Renin-Angiotensin System and Cardiovascular Functions

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The renin-angiotensin system plays critical roles in maintaining normal cardiovascular functions and contributes to a spectrum of cardiovascular diseases. Classically, the renin-angiotensin system is composed of AGT (angiotensinogen), renin, angiotensin-converting enzyme (ACE), Ang II (angiotensin II), and 2 Ang II receptors (AT1 and AT2 receptors).[1,2] AGT, a protein with 452 amino acids, is cleaved by renin to produce Ang I. Ang I is a decapeptide, which is then cleaved by ACE to produce Ang II. Ang II is an octapeptide, acting through binding to its receptors, AT1 and AT2 receptors. AT1 receptor is the major receptor for Ang II to regulate many physiological and pathophysiological functions.[3–6] In mice, AT1 receptor has 2 subtypes, AT1a and AT1b, which have >90% sequence homology, but distinctive distributions and functions.[4,7–12] AT1a receptor is important for blood pressure regulation and contributes to atherosclerosis and aortic aneurysms,[5,13,14] whereas AT1b receptor has no evident contribution to these functions[15] but is associated with vasculature contractility.[16,17] AT2 receptor is abundant during fetal development but becomes low in most tissues after birth.[18]

In the past 2 decades, many new components in this system have been discovered. These include ACE2, a homologue of ACE, which converts Ang II to Ang(1–7) or converts Ang I to Ang(1–9).[19,20] The G protein–coupled receptor Mas1 was identified as the receptor of Ang(1–7).[21]

This review highlights some recent publications in *ATVB* that have provided insights into understanding the classic components of the renin-angiotensin system and its alternative components contributing to cardiovascular functions. We will focus on effects of this hormonal system on cardiac dysfunction, hypertension, atherosclerosis, and aortic aneurysms.[22–29]

Angiotensinogen

AGT is the only known substrate of the renin-angiotensin system to produce all downstream angiotensin peptides. AGT regulates blood pressure as demonstrated by multiple mouse models, including global AGT-deficient mouse model and human AGT and renin transgenic mouse model.[30–33] AGT was also implicated in atherosclerosis using a transgenic mouse model expressing both human angiotensinogen (*Agt*) and renin genes.[34] Two recent studies have provided direct evidence that AGT regulates blood pressure and contributes to atherosclerosis through Ang II–mediated mechanisms.[35,36] These studies used multiple genetic manipulations, including AGT hypomorphic mice, bone marrow transplantation, hepatocyte-specific AGT-deficient mouse model, and adeno-associated viral infection to repopulate the manipulated *Agt* in vivo. These studies demonstrate that hepatocyte-derived AGT is the predominant source to regulate blood pressure and promote atherosclerosis. A pharmacological approach using antisense oligoneucleotides has also opened a door to directly target AGT for preventing high blood pressure and atherosclerosis.[36]

Renin

Renin is the rate-limiting enzyme of the renin-angiotensin system and the only enzyme known to cleave AGT. These properties make renin a potentially attractive target to inhibit the renin-angiotensin cascade and improve Ang II–mediated cardiovascular dysfunctions.[37,38] Inhibition of renin reduces blood pressure and atherosclerosis in animal models.[6,36,39–43] Unfortunately, renin inhibitors in patients with cardiovascular diseases have not provided superior beneficial effects beyond the well-established ACE inhibitors or AT1 receptor blockers.[44]

Despite some disappointing findings in human studies of renin inhibition, it has not discouraged research to understand renin-related mechanisms of cardiovascular diseases. The juxtaglomerular cells of the kidney are the major source of renin production and secretion. As an important organ in blood pressure regulation and cardiovascular functions, renal denervation aiming to reduce sympathetic nerve activity has drawn significant attention, although there are conflicting findings that need further research.[45–48] A recent study using pigs discovered that this approach reduced blood pressure and improved cardiovascular functions through its influence on kidney-brain-heart axis with profound changes of plasma renin activity, implicating the involvement of the renal renin-angiotensin system regulation in the process.[49]

