

## Angiotensin II induces inflammation leading to cardiac remodeling

Lixin Jia<sup>1,2</sup>, Yulin Li<sup>1</sup>, Chuanshi Xiao<sup>2</sup>, Jie Du<sup>1</sup>

<sup>1</sup>The Key Laboratory of Remodeling-related Cardiovascular Diseases, Capital Medical University, Ministry of Education, Beijing Institute of Heart Lung and Blood Vessel Diseases, Beijing Anzhen Hospital Affiliated to the Capital Medical University, Beijing 100029, China, <sup>2</sup>Department of Cardiology, the Second Hospital of Shanxi Medical University, Taiyuan, 030001, Shanxi, China

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### 1. ABSTRACT

Hypertension, especially for elevated renin-angiotensin II (Ang II), induces cardiac fibrosis and remodeling. Ang II, acting via its receptors, causes both hemodynamic and nonhemodynamic effects. These effects trigger a series of inflammatory responses. Recent studies have demonstrated that hypertension stimulates infiltration of leukocytes into heart, and interaction among macrophages, T cells, and monocytic fibroblast precursor cells regulates the imbalance of pro-inflammatory and anti-inflammatory factors. Several studies have demonstrated that the inflammatory microenvironment in hypertensive heart promotes a forward feedback infiltration of leukocytes, differentiation of monocytes, and formation of myofibroblasts. An increased number of myofibroblasts, the dominant source of extracellular matrix production, results in deposition of collagen and cardiac remodeling. A thorough understanding of the pathological process underlying hypertension-induced cardiac remodeling may help in prevention and treatment.

### 2. INTRODUCTION

The dysregulated renin-angiotensin system (RAS) plays a key role in the development of cardiovascular diseases. Angiotensin II (Ang II), a core effector of RAS, is a multifunctional peptide with pleiotropic actions, modulating vasomotor tone, cell growth, senescence, apoptosis, migration and extracellular matrix (ECM) deposition (1). The increase in angiotensin converting enzyme (ACE) activity and concentration of Ang II causes inflammation. Ang II has an important proinflammatory effect on cardiovascular diseases by triggering vascular damage, inducing adhesion molecule activity, recruiting inflammatory cells, increasing cytokine expression and repairing tissue. The physiological effects of Ang II are mediated by Ang II receptor subtype 1 (AT1R), which is widely distributed in many organs. Cardiopathological fibrosis, including accumulation of ECM, is a final fate of various CVDs, leading to increased ventricular stiffness, with diastolic function failure and then systolic cardiac dysfunction (2,3). ACE inhibitor (ACEI)

and Ang II receptor blocker (4) slow down the development of left ventricular remodeling (2). Recent studies have demonstrated that inflammation is involved in the whole process of cardiac fibrosis. The present review focuses on the key inflammatory events linking Ang II-induced inflammation and cardiac fibrosis.

