

A H(a)rd Way to Adapt in Cardiac Hypertrophy

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HHeart is a highly regulated organ with remarkable abilities to adapt in response to physiological or pathological stresses.¹ Cardiomyocyte hypertrophy and remodeling develop initially as compensatory steps to cope with increased hemodynamic load or loss of viable myocardium, whereas maladaptive changes contribute to transition to decompensation and overt heart failure. In the past decade, many biological processes have been uncovered to contribute to the initiation and progression of cardiac hypertrophy at molecular level, morphological level, and functional level.^{2–8} The complex network of stress response pathways in heart often serves as both culprits and potential therapeutic targets, and therefore uncovering these pathways has become a focus of intense investigation in the field of molecular cardiology.

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Protein synthesis and quality control within endoplasmic reticulum (ER) are critical to cellular homeostasis and are tightly regulated by a highly conserved ER stress response signaling network⁹ (Figure). The outcome of the ER stress response includes attenuated de novo protein synthesis by protein kinase R-like endoplasmic reticulum kinase (PERK)-mediated inhibition of translation initiation,¹⁰ increased protein folding capacity via inositol-requiring enzyme 1 (IRE-1)/X-box binding protein 1 (Xbp-1)/activating transcription factor 6 (ATF-6)-mediated transcriptional activation of ER chaperone genes,¹¹ such as binding immunoglobulin protein (BiP), and enhanced protein degradation capacity by ER-associated protein degradation (ERAD).¹² This is an integrated and elegant feedback system to ensure that the cellular ER capacity matches with the dynamic changes in ER protein load. Although ER stress response functions as a compensatory and protective mechanism under physiological conditions, overactivation of the ER stress response can lead to pathological consequences. Indeed, excessive ER stress signaling has been implicated in a large number of human diseases affecting systems from neural immunity to metabolism.^{13,14} In the heart, ER stress induction is a common phenomena in stressed myocardium.^{15,16} Among

the 3 downstream consequences of ER stress signaling, the cardioprotective effects of suppressing protein synthesis by protein kinase R-like endoplasmic reticulum kinase¹⁷ or enhancing ER protein folding capacity by Xbp-1/ATF-6/BiP^{18–20} against pathological remodeling have been demonstrated. In this issue, a report by Doroudgar et al²¹ has revealed the essential role of 3-hydroxy-3-methylglutaryl coenzyme A reductase degradation protein 1, or Hrd1, as an ER-targeted E3 ubiquitin ligase critical to ERAD in cardioprotection against pressure-overload-induced hypertrophy in heart. Thus, all 3 major downstream targets of ER stress signaling, including protein synthesis, folding capacity, and targeted degradation, have now been demonstrated to be critical to cardiac adaptation to stress.

The current report by Doroudgar et al²¹ is an extension of a previous work in the laboratory of Glembotski, which showed the cardioprotective function of the ER stress regulator ATF-6 in the heart.²² This work led to the identification of the genes induced in ATF-6 transgenic hearts, including a known ERAD regulator Hrd1.^{23,24} In the current study,²¹ Hrd1 is shown to be a direct downstream target gene induced by ATF-6 and Xbp-1 in response to ER stress in cardiomyocytes. Using degradation of an exogenously introduced HA-tagged T-cell antigen receptor α -chain as a functional readout for the ERAD function, the authors report that Hrd1 induction is essential to augmented ERAD activity in the ER-stressed cardiomyocytes. Loss-of-function studies targeted to Hrd1 in vitro establish that Hrd1 expression is necessary for cardiomyocyte survival under ER stress. Remarkably, targeted suppression of Hrd1 expression in vivo exacerbates pathological remodeling and functional decompensation in pressure-overload heart. Therefore, Hrd1 expression is a critical component of ER stress response in cardiomyocytes with important cardioprotective function against pathological remodeling. More importantly, authors use adeno-associated virus 9-mediated gene transfer to achieve targeted Hrd1 expression in intact heart. Hrd1 overexpression significantly attenuates cardiac hypertrophy and preserves cardiac function against pressure overload. Taken together, this evidence suggests that Hrd1-mediated ERAD regulation is not only essential for compensatory adaptation in stressed heart but also can be potentially targeted to ameliorate pathological remodeling.

Adaptation and maladaptation are key to understanding the critical transition from compensated hypertrophy to decompensated heart failure. Several studies, including the current report,²¹ have demonstrated that the signaling components involved in all aspects of ER stress pathways are indeed part of the cellular adaptation and maladaptation process in the stressed heart. ER capacity and flux seem to be a critical player in heart, where the resolution of ER stress can significantly affect the functional outcome under pathological stress. Although insufficient ER capacity can exacerbate cardiac pathology and heart failure, enhanced ER capacity attenuates pathological remodeling and dysfunction. It is known that misfolding of ER

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

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DOI: 10.1161/CIRCRESAHA.115.307164.)

