

To mark the 60th birthday of *Circulation Research* (1953-2013), the editors have commissioned *Circulation Research Classics*, a series of commentaries highlighting seminal articles published in the journal over the past six decades that have importantly shaped cardiovascular research. Written by leading experts, *Circulation Research Classics* are intended to describe the impact of these articles on the field by putting them in a historical perspective. The concept of “classic” is inextricably linked to time—a classic is something that maintains its value regardless of its age. Thus, an important consideration in selecting the articles to be highlighted is that they have stood the test of time, which is the most reliable indicator of the value of scientific work. By looking back at the illustrious past of *Circulation Research*, we hope to promote a deeper appreciation of the contributions of this journal to the advancement of knowledge.

Angiotensin II, From Vasoconstrictor to Growth Factor A Paradigm Shift

Sasa Vukelic, Kathy K. Griendling

Angiotensin II (Ang II) is today considered as one of the essential factors in the pathophysiology of cardiovascular disease, producing acute hemodynamic and chronic pleiotropic effects. Although now it is widely accepted that these chronic effects are important, Ang II was initially considered only a short-acting, vasoactive hormone. This view was modified a quarter of a century ago when Dr Owens and his group published an article in *Circulation Research* with initial evidence that Ang II can act as a growth factor that regulates cell hypertrophy. They showed in a series of elegant experiments that Ang II promotes hypertrophy and hyperplasia of cultured rat aortic smooth muscle cells. However, Ang II had no effect on hyperplasia. These findings led to a paradigm shift in our understanding of the roles of growth factors and vasoactive substances in cardiovascular pathology and helped to redirect basic and clinical renin–angiotensin system research during the next 25 years. Ang II is now known to be a pleiotropic hormone that uses multiple signaling pathways to influence most processes that contribute to the development and progression of cardiovascular diseases, ranging from hypertrophy, endothelial dysfunction, cardiac remodeling, fibrosis, and inflammation to oxidative stress.

The renin–angiotensin system (RAS) is now considered one of the essential factors in the pathophysiology of cardiovascular disease. The main effector of the RAS, angiotensin II (Ang II), contributes to the development of cardiovascular disease as both an endocrine and a local autocrine/paracrine hormone, producing acute (vasoconstriction, water/salt retention) and more importantly chronic (hypertrophy, hyperplasia, oxidative

stress, fibrosis, and inflammation) effects. Today, it is widely accepted that these chronic effects have a critical role in the development and progression of cardiovascular diseases, such as hypertension, atherosclerosis, and heart failure. Initially, Ang II was considered predominantly as a short-acting, vasoactive hormone, and its role in the pathology of cardiovascular disease was thought to result from acute hemodynamic changes. This view was modified a quarter of a century ago when Dr Owens and his group published an article in *Circulation Research* with initial evidence that Ang II can act as a growth factor that regulates cell hypertrophy.¹ This article completely changed our perspective on both the pathophysiology of cardiovascular diseases and the critical contribution of Ang II to them, and this is the focus of the current commentary.

Research on Ang II as a central component of the RAS began more than a century ago in 1898 with studies performed by Scandinavian researchers.² They reported a vasoconstrictor effect of a substance from renal extracts, which they subsequently named renin based on its origin. Interest in the nature of this vasoactive substance released by the kidney was renewed in 1934 when Goldblatt et al³ demonstrated that clamping dog renal arteries produced chronic hypertension. In the late 1930s, 2 independent groups in Argentina and the United States used the Goldblatt renal ischemia technique to demonstrate secretion of a pressor agent with effects similar to renin.^{4,5} This short-acting vasoconstrictor was later identified as an octapeptide product of renin and named Ang.⁶ During the next half-century, a tremendous amount of research was performed describing in detail the interdependence of the RAS components and the mechanism of action of Ang II, the primary effector molecule of this system.⁷

Up to this point, research efforts were mainly focused on the role of Ang II as an acute regulator of vasomotor tone. The first Food and Drug Administration–approved angiotensin-converting enzyme (ACE) inhibitor, captopril, was developed for the treatment of essential hypertension in 1977,⁸ based on early experimental data on the effect of Ang II on blood pressure in hypertension and chronic heart failure.⁹ ACE inhibitors proved to be clinically successful in reducing symptoms of hypertension and heart failure,¹⁰ despite the fact that there was no experimental evidence indicating

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From the Division of Cardiology, Department of Medicine, Emory University, Atlanta, GA.