### 3. ANG II AND INFLAMMATION

Ang II infusion stimulates the expression of P-selectin, L-selectin, and E-selectin and P-selectin expression via AT1. Increased vascular permeability occurs as a direct consequence of pressure-mediated mechanical injury to the endothelium. Increased vascular permeability expands endothelial gaps and the intracellular junction. Adhesive leukocytes on the endothelium begin to transmigrate into tissue. Shulman *et al.* found that Ang II stimulates the synthesis and secretion of vascular permeability factors, also known as vascular endothelial growth factor (VEGF), in patients with glomerular diseases, primarily through the AT1R on vascular smooth muscle cells (VSMCs) and endothelial cells (ECs). VEGF regulates angiogenesis, vascular permeability and inflammation, independent of Ang II-induced increase in blood pressure change. Through a set of intracellular signaling pathways, Ang II induces vascular endothelial injury and dysfunction. For example, Ang II activates NADPH oxidase, generates oxidative stress and nitrogen species, and triggers DNA breakage in endothelium (5). In a Dahl salt-sensitive hypertensive rat model, Ang II activated the endothelial apoptotic pathway, endothelial nitric oxide synthase (eNOS) uncoupling, in hypertensive heart failure (6). In clinical trials, blocking Ang II effects by Ang II receptor blocker (ARB) reduced vascular endothelial damage (7). Using intravital microscopy, Alvarez *et al.* found that after Ang II infusion in rat arterioles, the inflamed endothelium expressed adhesion molecules and cell adhesion molecules and caused release of mediators such as selectin, cell adhesion molecules and integrins, intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (8). Ang II treatment stimulated these adhesion molecules moving to the surface and initiated a series of pathological processes. The process included leukocyte adhesion and transmigration. Selectins, lectin-like molecules, present on leukocytes (L-selectin), ECs (E-selectin) and platelets (P-selectin), are involved in rolling of leukocytes. Ang II infusion stimulates the expression of P-selectin, L-selectin, and E-selectin expression via AT (9). In addition, Larsson *et al.* reported that intravenous infusion of Ang II in healthy volunteers elevated arterial blood pressure and activated platelets (10); platelet-leukocyte interactions promoted mutual cell activation and facilitated the secondary capture of leukocytes (11). Selectins also prime leukocytes for integrin-mediated leukocyte adhesion. Wang *et al.* found impaired leukocyte adhesion in P-selectin-deficient mice, which was rescued by soluble P-selectin mediated by the P-selectin glycoprotein ligand 1 pathway (12). Integrin is essential for cell interaction and cell communication. Upregulated and activated integrin increases its affinity to adhesion molecules, thus resulting in firm adhesion between ECs and leukocytes. In cultured VSMCs. Using a

co-culture system, Ieda *et al.* found that embryonic cardiac fibroblasts regulated myocardial proliferation in a paracrine fashion through integrin-1 $\beta$  signaling (13). Ang II also acts as an autocrine fashion, a recent study used transgenic mice with cardiac-specific expression of a transgene fusion protein that releases Ang II from cardiomyocytes (Tg-ANG II) and found that, in animals with hypertension, cardiac Ang II, acting via AT1R, enhances inflammation, oxidative stress, and cell death, contributing to cardiac fibrosis (14).

### 4. ANG II AND CHEMOKINES

Leukocytes move towards the injury site along the chemical gradient. Chemokines, with low-molecular-weight protein, induce leukocyte trafficking. Chemokines, mostly involved in inflammation and remodeling, are subdivided into 4 families (CC, CXC, XC, CX3C). In CC chemokines, the first 2 cysteines are adjacent to each other, whereas in the CXC chemokines, one amino acid separates the first 2 cysteine residues. Infusion of Ang II in rats stimulates the production of various chemokines (15,16). Ang II can induce leukocyte infiltration into hearts, which generates and releases CC and CXC chemokines (2,16,17). Monocyte chemoattractant protein (MCP-1/CCL2) plays a key role in regulating monocyte and T-lymphocyte recruitment. Moreover, an ACE inhibitor or ARB reduced macrophage infiltration by inhibiting MCP-1 production. Haudek *et al.* reported that Ang II-infusion-induced cardiac fibrosis required the induction of MCP-1, which modulated the uptake and differentiation of a bone-marrow-derived monocyte fibroblast precursor population (18). Angiogenesis, the growth of new blood vessels, is a critical biological event that occurs during chronic inflammation and vascular remodeling (19,20). Strieter *et al.* showed that CXCL8 regulated vascular remodeling by modulating angiogenesis in pulmonary fibrosis (21). Two pairs of distinct chemokine-chemokine receptors, known as MCP-1/CCR2 and fractalkine/CX3CR1, play a key role in vascular remodeling by mediating lesion leukocyte infiltration and increasing neointimal SMC expansion directly (22). Kodali *et al.* demonstrated that the proinflammatory chemokines eotaxin and stromal-cell-derived cell factor-1 stimulate matrix metalloproteinase-2 (MMP-2) expression in arterial SMCs (23), whereas MMPs facilitated leukocyte infiltration by degrading ECM. The CC and CXC chemokines showed cross-talk. A CXCR2 antagonist reduced Ang II-infusion-induced release of the CC chemokines MCP-1, CCL3 and CCL5, followed by reduced neutrophil and mononuclear cell infiltration (24). In a model of Apo E treated with ACEI, Abd *et al.* showed that inhibition of Ang II down-regulated expression of the C-C chemokine receptor 9 (CCR9) and chemokine ligand 25 (CCL25). Moreover, inhibition of CCR9 by RNA interference in hematopoietic progenitors of Apo E-deficient mice significantly retarded the development of atherosclerosis (25).

