, MCP-1, t-PA, CNP, prostacyclin, adrenomedulin, thrombomodulin and tenasin) [9,98]. Gene expression modulated by mechanical forces is also affected by different forms and magnitudes of forces. Laminar pulsatile flow and non-laminar disturbed flow leads to different gene expression profiles [97-99]. Some gene expression is increased at low shear stresses but decreased by moderate and high shear stresses [9,98]. Modulation of gene expression and activation of many enzymes in response to mechanical force stimulation play important roles in signaling networks and in the regulation of cellular functions.

Recent studies demonstrated that microRNAs (miRNA), small noncoding RNAs, participate in the regulation of gene expression by interacting with the 3′-UTR of the target mRNA. This interaction results in mRNA degradation and/or inhibition/activation of protein translation [100]. Turczyńska et al. reported that miRNA-145 is essential for stretch-induced L-type calcium channel expression in vascular smooth muscle contractile differentiation [101]. MiRNA-146a is also a mechanosensitive miRNA that is rapidly up-regulated by oscillatory pressure and plays an important role in regulating mechanically induced inflammation in lung epithelia [102]. Stretch-induced activation of AMPK in vascular smooth muscle is in part regulated by reduced levels of miRNA-144/451 [103]. MiRNAs appear to play an important role in cell signaling regulated by mechanical forces. Altering miRNA expression levels can prevent and even reverse the acquisition of cell synthetic phenotype *in vivo*, thereby implicating miRNAs as exciting future therapeutic targets for vascular proliferative disease.

Mechanical forces play an important role in the regulation of cell signaling networks, however, which signaling pathway could be activated and how many signaling pathways would be activated are dependent on cell types, cell states (development or pathogenesis) and force patterns. On the other hand, mechanical forces lead to the alteration of agonists, receptors, transducers and downstream effectors, these changes could show cross effect in the regulation of cell signaling networks. Meanwhile, mechanical forces induce different signaling pathways at different time frames such as channels and PI-PLC activation in seconds, protein phosphorylation in minutes and gene expression in hours. This complex system remains largely unknown.

Hypertension and chronic kidney disease

Hypertension represents a complex, multifactorial disease and contributes to the major causes of morbidity and mortality

in industrialized countries: ischemic and hypertensive heart disease, stroke, peripheral atherosclerosis and renal failure [1,4,104]. Under hypertensive conditions, mechanical stress induces the damage of podocytes which leads to cell hypertrophy, foot process effacement, cell body attenuation, pseudocyst formation, cytoplasmic overload with reabsorption droplets, and, finally, detachment from the glomerular basement membrane [105,106]. Following podocyte loss, the inability of podocytes to proliferate contributes to the development of glomerulosclerosis [15,17]. With loss of nephron mass, intraglomerular pressure increases and resident glomerular cells are exposed to increased mechanical forces. Glomerular capillary hypertension perpetuates further damage to resident podocytes, alters glomerular haemodynamics, fails to serve as a glomerular filtration barrier, and leads to proteinuria and progressive loss of kidney function resulting in glomerulosclerosis and end-stage renal failure [16,107-110].

Diabetic nephropathy is the most common cause of progressive chronic kidney disease in the developed countries. It is thought to result from interactions between metabolic (hyperglycaemia) and haemodynamic (glomerular hypertension) factors [107,111-114]. High glucose activates different signaling pathways within diabetic renal tissues. These signaling pathways induce oxidative stress, polyol pathway flux, hexosamine flux and accumulation of advanced glycated end-products as well as significant increases in angiotensinogen, AII and AT_1 receptor levels. Many of these signaling pathways also regulate podocyte apoptosis [112-114]. There is evidence from human disease that the number of podocytes is significantly reduced in both type 1 and type 2 diabetic patients [112-117]. Forces increases and damages resident glomerular cells

The mechanical properties of tissues and cells are commonly characterized by measuring their elasticity, their recoverable deformation in response to a force. Recently, many examples from clinical and whole animal studies have shown that changes in tissue stiffness are related to specific disease characteristics [118]. Using atomic force microscopy and a new technique, capillary micromechanics, to measure glomerular biomechanics in normal and two disease mouse models [$Col4a3^{-/-}$ mice (Alport model) and $Tg26^{HIV/nl}$ mice (HIV-associated nephropathy model)], one report demonstrated that the glomeruli from both disease models exhibited significant mechanical abnormalities (reduces 30% stiffness, the diseased renal glomeruli are getting soft) and were significantly more deformable than normal glomeruli [119]. This increased deformability of glomeruli could directly contribute to disease by permitting increased distension with haemodynamic force or represent a mechanically inhospitable environment for glomerular cells.

In summary, hypertension is a major risk factor for stroke, heart attacks, heart failure, aneurysms of the arteries (e.g. aortic aneurysm), peripheral arterial disease, and is a cause of chronic kidney disease. Hypertension-related nephrosclerosis is a top cause of progressive renal damage and failure. Hypertension-caused injury of podocytes; loss of nephron mass, proteinuria and progressive loss of kidney function are an accompanying modulation of different gene expression and signaling activation. Understanding the molecular mechanism of hypertension and podocyte injury has high potential to identify novel target(s) for pharmacologic consideration and to search for new therapeutic strategies for patients with hypertension and renal disease.

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