Correspondence to Kathy K. Griendling, PhD, Emory University, Division of Cardiology, 101 Woodruff Circle, WMB 308, Atlanta, GA 30322. E-mail kgriend@emory.edu
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that the inhibition of Ang II synthesis is more beneficial than other modalities of antihypertensive therapy. Interestingly, Dr Owens' group was later one of the first to notice a difference in effects between classes of antihypertensive medications.¹¹ However, at that time the RAS was still considered to be an endocrine system in which Ang II had a central role as a potent, short-acting pressor. Furthermore, because of an unfavorable side effect profile of early ACE inhibitors, they were not initially considered as a first choice medication in the treatment of hypertension.¹²

The dynamics of both basic and clinical RAS research changed in the late 1980s when evidence first emerged that Ang II can function as a local autocrine and paracrine factor regulating growth of components of the cardiovascular system. Dr Owens' seminal article was the first to show the direct growth effect of Ang II in vascular smooth muscle cells (VSMCs).¹ In this article, based on his group's previous findings of the correlation between hypertension and VSMC hypertrophy,¹³ as well as the differential effectiveness of various antihypertensive drugs on the reversal of hypertrophy,¹¹ he postulated that chronic treatment with a contractile agonist such as Ang II can induce hypertrophy of VSMCs. In a series of elegant experiments, the authors proved without doubt that Ang II is an extremely potent inducer of receptor-dependent hypertrophy in VSMCs. This effect was accompanied by the development of hyperploidy, but not hyperplasia,

and was fully reversible with a specific Ang II antagonist. Dr Owens' group later confirmed these cell culture-based results in tissues.¹⁴

These findings helped to redirect basic and clinical RAS research. Ang II is now known to be a pleiotropic hormone that can influence virtually every process necessary for the development and progression of cardiovascular diseases ranging from hypertension, atherosclerosis, restenosis, and chronic kidney disease to heart failure (Figure). Chronic Ang II exposure promotes hypertrophy of VSMCs, phenotype modulation and differentiation, endothelial dysfunction, cardiac remodeling, fibrosis, inflammation, and oxidative stress.^{1,15} Dr Owens' research efforts in later years showed that Ang II, in addition to hypertrophy, may play an important role in a regulation of differentiation and phenotype switching in VSMCs.¹⁶ His group has critically contributed to our understanding of the molecular regulation of expression of VSMC marker genes.¹⁷⁻¹⁹

Once the vasoactive agonist Ang II was established as growth factor, the converse was also described. Platelet-derived growth factor and epidermal growth factor were found to be vasoconstrictors, suggesting that growth factors and vasoconstrictors shared signaling.^{20,21} Similarly, other vasoactive factors, such as thrombin, were shown to have mitogenic effects on VSMCs.²²

These novel findings changed the approach to understanding receptor-mediated signaling pathways. Because initially