### 5. ANG II AND INFLAMMATORY CELLS

Ang II infusion induces the expression of chemokines and infiltration of inflammatory cells into the myocardium. Macrophages and T lymphocytes mostly

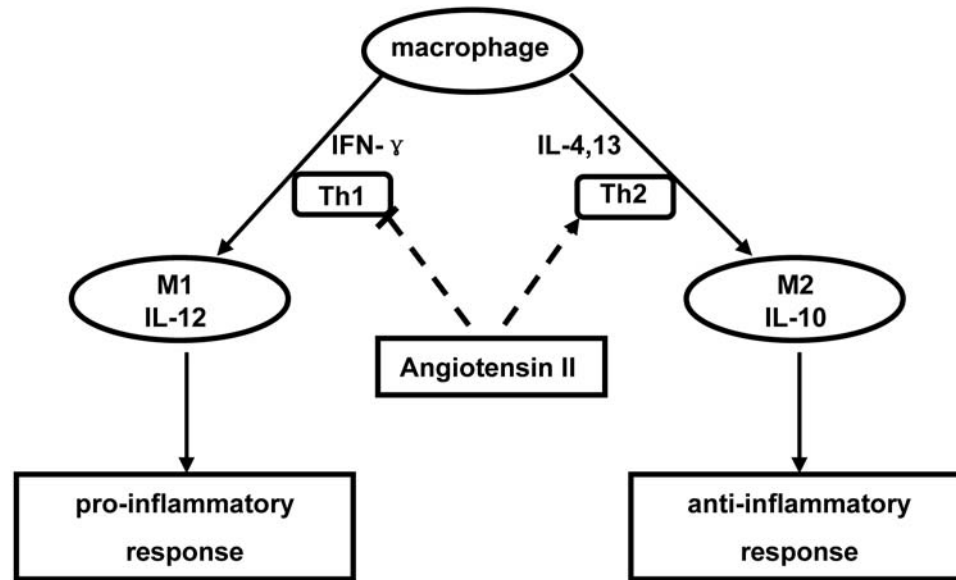
contribute to the development of inflammation and remodeling (26,27). AT1R is expressed in macrophages and T and B lymphocytes. Circulating blood-derived monocytes mature into tissue macrophages, with involvement of macrophage-colony stimulating factor. De Ciuceis *et al.* showed that genetic deletion of macrophage-colony stimulating factor blocked Ang II infusion-induced endothelial dysfunction, vascular remodeling, and oxidative stress (28). In an Ang II infusion-induced aortic dissection mouse model, Tieu *et al.* found that Ang II stimulated interleukin 6 (IL-6) production, promoted macrophage recruitment and macrophage-derived MCP-1 expression and accelerated macrophage-mediated vascular inflammation and remodeling (29).