Angiotensin-Converting Enzymes

In contrast to the rate-limiting and substrate-specific properties of renin, ACE is not sensitive to Ang II concentration changes, and it is an enzyme that cleaves not only Ang I but also many other substrates including bradykinin (a vasodilator) and N-acetyl-Ser-Asp-Lys-Pro (a hemoregulatory peptide).[50–53] There is a highly consistent literature demonstrating that ACE inhibition reduces blood pressure and atherosclerosis in animal models.[6,54,55] ACE inhibitors are one major class for treatment of hypertension, cardiovascular dysfunctions, and diabetic nephropathy in patients.[56–60] Recent studies have also added new mechanistic insights into guiding the use of ACE inhibitors. It was found that high serum concentration of

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homocysteine decreased antihypertensive effect of enalapril, an ACE inhibitor, in chronic hypertensive patients.[61]

ACE is ubiquitously present in many cell types, tissues, and organs.[62,63] Leukocyte or smooth muscle cell–derived ACE contributed to atherosclerosis as demonstrated by bone marrow transplantation and cell-specific depletion of ACE, respectively, in mouse models,[54,64] although their effects were less potent than pharmacological inhibition of ACE systemically.[6] ACE is abundant in endothelial cells.[65] However, depletion of ACE in this cell type had no effects on atherosclerosis.[64] Global genetic depletion or pharmacological inhibition of ACE reduced blood pressure,[6,66] but depletion of ACE in leukocyte, endothelial cells, or smooth muscle cells did not affect blood pressure.[54,64] Despite a well-known enzyme discovered half century ago[67,68] with impressive success of its inhibitors in clinical patients,[69] it is still a long road to define mechanisms by which ACE contributes to multiple cardiovascular functions, including its cellular source that influences blood pressure regulation.

Angiotensin II

As the major bioactive peptide of the renin-angiotensin system, there are broad views of mechanistic insights into understanding how Ang II contributes to multiple cardiovascular physiological and pathophysiological functions. We provide a brief review of the following diseases published recently in *ATVB*. For most of these studies, the approach used was chronic subcutaneous infusion of Ang II.[70,71]

Cardiac Dysfunction

Ang II induces several forms of cardiac dysfunction including hypertrophy, arrhythmia, and ventricle function failure.[72,73] Basigin is a transmembrane glycoprotein that has multiple functions.[74] In a mouse model of transverse aortic constriction, genetic reduction of basigin led to less cardiac hypertrophy, fibrosis, and heart failure.[75] Deficiency of smooth muscle stromal interaction molecule 1, an endoplasmic reticulum $Ca2^+$ sensor, also prevented Ang II–induced cardiac hypertrophy.[76] These findings are consistent with that renin-angiotensin inhibition is crucial for improving cardiac dysfunction.

Hypertension

There are many factors contributing to hypertension.[77–79] Salt intake is believed to be a critical factor for high blood pressure.[80] Ang II is also a well-recognized contributor to high blood pressure.[81,82] However, high salt intake suppresses the renin-angiotensin system, whereas low dietary salt increases Ang II production.[83,84] In accord with the paradox between salt intake and the renin-angiotensin regulation, dietary salt intake in blood pressure regulation and its consequent cardiovascular events have also been inconsistent, as reported in both human studies and animal models,[85–91] implicating complex molecular mechanisms involved in salt versus Ang II–mediated hypertension and related cardiovascular dysfunctions.

