A New (Heat) Shocking Player in Cardiac Hypertrophy

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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 hypertrophic growth involves alterations in gene regulation, excitation–contraction coupling, extracellular matrix remodeling, and energy metabolism.

Among molecules known to regulate hypertrophic gene 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 report[4] implicated the class I HDAC member HDAC2 as a positive regulator of hypertrophy and showed that this prohypertrophic activity is acetylase-dependent and possibly involves release of repressors of Akt signaling by interaction with an atypical homeodomain protein, Hop.[5,6] On the other hand, HDAC3 (another class I family member) appears to regulate metabolism and differentiation in heart, independent from effects on 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.[1] 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 al[14] 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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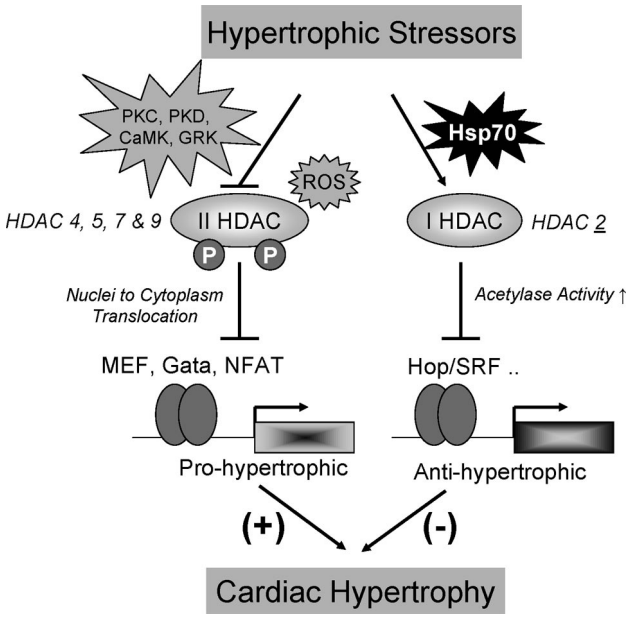

Figure. Distinct roles of HDACs to regulate cardiac hypertrophy. Various hypertrophic stressors are known to induce class II HDACs by promoting their relocalization from nucleus to cytoplasm, thereby removing their inhibition of prohypertrophic cardiac transcription. Recent studies, including those examined in the article by Kee et al,[14] suggest an alternative mechanism for the participation of the class I HDAC2 in hypertrophy. 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 functioning within the nucleus to alter HDAC2 activity in a manner opaque to the subcellular localization studies performed in the present article? That both proteins localize to the nucleus and that this intracellular address is unchanged by hypertrophic stimuli raise the possibility that Hsp70 coordinates protein interactions between HDAC2 and its modifiers/substrates. This idea is supported by the data in the present study showing that although Hsp70 and HDAC2 interact directly in the absence of other proteins, this interaction alone is insufficient to significantly induce HDAC2 activity. Increased HDAC2 activity is only observed when Hsp70 is added concomitant with the cellular lysate, again highlighting the need to understand the molecular identities of HDAC and Hsp70 modifiers and their collective relationship to cell growth. Yet, it is surprising that in Hsp70-null heart, hypertrophic induction of HDAC2 activity is completely abolished. Rectifying this observation with the other molecules involved in HDAC-dependent cell growth will provide a molecular basis for and lend credibility to this working model.

Second, Hsp70 is widely expressed, has many interacting partners (such as calcineurin) and has been implicated in cardiac protection against ischemic stress and other cardiac dysfunctions, especially those involving sarcoplasmic reticulum calcium regulation.[18–20] Hsp70-null mice are reported to have impaired SR calcium handling in hypertrophy.[21] It is not clear whether the attenuated hypertrophy observed in Hsp70-null heart can be solely attributed to its regulatory function toward HDAC2. Although the authors have begun to explore this avenue, unequivocal determination of the isoform-specific roles of Hsps and HDACs in this relationship will require additional studies using both recombinant proteins to examine direct interactions, as well as protein interaction (and perhaps imaging) approaches in the whole cell/organ. Finally, HDACs have nonhistone targets that potentially play important roles in the development of hypertrophy.[22] Indeed, in addition to hypertrophy, contractile dysfunction and remodeling of the extracellular matrix are also observed in HDAC2 transgenic hearts.[4] The role of Hsp70 in these phenotypic manifestations remains unknown.

Resolution of these and other critical uncertainties must precede evaluation of the clinical value of Hsp70 in hypertrophy or other cardiac disease. The present study identifies a new player in cardiac hypertrophy but, moreover, underscores the essential role of isoform-specific protein interactions in signaling specificity. Until we know the proteins interacting with HDAC2 (and Hsp70) in the normal and diseased heart, targeted modulation of their function will lack the context dependency required for fidelity. Furthermore, this study highlights the underlying challenges to design therapeutic strategies using HDAC2 or Hsp70 as potential targets. Hsp70 may be both protective and deleterious by virtue of interacting with different partners. On the other hand, HDAC2 appears to be the only HDAC family member examined thus far that has strong prohypertrophic activity. Therefore, any manipulation of Hsp70 or HDAC activity using small molecules must consider specificity in addition to potency to achieve selective enhancement of beneficial effects while minimizing the damaging ones.

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Disclosures

None.

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