In response to various hypertrophic stimuli, the heart undergoes alterations in structure and function. One mechanism by which the heart adapts to physiological and pathological stimuli is an increase in size of individual cardiac myocytes, and when those stimuli are removed, the size of the myocytes can decrease. Modulation of cardiac size thus requires a very careful balance between protein synthesis and protein degradation, and any imbalance in these systems could be of potential damage to the heart. Increased protein synthesis in hypertrophied hearts is accompanied by "protein quality control" to eliminate aggregated unfolded proteins, but a failure of this monitoring system eventually leads to cardiac dysfunction.1 Heat shock proteins (HSPs) have chaperone-like properties that can bind to unfolded proteins and prevent their denaturation and aggregation.2 In recent genome surveys of mice, rats, and humans, small-molecular-weight heat shock proteins (sHSPs ≈ 15 to 30 kDa) have been identified. αB crystalline (CryAB) is a member of the sHSPs that is expressed at high levels in cardiomyocytes.3 CryAB has chaperone-like properties and also binds to both desmin and cytoplasmic actin which helps to maintain cytoskeletal integrity. Previous studies have shown that a mutation in CryAB mimics a form of desmin-related cardiomyopathy.3 Overexpressing CryAB in cultured cardiomyocytes and in transgenic mouse hearts protects against ischemia/reperfusion–induced cell death4,5; on the other hand, double knockout of the small heat shock proteins CryAB/SHSP2 induces abnormal cardiac growth and defective myocardial relaxation.6

In this issue of Circulation Research, Kumarapeli et al7 address and confirm the roles of CryAB in response to a different type of cardiac insult: pressure overload. Additionally, they used neonatal rat cardiac myocytes (NRCMs) overexpressing CryAB to determine its effects on agonist stimulation. After 2 weeks of thoracic aortic constriction (TAC) in nontransgenic (NTG) mice, there were significantly increased levels of CryAB protein with concomitant increases in phospholamban expression. Compared to NTG mice, KO mice displayed both systolic and diastolic dysfunction, with greater increase in fetal genes at 18 weeks of age under basal conditions. Thus, CryAB and HSPB2 are required to maintain normal cardiac function in both basal conditions, as well as in response to a general stress.8

Another issue addressed by this article is the connection between CryAB and the calcineurin/NFAT pathway, long implicated in pathological cardiac hypertrophy. Genetic manipulation of signaling pathways in mice and biochemical analyses have shown that calcium/calmodulin (Ca2+/CaM)-dependent signaling plays a pivotal role in pathological cardiac hypertrophy.9 An increase in cytoplasmic Ca2+ binds to calmodulin and activates calcineurin, which can dephosphorylate NFATs (nuclear factors of activated T-cells). Dephosphorylated NFATs migrate into the nucleus and promotes gene expression. Recent work delineates several negative regulators of calcineurin pathway. The z-disc protein calsarcin (CS)1 prevents cardiomyocyte hypertrophy in response to several Gq-coupled agonists such as angiotensin II, phenylephrine, and endothelin-1. Overexpression of CS1 results in suppression of cardiac hypertrophy in response to Gq agonist stimulation without impairment of contractile function. Deficiency of CS1 sensitizes mouse hearts for calcineurin signaling and thereby exacerbates pathological cardiac hypertrophy.10 However, calsarcin-deficient mice subjected to exercise exhibited no differential hypertrophic growth.11 Similar results were reported in hearts from forkhead box transcription factors, O subfamily (Foxo)3-null mice that exhibit increased modulatory calcineurin interacting protein (MCIP)1.4, a direct downstream target of the calcineurin/NFAT pathway, and a hypertrophic phenotype with normal systolic function at baseline.12 These results suggest that inhibition of the hypertrophic response is not necessarily associated with a decrease in cardiac function.

Eunhee Chung, Leslie A. Leinwand

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Molecular, Cellular, and Development Biology, University of Colorado, Boulder.

Correspondence to Dr Leslie Leinwand, Professor, University of Colorado, Department of Molecular, Cellular, and Development Biology, Campus Box 347, Boulder, CO 80309-0347. E-mail leslie.leinwand@colorado.edu

Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.108.189720

© 2008 American Heart Association, Inc.
Both in vivo and in vitro models were used by Kumarapeli et al. to define the role of CryAB in the calcineurin/NFAT pathway. The MCIP1.4 isoform has been shown to be tightly regulated and required for the conversion of HSFI monomers to form homotrimers, which bind to specific recognition motifs, termed heat shock elements (ie, inverted repeats of nGAAn), located within promoter regions of target genes, and activates transcription of HSPs. Pressure overload or neurohormonal activation triggers calcineurin/NFAT signaling pathways. Activation of CryAB inhibits cardiac hypertrophy, at least in part, by blunting calcineurin/NFAT signaling pathways. Foxo indicates Forkhead box transcription factor; HSE, heat shock element.

This study addresses the critical role of CryAB in the early phase of the cardiac hypertrophic response to pressure overload. A schematic representation of the role of Hsps in cardiac hypertrophy. Activation of hsp gene expression is highly conserved and required for the conversion of HSFI monomers to form homo trimers, which bind to specific recognition motifs, termed heat shock elements (ie, inverted repeats of nGAAn), located within promoter regions of target genes, and activates transcription of HSPs. Pressure overload or neurohormonal activation triggers calcineurin/NFAT signaling pathways. Activation of CryAB inhibits cardiac hypertrophy, at least in part, by blunting calcineurin/NFAT signaling pathways. Foxo indicates Forkhead box transcription factor; HSE, heat shock element.

This study addresses the critical role of CryAB in the early phase of the cardiac hypertrophic response to pressure overload. A schematic representation of the role of Hsps in cardiac hypertrophy. Activation of hsp gene expression is highly conserved and required for the conversion of HSFI monomers to form homo trimers, which bind to specific recognition motifs, termed heat shock elements (ie, inverted repeats of nGAAn), located within promoter regions of target genes, and activates transcription of HSPs. Pressure overload or neurohormonal activation triggers calcineurin/NFAT signaling pathways. Activation of CryAB inhibits cardiac hypertrophy, at least in part, by blunting calcineurin/NFAT signaling pathways. Foxo indicates Forkhead box transcription factor; HSE, heat shock element.

References

factors blunt cardiac hypertrophy by inhibiting calcineurin signaling. 

**Circulation.** 2006;114:1159–1168.


**Circ Res.** 2000;87:e61–e68.


**Circ Res.** 2006;99:1411–1418.


**Key Words:** pressure overload ▪ heat shock proteins ▪ cardiac hypertrophy ▪ calcineurin/NFAT signaling
Rescuing Cardiac Malfunction: The Roles of the Chaperone-Like Small Heat Shock Proteins
Eunhee Chung and Leslie A. Leinwand

Circ Res. 2008;103:1351-1353
doi: 10.1161/CIRCRESAHA.108.189720

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/103/12/1351

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/