Macrophages play multiple and complex roles. They are responsible for phagocytosis of dead cells and debris and clearance of apoptotic cells. As well, macrophages directly secrete the cytokines and growth factors regulating fibroblasts and other cells. Circulating monocytes that migrate into tissue undergo differentiation into 2 distinct subsets in response to the microenvironment: classically activated macrophages (M1s) and alternatively activated macrophages (M2) (30). M1s are activated after exposure to interferon  $\gamma$  (IFN- $\gamma$ )-dependent response, which propagates inflammation. M1 macrophages are characterized by a high capacity to present antigen, high IL-12 production, and high production of nitric oxide and other reactive intermediates, therefore M1 macrophages with this phenotype, are proinflammatory. On the other hand, "alternatively activated" or M2 macrophages are hyporesponsive to proinflammatory stimuli with an enhanced IL-10 production. M2 macrophages are activated by IL-4- or IL-13-mediated response, which inhibits inflammation, promotes cell proliferation and stimulates angiogenesis. Ang II may modulate macrophage polarization. A recent study have shown that macrophages from mice lacking mineralocorticoid receptor in myeloid cells exhibited M2 macrophage phenotype. Mineralocorticoid receptor deficiency in macrophages prevented Ang II-induced cardiac fibrosis, and vascular damage. Therefore mineralocorticoid receptor regulates macrophage polarization and Ang II-induced fibrotic responses (31). AT1R was expressed on macrophages. Aki *et al.* demonstrated that in a model of anti-glomerular basement membrane glomerulonephritis, inhibition of Ang II reduced glomerular infiltration of macrophages and suppressed M1 cytokines production, while high-dose ARB increased the numbers of M2 macrophages and suppressed inflammation (32). Moreover, macrophages from mice with enhanced macrophage-specific ACE expression prone to differentiated into M1 macrophage to suppress tumor formation (33). Indeed human macrophage ACE expression was also upregulated by IL-4 and IL-13, which promote the "alternative" M2 activation of macrophages and decreased by LPS and IFN- $\gamma$ . Mechanistically, AMPK increased ACE expression and prevented the pro-inflammatory cytokine production by macrophages (34).

T lymphocytes play an important role in the genesis of Ang II-induced hypertension and vascular dysfunction. In 1986, clinical observations suggested that T

cells were linked to hypertension; administration of T lymphocytes during cancer treatment increased blood pressure (35). Indeed, RAG-1-/- mice, deficient in T and B lymphocytes, did not show hypertension and did not develop abnormalities of vascular function during Ang II infusion and these abnormalities were restored by transferring T but not B lymphocytes (36). The mechanism involves a pathway of Ang II infusion activating NADPH oxidase subunits and reactive oxygen species (ROS), modulating T lymphocyte activation, increased tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IFN- $\gamma$  levels and, ultimately, hypertension caused by AT1R (36). In a study involving specific antagonists and T cells from AT1R- and AT2R-deficient mice, Hoch *et al.* showed that an endogenous RAS in T lymphocytes was involved in regulating T-lymphocyte function, NADPH oxidase activity and TNF- $\alpha$  production (37). Furthermore, the adaptive immune response plays an important role in Ang II-induced hypertension. Various hypertensive stimuli cause T-cell activation and infiltration into target organs leading to increase in blood pressure. T-cell activation requires T-cell receptor ligation and costimulation. The latter often involves interaction between B7 ligands (CD80 and CD86) on antigen-presenting cells with the T-cell coreceptor CD28. A recent study showed that blockade of B7-dependent costimulation with CTLA4-Ig reduced both Ang II - induced hypertension. Furthermore, in mice lacking B7 ligands, Ang II can not increase blood pressure elevation and vascular inflammation, and these effects were restored by transplantation with wild-type bone marrow, these results indicate T-cell co stimulation via B7 ligands is essential for development of experimental hypertension (38).

T-helper (Th) lymphocytes are subdivided into Th1, Th2 and Th17 cells by their unique pattern of cytokine secretion and functions. Ang II alters the balance of Th1/Th2. Shao *et al.* reported that Ang II infusion induced an increase in the production of the Th1 cytokine IFN- $\gamma$  and a decrease in that of the Th2 cytokine IL-4 in rats, whereas administration of the AT1R blocker prevented the imbalance of Th1/Th2 subsets (39). The changes in imbalance of Th1/Th2 regulates cardiac remodeling; for example, an elevated Th1 immune condition led to pro-fibrotic activity and increased ventricular stiffness, but an Th2 immune condition reduced cardiac collagen disposition (40). Madhur *et al.* reported that Ang II infusion stimulated IL-17 production from Th17 lymphocytes in the aortic media. Indeed, IL-17-deficient mice did not show hypertension after Ang II infusion and showed undamaged vascular function and decreased superoxide production, as well as less T-lymphocyte infiltration (41). Treatment with ACEI induced proliferation of regulatory T lymphocytes and suppressed autoreactive Th1 and Th17 proliferation in an animal model of multiple sclerosis (42). Kvakani *et al.* demonstrated that adoptive transfer of regulatory T lymphocytes inhibited CD4<sup>+</sup>, CD8<sup>+</sup>, CD69<sup>+</sup> cell and macrophage infiltration, ameliorated cardiac damage and explained the improved electric remodeling independently of blood pressure in Ang II-infused hypertensive mice (43). (Figure 1).