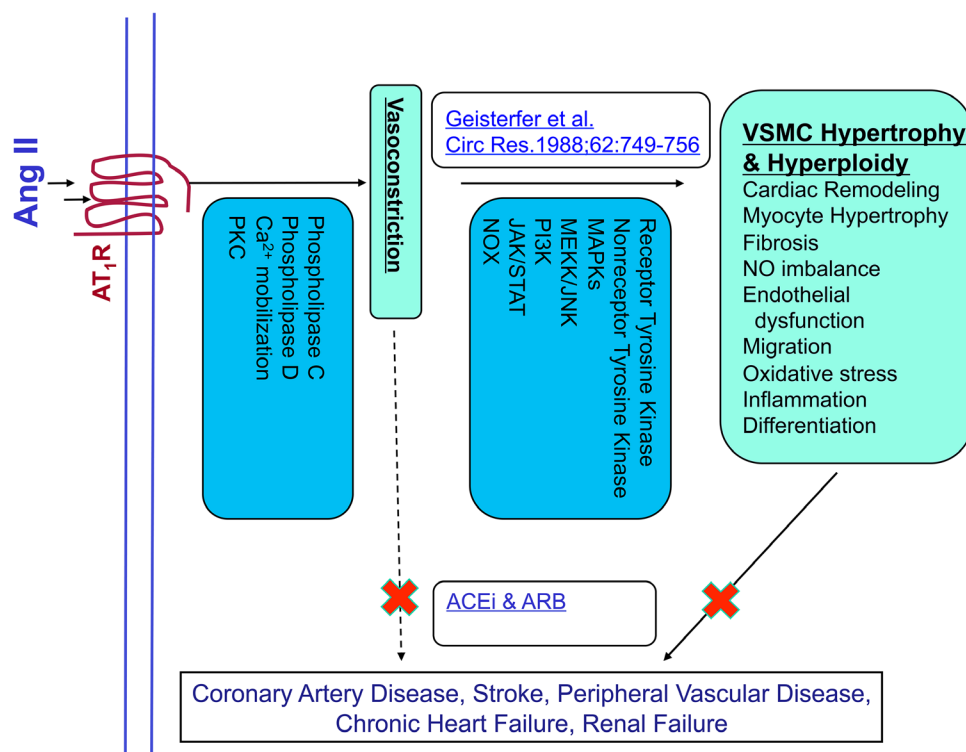


Figure. Paradigm shift in Angiotensin research: From vasoactive, short-acting hormone to pleiotropic growth factor and immunomodulator. Dr Owens' findings that Angiotensin II (Ang II) is not just an acute vasoactive substance but also a potent growth factor inspired multiple new studies in different basic research fields from inflammation to tyrosine kinase signaling. These basic research results served as a starting point for clinical research studies that caused a change in therapeutic practices, with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) becoming cornerstone of therapy. AT₁R indicates angiotensin II receptor, type 1; JAK, janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEKK, MAP kinase kinase; NO, nitric oxide; NOX, nicotinamide adenine dinucleotide phosphatase oxidase; PI3K, phosphatidylinositol 3-kinases; PKC, protein kinase C; STAT, signal transducers and activators of transcription; and VSMC, vascular smooth muscle cell.

Ang II was considered to be a predominantly vasoactive hormone, in the 1980s, the majority of signaling research was focused on the stimulation of phospholipase C and Ca²⁺ mobilization via G protein-coupled receptors, as well as activation of phospholipase D and protein kinase C and their effect on smooth muscle contraction.¹⁵ However, when Dr Owens' article described the prohypertrophic effects of Ang II, basic research in the 1990s shifted to studying the activation of tyrosine kinases, transactivation of receptor tyrosine kinases, and activation of nicotinamide adenine dinucleotide phosphatase oxidases (Figure). In one of the earliest reports, Tsuda et al²³ demonstrated that vasoconstrictors such as Ang II can specifically stimulate the tyrosine phosphorylation of multiple proteins in vascular smooth muscle cells. This early success sparked research efforts that identified numerous additional tyrosine-phosphorylated proteins. Of special significance was the discovery of Ang II-induced transactivation of receptor tyrosine kinases (epidermal growth factor, platelet-derived growth factor, insulin receptor) and nonreceptor tyrosine kinases (c-Src family kinases, focal adhesion kinase, and Janus kinases) leading to phosphorylation and modulation of activity of multiple downstream targets such as mitogen-activated protein kinases (summarized in the work by Mehta and Griendling¹⁵). Another important line of research that followed was the signaling mediated by activation of the nicotinamide adenine dinucleotide phosphatase oxidases and reactive oxygen species synthesis.²⁴ Ang II was initially considered a nonspecific, potent mediator of oxidative stress but was later shown to use reactive oxygen species as specific second messengers that mediate signaling in different pathways that can contribute to the development of cardiovascular diseases. Ang II was shown to mediate VSMC growth, differentiation, migration, fibrosis, and remodeling as a basis of its physiological and pathological roles (Figure).

These findings led to a shift in clinical research and ultimately therapeutic approaches. In the 1980s, the focus of clinical research was on the hemodynamic effects of ACE inhibitor therapy²⁵ and its correlation with symptomatic improvement in congestive heart failure and hypertension.²⁶ In the 1990s, after publication of Dr Owens' study and based on new basic science findings of the pleiotropic effects of chronic Ang II stimulation beyond its acute hemodynamic effects, the focus of clinical studies changed to the effect of ACE inhibitors on mortality. This is an example of translational research at best. Dr Owens' article created a paradigm shift in our understanding of the role of Ang II in cardiovascular pathology and inspired multiple new basic research studies that served as a starting point for further clinical research. Subsequently, ACE inhibitors were shown to promote survival of patients with congestive heart failure, myocardial infarction, coronary artery disease, and hypertension.^{27–29} It also became clear that they have a renoprotective effect independent of their effects on blood pressure.³⁰ These results confirmed hypothesis originating from basic research that ACE inhibitors, in comparison with other classes of antihypertensive medications, have pleiotropic, disease-modifying effects beyond decreasing blood pressure. This triggered a complete change in therapeutic approaches. Consequently, ACE inhibitors and Ang II

receptor blockers have become an indispensable and primary component of cardiovascular disease treatment.^{31–33}

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