Batchu et al[78] found that Axl, a receptor tyrosine kinase, in T lymphocytes exerted a significant role in Ang II–mediated blood pressure regulation. This finding is consistent with reports by Guzik et al[92] and Norlander et al[93] that T-lymphocyte–mediated immune response contributed to Ang II–induced high blood pressure, although this needs to be validated in human studies. In addition to immune cells, smooth muscle cells are a critical cell type in Ang II–mediated blood pressure regulation. Smooth muscle 22α is a cytoskeleton-associated protein in smooth muscle cells. Smooth muscle 22α deficiency in mice reduced Ang II–induced high blood pressure and senescence of vascular smooth muscle cells.[93,94] These phenotypes were proposed to be associated with many mediators including p53-dependent pathway.[95] Activation of the α7 subtype of nicotinic acetylcholine receptors (α7nAchR) inhibited Ang II–induced senescence in cultured vascular smooth muscle cells and wild-type mice, but not in mice with α7nAchR deficiency. This effect was associated with sirtuin 1 activity because inhibition of sirtuin 1 abrogated this effect.[96] microRNA-143 and 145 are abundant in vascular smooth muscle cells and regulate myogenic tone.[97] Depletion of these 2 microRNAs did not affect Ang II–induced high blood pressure but caused more severe arterial wall disruption, vascular remodeling, and inflammation.[98] Another recent study identified cellular repressor of E1A-stimulated genes as a mediator of Ang II–induced vascular remodeling.[99] From these recent studies, we can gather that Ang II–mediated hypertension is a complex process that involves a large spectrum of molecules and many cell types.

Atherosclerosis

Atherosclerosis is a complex disease involving diverse mechanisms including disordered lipoprotein metabolism, inflammation, endothelial dysfunction, reactive oxygen species, and endoplasmic reticulum stress.[29,100–103] Animal models are a common tool to study these mechanisms and exploring potential therapeutic targets. For example, application of drugs using nanoparticles holds promise to optimize drug delivery and efficacy. In apolipoprotein E–deficient (*Apoe*$^{-/-}$) mice fed a high-fat diet and infused with Ang II, nanoparticles containing pioglitazone, an antidiabetic drug that also had peroxisome proliferator–activated receptor-γ agonistic effects, was injected intravenously on a weekly basis for 4 weeks. Although pioglitazone administration did not change atherosclerotic lesion size and macrophage content, it reduced Ly-6C high monocytes, matrix metalloproteinase activity, and cathepsin activity.[104]

In addition to mouse models, rabbits have been frequently used to study atherosclerosis. In one study, infusion of Ang II to Watanabe heritable hyperlipidemic rabbits led to high death rate (50% for Ang II 100 ng/kg per minute and 92% for Ang II 200 ng/kg per minute) because of acute myocardial infarction with coronary plaque erosion, rupture, and thrombosis.[105] Because plaque rupture and thrombosis are high-risk complications in humans,[106] this model would be optimal to study mechanisms related to the human disease. In another study, Honda et al[107] infused Ang II to Japanese White rabbits when they were fed a high-cholesterol diet and injured using balloon catheter to femoral arteries. This procedure also led to atherothrombotic occlusions. Ezetimibe, a lipid-lowering drug used in patients, profoundly decreased this fatal pathology, providing rationale to determine its extended effects in patients.[107]

Thoracic Aortic Aneurysms

Thoracic aortic aneurysms (TAA) manifest as profound dilation of the thoracic aorta, accompanied by compromise of

aortic wall integrity, dissection, or rupture.[108–112] Many genetic disorders are involved in this disease process including fibrillin-1,[113,114] TGF (transforming growth factor)-β ligands and receptors,[115–120] smooth muscle cell–specific isoforms of α-actin (encoded by *Acta2*), and myosin heavy chain (encoded by *Myh11*).[109] In addition to these genetic manipulations, infusion of Ang II also leads to TAA, predominantly localized to the ascending aortic region.[121–124]

The aortic wall is composed of the intima, media, and adventitia. Among the cell types of the aorta, smooth muscle cells are the most abundant cell type and have been the most frequently studied cell type in the development of TAA. Vascular smooth muscle cell phenotypes are associated with aortic aneurysm formation and its pathological process.