**Figure 1.** Angiotensin II promotes to macrophage polarization.

## 6. ANG II AND IMBALANCE OF INFLAMMATORY OR ANTI-INFLAMMATORY CYTOKINES

Cytokines regulate the activation and growth of inflammatory cells. Ang II stimulates NF- $\kappa$ B activation and ROS production through both AT1R and AT2R, thus leading to coordinated increases in the expression of genes and proinflammatory cytokine secretion. Ang II infusion stimulated the production of proinflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , IL-6 and inducible nitric oxide synthase (iNOS) in many organs such as heart, liver, kidney, brain and retina (44,45,46,47). Gurantz *et al.* reported that IL-1 $\beta$  and TNF- $\alpha$  act coordinately to increase AT1R density in post-myocardial infarction in rat (48). These studies suggested a vicious cycle of Ang II-induced myocardial cytokine production and cytokine-induced increase in Ang II activity. This situation is further demonstrated by a study of transgenic mice showing that myocardium-specific overexpression of TNF- $\alpha$  promoted cardiomyocyte apoptosis and led to fibrotic and dilated hearts with decreased cardiac function, with increased proinflammatory cytokine expression, whereas TNF- $\alpha$  neutralizing antibody treatment rescued these features in part (49). A myocardial infarction mouse model showed that genetic deletion of TNF- $\alpha$  suppressed inflammatory cell infiltration in the early phase and protected against cardiac rupture, cardiac dysfunction and myocardial apoptosis (50). Yamamoto *et al.* found that ARB treatment ameliorated TNF- $\alpha$ -induced reduction in eNOS expression and cell injury by inhibiting superoxide production or NF- $\kappa$ B activation in human umbilical vein endothelial cells (6). TNF- $\alpha$  exerts distinct biological effects through the TNF- $\alpha$  R1 and R2 receptors. With a myocardium infarction model of 2 strains of knockout mice (R1 $^{-/-}$  and R2 $^{-/-}$ ), TNF- $\alpha$  R1 signaling was found to be cardiotoxic by upregulating IL-1 $\beta$ , IL-6 and MCP-1 production, whereas TNF- $\alpha$  R2 signaling was protective (51). However, the role of TNF- $\alpha$

R1/R2 in Ang II-induced cardiac injury and repair has not been well investigated.

IL-1 $\beta$  signaling promotes the development of cardiac remodeling, exclusively through IL-1 receptor (IL-1R). IL-1R-null mice exhibited less infiltration of leukocytes and low expression of chemokines and cytokines. Reduced inflammation in IL-1R $^{-/-}$  mice was followed by reduced collagen deposition, less myofibroblast formation, and attenuated fibrotic response after myocardial infarction (52).

IL-6 acts via a receptor complex consisting of the cognate IL-6R (IL-6R) or the soluble IL-6R (sIL-6R) and glycoprotein 130 (gp130). Administration of the inhibitor of gp130 did not induce hypertension in response to Ang II infusion, and Ang II infusion did not lead to hypertension or cardiac hypertrophy in IL-6 $^{-/-}$  mice (53), indicating that IL-6 is required for mediating Ang II-induced vascular inflammation and remodeling.

Osteopontin (OPN), a key component of recruitment of macrophages and ECM, was found increased in cardiac hypertrophy, and its knockout attenuated fibrosis (54,55,56). Ang II infusion stimulated OPN expression in VSMCs, and knockout of OPN gene suppressed CD68 $^{+}$  macrophage infiltration, CCR2 production and VCAM expression. Knockout of OPN finally attenuated the formation of atherosclerosis and aneurysm in Apo E $^{-/-}$  mice (55,57). Recombinant IL-18 treatment stimulated OPN expression in cultured cardiac fibroblasts, whereas IL-18 neutralizing antibody abolished the increase in OPN expression. A mutation in the transcriptional factor IFN regulator factor 1 blocked the upregulation of IL-18 and OPN in cardiac fibroblasts. In addition, IFN regulator factor 1 mutant mice showed a reduced response to pressure-overload-induced expression of IL-18 and OPN, cardiac fibrosis and diastolic dysfunction (58).

