



EDITORIAL COMMENT

Angiotensin II-induced cardiomyocyte hypertrophy: A complex response dependent on intertwined pathways

Hipertrofia cardiomiocitária induzida por angiotensina II: Uma resposta complexa dependente de vias entrelaçadas

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Available online 18 January 2021

Heart failure is a disabling condition and one of the leading causes of hospitalization in industrialized countries. Up to 6.2 million adults were diagnosed with heart failure between 2013 and 2016 in the USA, a significantly higher number than estimated for previous periods.¹ Furthermore, total costs associated with the disease are predicted to rise to \$69.8 billion in 2030 in that country.^{1,2} Heart failure is primarily an age-related disease, affecting about 10% and 8% of men and women aged over 60 years, respectively,² with a total incidence of 21 per 1000 population in those older than 65.¹ Although survival after diagnosis has improved in recent decades, five-year mortality is still close to 50%,³ even though the prognosis of many of the underlying conditions (such as myocardial infarction and severe hypertension) has improved markedly. This apparent discrepancy can be explained by the fact that although the risk of mortality from each of these individual disorders has decreased,⁴ patients still have the disease and new acute episodes may occur. Thus, many surviving patients eventually develop severely depressed cardiac function and markedly reduced quality

of life. Heart failure is predicted to remain one of the most important health problems, not only in industrialized nations, but also in developing countries.²

Heart failure is associated with the development of adverse ventricular remodeling. This term encompasses a series of changes including cardiomyocyte hypertrophy, myocardial wall thickening (and thinning in infarcted areas), chamber dilation, collagen deposition and cell death. When subjected to a stress such as myocardial infarction or hypertension, the heart responds with an increase in cell size in order to normalize wall stress and function.^{2,5} However, chronic stress leads to an inflammatory process, associated with collagen deposition and cardiomyocyte death.^{2,5} Inappropriate activation of the renin-angiotensin-aldosterone system plays a key role in this process, of which angiotensin II (Ang II) is the main effector.⁶

Ang II is an octapeptide that exerts a variety of actions in the cardiovascular system.⁷ Early signaling events stimulate actin-myosin interactions. This effect, which is dependent on activation of Ang II type 1 (AT1) receptors, leads to an elevation in blood pressure and enhanced cardiac contractility. On the other hand, late signaling increases protein synthesis, activates different intracellular pathways, and enhances growth factor production.^{7–10} Activation of these pathways leads to cardiomyocyte hypertrophy, resulting in

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an increase in heart mass. Although part of the hypertrophic response to Ang II may occur indirectly, as a consequence of raised blood pressure, it has been demonstrated that Ang II also induces cardiomyocyte hypertrophy directly, through activation of AT1 receptors.¹¹ Cardiac hypertrophy begins as an adaptive process required to sustain cardiac output, but rapidly progresses to a maladaptive response triggering cell death and fibrosis, both factors being responsible for reducing contractility and causing diastolic dysfunction.^{7,8,12}

Following AT1 receptor activation, the cardiomyocyte hypertrophic response to Ang II involves a wide variety of intertwined intracellular signaling pathways, including mediators such as p38 extracellular signal-regulated kinase (MAPK), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway.^{6,7} In addition to these conventional mediators, recent studies have added others, including tumor necrosis factor alpha,¹³ Toll-like receptor 4,¹⁴ and CD38, a type II transmembrane glycoprotein,¹⁵ among many others. The study by Yuan and coworkers¹⁶ published in the current issue of the *Journal* provides important experimental evidence that the protein kinase C epsilon (PKC ϵ)/protein kinase D (PKD)/extracellular signal-regulated kinase 5 (ERK5)/myocyte enhancer factor 2D (MEF2D) pathway is also involved in the early events leading to cardiomyocyte hypertrophy. In this paper, the authors nicely demonstrate that Ang II induces PKC ϵ -dependent phosphorylation of PKD, leading to ERK5 phosphorylation and translocation into the nucleus, and consequently to activation of MEF2D.¹⁶ Importantly, small interfering RNA treatment targeting PKC ϵ , PKD or ERK5 attenuated expression of atrial natriuretic peptide and brain natriuretic peptide messenger RNA, two hypertrophic markers, and reduced cell size in neonatal rat cardiomyocytes.¹⁶

The involvement of PKD, ERK5 and MEF2D in the hypertrophic response to Ang II is consistent with previous studies demonstrating a role for these proteins in increases in cell size observed under different conditions.^{17,18} However, most of these studies analyzed their involvement in isolation. Yuan et al. have linked them into a common pathway, activation of which results in an increase in cell size.¹⁶ These findings provide new insights into the molecular mechanisms of some of the alterations involved in left ventricular remodeling and may be the basis for developing new therapeutic strategies aimed at improving patient prognosis and reducing the incidence of heart failure. Nevertheless, it is important to bear in mind that not all mediators are necessarily involved in all alterations occurring during ventricular remodeling. This is the case, for example, with connexin 43, which has been shown to be involved in the fibrotic process, but not in cardiomyocyte hypertrophy.¹⁹ Thus, it is not known how modulation of one particular pathway would affect the entire remodeling process. Furthermore, it remains unclear whether activation of the PKC ϵ /PKD/ERK5/MEF2D pathway described by Yuan et al. in neonatal rat cardiomyocytes¹⁶ would also occur in entire adult hearts, and especially in patients developing heart failure. These exciting results should therefore be confirmed and expanded by future research, before the possible

therapeutic application of modulation of this pathway are explored.

Funding

This study was supported by the Spanish Ministry of Economy and Competitiveness and Instituto de Salud Carlos III (PI17/01397 and CIBERCIV), and cofinanced by the European Regional Development Fund (ERDF, 'a Way to Build Europe'). Antonio Rodríguez-Sinovas has a consolidated Miguel Servet contract.

Conflicts of interest

The authors have no conflicts of interest to declare.

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