Components of TGF-β signaling pathways are important for maintaining aortic wall integrity. However, its effects on TAA and abdominal aortic aneurysm (AAA) formation are controversial. Inhibition of TGF-β by neutralizing antibodies augmented aortic rupture rate and aortic dilation in both abdominal and thoracic aortic regions in Ang II–infused mice[125–127] but attenuated development of TAA in a Marfan mouse model.[114] To explore the conflicting findings in different mouse models and different locations of aortic aneurysms, a recent study determined mechanisms of TGF-β signaling in Ang II–induced TAA and AAA, combined with smooth muscle cell–specific TGF-β receptor 2 deficiency.[128] Systemic TGF-β neutralization augmented AAA but had no effects on TAA. In contrast, smooth muscle cell–specific TGF-β receptor 2 deficiency augmented TAA but had no apparent effects on the abdominal aorta.[128] This study emphasizes the distinctive mechanisms between TAA and AAA.[129]

MicroRNA-21 was identified as a critical modulator of proliferation and apoptosis of smooth muscle cells during development of AAA. Overexpression of microRNA-21 reduced AAA, and inhibition of this microRNA augmented AAA in 2 common mouse models.[130] A recent study discovered that in mice with Smad3 heterozygous background, aortic miR-21 expression was increased by Ang II infusion, and systemic microRNA-21 deletion exacerbated Ang II–induced TAA formation.[131] This study, combined with studies using TGF-β receptor 2 genetically manipulated mice, provides evidence for the importance of TGF-β–mediated mechanisms in the development of TAA.

In addition to components that are important for maintaining the aortic wall structure and integrity, embryonic origins of smooth muscle cells determine their phenotypes and functions. Embryonic origins of smooth muscle cells in the aorta are complex.[132] A recent study provided evidence that smooth muscle cells in the ascending aortic region were derived from 2 embryonic origins, with second heart field contributing to the outer layers and cardiac neural crest for the inner medial layers.[133] This study adds new insights into understanding mechanisms of TAA from an evolutionary viewpoint.[134]

Besides critical roles of smooth muscle cells, inflammation is a feature of TAA. Contractile dysfunction in smooth muscle cells is present in aortas of patients with sporadic TAA and dissection and is associated with activation of NLRP3 (nucleotide oligomerization domain–like receptor family, pyrin domain containing 3)-caspase-1 inflammasome.[135] A recent study reported that NLRP3 or caspase-1 deficiency in mice significantly reduced Ang II–induced contractile protein degradation and aortic aneurysm formation in both thoracic and abdominal aortic regions.[135]

Abdominal Aortic Aneurysms

AAA is defined as pathological dilation of the abdominal aorta. Same as individuals afflicted with TAA, aortic rupture is a fatal consequence of AAA.[110,112,136,137] There are three commonly used mouse models to study AAA: perfusion of elastase into the infrarenal aorta,[138] periaortic application of calcium chloride,[139] or subcutaneous infusion of Ang II.[70,140] Modifications of these mouse models have also provided mechanistic insights. For example, coadministration of β-aminopropionitrile with Ang II,[141,142] coadministration of TGF-β–neutralizing antibody with Ang II[125] or administration of TGF-β–neutralizing antibody to mice with elastase-induced AAA,[25] or application of calcium chloride with phosphate-buffered saline onto the infrarenal aorta.[143]

Hypercholesterolemia augments Ang II–induced AAA.[144,145] Therefore, *Apoe*$^{-/-}$ mice and low-density lipoprotein receptor–deficient mice are the 2 commonly used mouse models for Ang II–induced AAA studies.[70,71,140] Although Ang II–infused mouse model has become a popular model to study AAA, breeding mice to a hypercholesterolemic background has hampered its more broad use.[146] A recent study provided a rapid approach for increasing plasma cholesterol and Ang II–induced AAA incidence in C57BL/6 mice by applying a gain-of-function mutation of mouse PCSK9 protein using an adeno-associated viral method,[147] which was also frequently used in atherosclerosis studies.[148–150]

Inflammation and extracellular matrix disruption and remodeling are important features of Ang II–induced AAA.[112,145,151–154] Publications describing Ang II–induced AAA were featured in a recent *ATVB* Highlights,[112] including molecules that promote inflammation involving not only macrophages but also T and B lymphocytes,[155–164] oxidative stress,[165–167] and many other factors.[112,145,168]