IL-10 is secreted predominantly by activated Th2 lymphocytes, M2 macrophages and Treg lymphocytes, with potent anti-inflammatory properties. IL-10 suppressed the inflammatory response by inhibiting the production of IL-1 $\beta$ , TNF- $\alpha$  and IL-6. Administration of ARB increased the urinary levels of the anti-inflammatory cytokine IL-10 (59). Zemse *et al.* reported that IL-10 counteracted impaired endothelium-dependent relaxation induced by Ang II by decreasing NADPH oxidase expression in cultured aortic rings *in vitro* (60). In IL-10-deficient mice, systemic administration of Ang II produced marked oxidative stress and modest damage of endothelial function (61).

In conclusion, Ang II initiates an imbalance of cytokines, increases the level of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$  and correspondingly decreases that of the anti-inflammatory cytokine IL-10, which magnifies inflammation and leads to left ventricular remodeling (62).

### 7. ANG II AND PRO-INFLAMMATORY SIGNALING PATHWAY

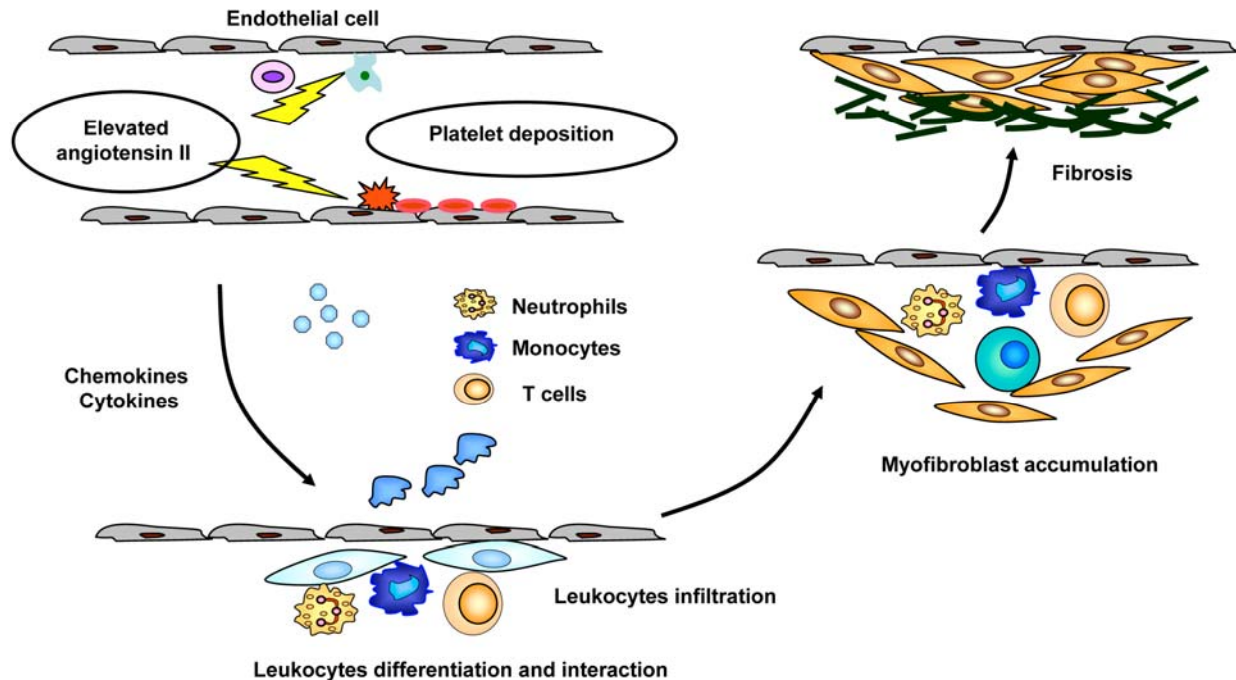
Ang II binds to the AT1R, which activates a series of signaling cascades involved in pro-inflammation. Ang II elicits an inflammatory response that appears to depend on the production of oxidant stress and activation of transcriptional factors (e.g., NF- $\kappa$ B, Ets-1 and Egr-1) (55,63,64). Several studies have suggested that ROS and reactive nitrogen species (RNS) play important roles in the regulation of Ang II signaling. In cardiac fibroblasts, stimulation with cytokines induces AT1R up-regulation, while nitric oxide (NO) decreases AT1R through cysteine modification of a NF- $\kappa$ B. The difference between the effects of ROS and NO on AT1R expression may be caused by the difference between intracellular location of ROS signaling and that of NO signaling (65). Oxidative stress is implicated in cardiovascular function by regulating the unbalanced expression of inflammatory genes, endothelial dysfunction and ECM formation. Ang II infusion is accompanied by an increase in oxidative stress via AT1R (4,66). In renin-overexpressed rats, Ang II-mediated cardiac oxidative stress, which promoted myocardial tissue remodeling, was inhibited by AT1R blockade and superoxide dismutase/catalase (67). Oudit *et al.* found that Ang II-mediated oxidative stress, neutrophil infiltration, and pathological hypertrophy were responsible for the age-dependent cardiomyopathy in ACE2<sup>-/-</sup> mice (68). ACEI or ARB treatment attenuated oxidative stress, thereby preventing cardiac remodeling (6,69). Ang II activated NADPH oxidase in ECs and VSMCs to generate ROS such as superoxide and hydrogen peroxide in mitochondria (70,71,72). C-Src, epidermal growth factor receptor (EGFR) transactivation and phosphatidylinositol-3-kinase, were upstream mediators in the Ang II-induced activation of NADPH oxidase. A recent study identified that Ang II via activation its receptor AT1R, stimulated an assembly of a CARMA3-Bcl10-MALT1 signalosome and led to activation of NF- $\kappa$ B. Knockout Bcl10 protected from developing Ang II-dependent atherosclerosis (73). Activation of NF- $\kappa$ B led to coordinated increases in the