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Circulation Research is available at <http://circres.ahajournals.org>

DOI: 10.1161/CIRCRESAHA.115.307164

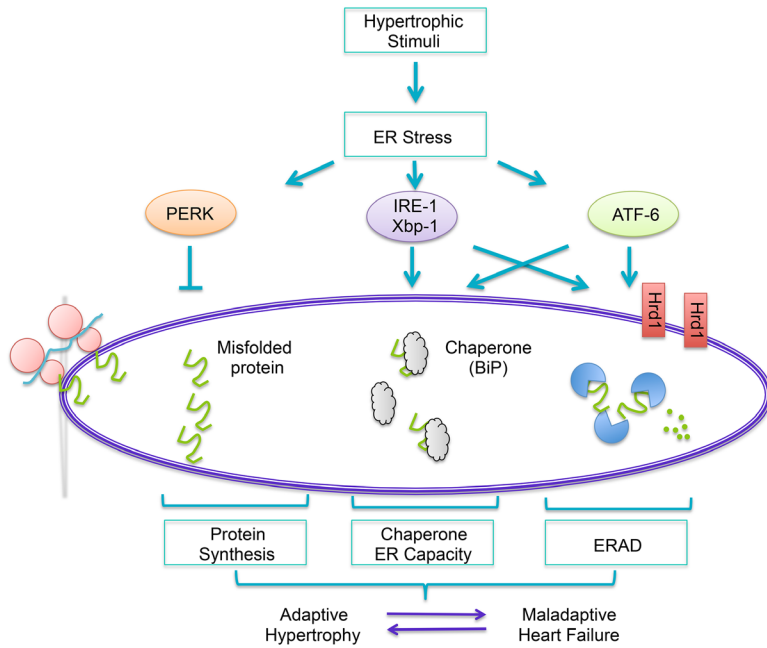


Figure. Illustration of adaptive ER stress pathways in cardiac hypertrophy. ATF-6 indicates activation transcription factor-6; Bip (also known as Grp78), binding immunoglobulin protein; ER, endoplasmic reticulum; ERAD, ER-associated protein degradation; Hrd1, 3-hydroxy-3-methylglutaryl coenzyme A reductase degradation protein 1; IRE-1, inositol-requiring enzyme 1; PERK, protein kinase R-like endoplasmic reticulum kinase; and Xbp-1, X-box binding protein 1.

proteins can be induced not only by increased protein synthesis load but also by a variety of pathological changes, such as protein oxidation, post-translational modifications, and reduced proteasome capacity. Therefore, it would be a logical extension from the current study to demonstrate whether Hrd1-mediated ERAD can also affect the pathogenesis of heart failure under different causes in addition to mechanical overload, such as ischemic-reperfusion injury or chronic adrenergic stimulation. Furthermore, although enhancing ER capacity (by ATF-6/Xbp-1) or reducing ER load (by PERK or Hrd1) confers significant protection against pathological modeling in heart, it is not clear whether the underlying molecular mechanism is limited to the ER. It has been shown previously that ER stress signaling has broad impact on cell metabolism and gene regulation beyond the confines of ER modulation^{18,25,26}; therefore, the cardioprotective mechanism may potentially involve not only more than the resolution of ER stress but also other cellular protective pathways in heart. Even more relevant to therapy, it would be critical to evaluate whether the maladaptive state of the ER stress can be reversed in heart by increasing ER capacity or reducing ER load. Targeted gene delivery using novel serotypes of AAV vectors as demonstrated in the current study or small molecules targeted to ER stress sensors²⁷ can be implemented at different time points after the onset of pressure overload or different stages of pathological remodeling. The outcome of such investigation can help to put this question to the test: whether rebalancing ER homeostasis can block or even reverse the progression of pathological hypertrophy and dysfunction. In that regard, the study by Doroudgar et al²¹ is an exciting first step in a long journey to understand and conquer heart failure.

Sources of Funding

This work was, in part, supported by Ministry of Science and Technology of China Grant 2012BAI02B05; National Institute of Health grants HL108186, HL103205, HL098954, and HL080111 (to Dr Wang). American Heart Association (AHA) Western States

Affiliate Post-doctoral Fellowship Award and AHA Science Development Grant (to H. Sun).

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KEY WORDS: Editorials ■ endoplasmic reticulum stress ■ ERAD pathway ■ heart failure ■ hypertrophy ■ protein folding

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circ Res. 2015;117:484-486

doi: 10.1161/CIRCRESAHA.115.307164

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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