A New (Heat) Shocking Player in Cardiac Hypertrophy

Thomas M. Vondriska, Yibin Wang

Hypertrophic growth of cardiac myocytes is a common result of different physiological and pathological stresses. It remains a subject of considerable debate whether hypertrophy is a compensatory process that becomes maladaptive in diseased hearts or a direct contributor to the pathogenesis of heart failure. Nevertheless, many types of stressors, mechanical or neural/hormonal, induce hypertrophy and this phenotype is an independent risk factor in heart failure. Therefore, much effort has been devoted to uncovering mechanisms of hypertrophic growth, with the expectation that intercepting this process clinically may halt the disease progression of heart failure. It is firmly established that stresses, mechanical or neural/hormonal, induce hypertrophy and this phenotype is an independent risk factor in heart failure.

Among molecules known to regulate hypertrophic gene expression, histone deacetylases (HDACs) have been identified as key players in the pathological setting. HDACs expression, histone deacetylases (HDACs) have been identified as key players in the pathological setting.1,2 HDACs function as corepressors by targeted modification of local accessibility of chromatin to transcriptional machinery. HDACs are counteracted by histone acetyl transferases (HATs) to achieve dynamic regulation of gene expression depending on prevailing cellular stress and/or developmental conditions. There are 3 classes (I, II, and IV) of “classic” HDACs, consisting of 11 family members in addition to 7 sirtuin family members. Among the classic HDACs, class II HDAC members (HDAC4, -5, -7, and -9) have all been shown to negatively regulate hypertrophy by repressing MEF/GATA/NFAT-mediated gene expression.3 Interestingly, such negative regulatory activity is acetylase activity independent. In contrast, a recent report4 implicated the class I HDAC member HDAC2 as a positive regulator of hypertrophic growth.7,8 The diversity of anti- versus prohypertrophic functions among different HDAC family members underscores some of the initial controversies with regard to the effects of HDAC inhibitors on the treatment of cardiomyopathy.7 Although many of these inhibitors have broad spectrum target specificity, it is possible that their effects selectively modulate individual isoforms, such as HDAC2. In addition to the functional complexity of HDAC isoforms, the mechanisms involved in their activation appear to be very different as well. Class II HDACs are phosphorylated at the onset of hypertrophic stimulation by a number of prohypertrophic kinases, including protein kinase C, protein kinase D, calmodulin kinase, and G protein–coupled receptor kinase 5.9–12 The phosphorylated class II HDACs are subsequently translocated out of the nucleus by 14-3-3 proteins, resulting in the release of transcriptional repression of hypertrophic genes. In addition, oxidative modification of type II HDAC is also a critical aspect of their nuclear export, leading to hypertrophic gene induction.13 In contrast, the mechanisms of class I HDAC activation in the heart are unclear.

In this issue of Circulation Research, Kee et al14 have investigated this important question and identified an unexpected new player, inducible heat shock protein Hsp70, as a regulator of HDAC2 activity. First, the authors demonstrate that various hypertrophic stimuli (including swimming, aortic banding, isoproterenol, phenylephrine, and angiotensin II) selectively induce HDAC2 among other class I HDAC isoforms, which is correlated with selective induction in Hsp70. This activation occurs in animals and isolated cells and precedes hypertrophic growth; furthermore, Hsp70 leads to HDAC2 activation in cell systems and induces hypertrophic gene markers and cell matrix reorganization. Having established the activation profiles of Hsp70 and HDAC2 in various settings of hypertrophy, the authors then make the novel observation that the hypertrophic growth and HDAC2 activation following stress is dependent on Hsp70 using knockout mice (cell studies suggest that Hsp70 delivery induces cell growth in cardiac myocytes). In agreement with these data, Hsp70 and HDAC2 interact directly in vitro and immunoprecipitate from cell lysates, and this interaction appears to be selective for Hsp70 versus other isoforms tested. Hypertrophic stimulation triggers transient induction of Hsp70 and enhanced interaction with HDAC2. Although the mechanisms are unclear, this interaction appears to induce HDAC2 enzymatic activity without changes of HDAC2 protein expression, phosphorylation, or intracellular localization. Almost as an aside, the authors also show that heat stress to the animal is itself sufficient to induce hypertrophy and this response is aberrant in the Hsp70-null animals. Although Hsp70 was originally discovered as a protein induced by heat shock, subsequent studies have demonstrated its activation in response to a host of cellular insults, including mechanical, ischemia/hypoxia, and neural/hormonal.15–17 Therefore, this generic stress response molecule may also have a highly

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From the Division of Molecular Medicine, Departments of Anesthesiology, Physiology and Medicine, Cardiovascular Research Laboratories, David Geffen School of Medicine, University of California, Los Angeles.

Correspondence to Yibin Wang, PhD, Division of Molecular Medicine, Departments of Anesthesiology, Physiology and Medicine, David Geffen School of Medicine at UCLA, Room BH 569, CSH, Los Angeles, CA 90095. E-mail yibinwang@mednet.ucla.edu

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The arrows and lines depict positive or negative functions with Hsp70, leading to repression of antihypertrophic genes. In this scenario, hypertrophic stressors induce association of HDAC2 with Hsp70, leading to repression of antihypertrophic genes. The arrows and lines depict positive or negative functions without implication of direct interactions.

Specific role in regulating cardiac hypertrophy under pathological stimulations (Figure).

By revealing a novel aspect of HDAC regulation in hypertrophy, this study raises a number of questions. First, what is the role of Hsp70 in HDAC2 signaling? It appears not to be the regulation of HDAC2 localization or through direct posttranslational modification. Could Hsp70 be acting to regulate access to substrates in a scaffolding role or be targeting of the American Heart Association.

References

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