expression of many genes whose production mediates inflammatory responses, including pro-inflammatory cytokines, chemokines (MCP-1 and IL-8), adhesion molecules (ICAM-1, VCAM-1), E-selectin and iNOS, which initiates and sustains the ongoing inflammation (55). Several stimuli such as high shear stress, oxidative stress, and the pro-inflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$ , related to cardiovascular diseases, were shown to activate NF- $\kappa$ B. Ang II activated NF- $\kappa$ B through AT1R, and Ang II stimulated proinflammatory factors via NF- $\kappa$ B activation (74,75,76). Inactivation of p65 by inhibiting IKK and ribosomal kinase blocked Ang II-induced vascular inflammation (12). NF- $\kappa$ B inhibition by pyrrolidine dithiocarbamate (PDTTC) ameliorated Ang II-induced increase in cardiomyocyte apoptosis, type I collagen expression, interstitial fibrosis and LV wall thickness (77).

### 8. ANG II AND MYOFIBROBLASTS

Activation of fibroblasts to myofibroblasts, which can express  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) and produce ECM components, is a key event in connective tissue remodeling. Myofibroblasts are a dominant source of collagen in cardiac remodeling. Residential fibroblasts can proliferate and differentiate into myofibroblasts in response to injuries and may be responsible for wound repair or pathological organ remodeling (78). However recently, Haudek *et al.* indicated that bone-marrow-derived CD34<sup>+</sup>/CD45<sup>+</sup> fibroblast precursors, which traffic to fibrotic tissue and the site of injury, can differentiate to myofibroblasts, whereas the structural fibroblasts are CD34<sup>+</sup>/CD45<sup>-</sup> cells (18). The recruitment of bone-marrow-derived fibroblast precursors was mediated through a chemokine-dependent mechanism. Ang II infusion resulted in the appearance of spindle-shaped, bone-marrow-derived CD34<sup>+</sup>/CD45<sup>+</sup> cells that express type I collagen (18). Genetic deficiency of MCP-1 prevented the Ang II-infusion-induced appearance of a CD34<sup>+</sup>/CD45<sup>+</sup> fibroblast precursor population and suppressed cardiac fibrosis (79). Emerging experimental evidence also suggested that the ECs could transdifferentiate into mesenchymal cells, which can express  $\alpha$ -SMA and could be another contributor to cardiac and vascular development, as well as pathophysiological vascular remodeling (18,80). Sopel *et al.* recently found that Ang II-infusion stimulated the expression of the SDF-1 $\alpha$ , and infiltration of CD133<sup>+</sup> cells. These data again suggest that mesenchymal progenitor cells are recruited, and may have a primary role, in the initiation of myocardial fibrosis (81).