In addition to extensive studies to define molecular mechanisms of AAA, some recent studies have emphasized the importance of studying sex differences.[29,169–171] One study used the 4 core mouse model to generate gonadal male mice with XX or XY chromosomes. This study found that gonadal male mice with an XY chromosome complement exhibited diffuse aortic aneurysms, whereas XX chromosome complement exhibited focal aortic dilation. Orchiectomy attenuated Ang II–induced TAA and AAA in male mice.[172]

Angiotensin II Receptors

AT1a Receptor

AT1a receptor, a subtype of Ang II receptor, is the major receptor for Ang II–mediated cardiovascular functions in mice. Global deficiency of AT1a receptor ablates atherosclerosis and attenuates Ang II–induced TAA and AAA.[5,14,39,173,174] This effect was not attributed to the presence of AT1a receptor on leukocytes[39,174] or smooth muscle cells,[14,122] whereas endothelial cell–specific depletion of AT1a receptor had modest protective effects on Ang II–induced TAA but not AAA and

atherosclerosis.[14,122] In agreement with these previous studies, using a well-established Marfan mouse model with genetic disruption of fibrillin-1 expression, Galatioto et al[175] found that endothelial cell–specific deletion, but not smooth muscle cell–specific deficiency, of AT1a receptor modestly attenuated TAA development and related aortic rupture.

AT2 Receptor

Although AT2 receptor remains low in most tissues and organs postnatally, many studies have reported increased presence of AT2 receptor under certain pathophysiological conditions as reviewed in a recent article.[176] Genetic deletion of AT2 receptor in mice had no effects on general health and development[177] but promoted angiogenesis within ischemic muscle.[178] A diabetic mouse model with a spontaneous mutation in the insulin 2 gene (Ins2+/C96Y) was bred with AT2 receptor–deficient mouse model. Hindlimb ischemia was induced by ligating femoral artery. Depletion of AT2 receptor augmented blood flow reperfusion and collateral vessel formation that were associated with SH2 domain-containing phosphatase 1 activity and vascular endothelial growth factor action.[179]

Alternative Pathways

This section introduces an enzyme, a bioactive peptide, and a receptor beyond the classic renin–angiotensin components.

Angiotensin-Converting Enzyme 2

ACE2 prevents atherosclerosis and aortic aneurysms, as demonstrated by deficiency of ACE2 accelerating atherosclerosis and Ang II–induced AAA in hypercholesterolemic mice.[180,181] Recently, Moran et al[182] reported that ACE2 deficiency in *Apoe*$^{-/-}$ mice augmented incidence of AAA and aortic rupture rate. Of note, deficiency of ACE2 also led to spontaneous AAA formation in the absence of Ang II. Resveratrol, a class of compounds produced by many plants, increased ACE2 and inhibited AAA growth in Ang II–infused mice.

Angiotensin (1–7) and Mas1

Recent studies have implicated that Ang(1–7) has protective effects on multiple cardiovascular functions through its interaction with Mas1.[183] Many studies reported that Ang(1–7)/Mas1-mediated actions counteracted actions of Ang II.[180,184–186] For example, Ang(1–7) had vasodilation effect that was mediated by Mas1, whereas Ang II had potent vasoconstriction effect.[187] One study reported that Ang(1–7)-induced NO-mediated vasodilation and increased telomerase activity of endothelial cells.[187] In another study, low dose of Ang(1–7) increased angiogenesis and vasodilation through its interaction with Mas1, which had equivalent effects as same low dose of Ang II. Among potential mechanisms, ERK1/2 was essential for Ang(1–7)-induced angiogenesis and vasodilation.[186,188]

Summary

Although the major renin-angiotensin members were discovered more than a half century ago, this system still attracts a large number of research work in different fields. This implicates the importance of this hormonal system in physiological and pathophysiological functions but also notes that there are many unknowns and conundrums of this system in our knowledge that require more extensive research work.

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Disclosures

None.

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