Ang II stimulated cardiac and lung fibroblast proliferation *in vitro* via activation of the AT1R (82,83,84). As well, Ang II increased the expression of collagen type I in a concentration- and time-dependent manner in cardiac fibroblasts (5,85). Treating cardiac fibroblasts with Ang II increased  $\alpha$ -SMA expression and collagen synthesis (86). Ang II protected cardiac fibroblasts against IL-1 $\beta$ -induced apoptosis by downregulating iNOS expression and phosphorylation of Akt/PKB (87). Ang II pre-treatment reduced fibroblast-like synoviocyte apoptosis in response to serum starvation and NO exposure through the activation of NF- $\kappa$ B and the blockage of a caspase cascade via AT1R;



**Figure 2.** Angiotensin stimulated inflammation and cardiac fibrosis. Elevated angiotensin II causes endothelial cells injuries and platelets deposition. These initial events leads to expression of cytokines, chemokines secretion, and infiltration of inflammatory cells followed by myofibroblasts formation, leading to cardiac remodeling.

while a specific AT1R blockade reverted this protective effect (88).

Evidence suggests that Ang II may have a direct effect on myofibroblasts. Both ACEI and ARB treatment inhibited the local proliferation of macrophages and myofibroblasts (89). ACE2 was expressed constitutively in human cardiac myofibroblasts but was not detected in VSMCs or ECs (90). Myocardin-related transcription factors (MRTFs) are serum response factor (SRF) cofactors that promote a smooth muscle phenotype, Small *et al* recently proposed a mechanism for myofibroblast activation, which showed that MRTF-A controls the expression of a fibrotic gene and smooth muscle cell differentiation in the heart. They found that knockout of MRTF-A prevent Ang II-induced cardiac fibrosis and this protective effect is associated with a reduction in expression of fibrosis-associated genes, including collagen Ia2, a direct transcriptional target of SRF/MRTF-A. These results established a role for MRTF-A in Ang II-induced myofibroblast activation and fibrosis (91).

## 9. PERSPECTIVES

Hypertension induces damage of multiple organs, including heart, kidney, brain, and eyes. Cardiac remodeling, characterized by excessive interstitial and/or perivascular ECM deposition, leads to increased ventricular stiffness with diastolic heart failure and then systolic cardiac dysfunction. Preventing cardiac remodeling should be the most effective way to

protect against cardiovascular events. Multiple studies demonstrated that cardiac remodeling is now accepted as chronic inflammation that has “gone out of control” in response to “injuries”, whereas elevated Ang II causes these injuries summarized in Figure 2. However, there are several important questions remain. For example, what are early events to mediate hypertension-induced cardiac remodeling? How interaction between different leukocytes contributes to cardiac remodeling? How does the network interplay of different cytokines contribute to cardiac remodeling? What is the mechanism for resolving and nonresolving of inflammation in the process of cardiac remodeling? What are the genetic variations attribute to these inflammatory pathways? Answering these question will certainly useful to develop novel diagnosis and therapeutic targets for complication of hypertension.

## 10. ACKNOWLEDGEMENT

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**Key Words:** Angiotensin II, Inflammation, Cardiac Remodeling, Macrophage, Review

## **Role of inflammation in angiotensin II-induced cardiac remodeling**

**Send correspondence to:** Jie Du, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing Anzhen Hospital Affiliated the Capital Medical University, Beijing 100029, China, Tel: 010-64456030, Fax: 010-64451050, E-mail: [jdu@bcm.edu](mailto:jdu@bcm.edu)

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