Proteosomal Regulation of Cardiac Hypertrophy
Is Demolition Necessary for Building?

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Left ventricular hypertrophy (LVH) is a common adaptive response of the heart to the increased workload associated with hypertension.1 Essential hypertension is characterized by an increase in total peripheral resistance.2 Mechanical modeling of the cardiovascular system suggests that a necessary consequence of increased downstream resistance to flow is increased pressure to maintain end organ perfusion. Energetically, increased pressure generation requires greater work to be performed by the existing cardiac mass or an increase in cardiac mass to normalize workload per unit of mass. The result of LVH is to normalize wall tension and workload. According to the law of Laplace, increased wall tension is induced by the increased pressure and may also be induced by an increase in the fluid-containing volume of the left ventricle because of the partially elastic expansion of the ventricle under greater pressure loads.3 Without hypertrophy, increased workload by the existing cardiac mass would require greater perfusion of the myocardium or decreased cardiac reserve. Increased wall tension has the potential to decrease myocardial compliance, thereby limiting myocardial perfusion. In this scenario, it is not surprising that inhibition of cardiac hypertrophy in response to increased peripheral resistance is detrimental. Indeed, Meguro et al4 found that inhibition of LVH due to pressure overload in mice resulted in an increase in death due to heart failure. Inhibition of postinfarction cardiac hypertrophy has also been shown to cause left ventricular dilation and diminishment of cardiac function.5 This topic is well reviewed by Morisco et al.6

Editorial

Empirical evidence is beginning to mount, however, that indicates cardiac hypertrophy may be maladaptive. LVH in the human population is poorly explained by blood pressure alone. Ambulatory blood pressure appears to be a better predictor of the variability in left ventricular mass than systolic blood pressure; however, less than 50% of the variability is explained.7 Furthermore, right ventricular hypertrophy coexists with LVH despite a lack of hemodynamic determinants, and antihypertensive therapies differ in their ability to reduce LVH despite shared efficacy in blood pressure reduction.8 Indeed, in uncomplicated hypertension, LVH has been found to be a significant independent predictor of cardiovascular events and all-cause mortality.7 These findings and other studies have stimulated interest in modulating LVH independently of blood pressure to reduce cardiac risk.9

Cardiac hypertrophy as a result of pressure overload has been successfully modulated in animal studies through a number of biochemical pathways. Calcium signaling through calcineurin has been a major approach,10 adenosine receptor stimulation has proved effective potentially through its antiadrenergic effects,11 and ribosomal control of protein synthesis through the mammalian target of rapamycin12 has inhibited pressure overload–induced LVH. These studies and others have stimulated a great interest in understanding the molecular mechanisms underlying cardiac hypertrophy to allow its manipulation independently of other hemodynamic factors.

Cardiac hypertrophy requires an increase in protein synthesis by individual cardiac myocytes.13 Protein synthesis and processing are becoming understood as a highly regulated quality control phenomenon similar to systems that provide fidelity in DNA synthesis. As such, many evolutionary conserved quality control mechanisms are present in all cells to allow for proper protein folding relevant to both normal physiology and disease.14 Part of this quality control mechanism involves the removal from the endoplasmic reticulum (ER) of improperly folded proteins that if allowed to accumulate would result in ER stress and potentially apoptotic cell death. Removal of aberrantly folded proteins from the ER has been shown to be mediated by the ER stress-inducible chaperone GRP78 for targeting to the proteasome for degradation.15 The ubiquitin-proteasome is a key component of the quality control mechanism in protein synthesis, and as many as 30% of newly synthesized proteins are degraded in the proteasome.16 The proteasome is a major component of all protein degradation in the cell. The 26S proteasome consists of 2 main subunits that act in an energy-dependent manner to recognize and digest ubiquitinated proteins.17 Cellular hypertrophy can be thought of as an increase in the cellular accumulation of proteins that results from a tip in the balance whereby synthesis of de novo proteins exceeds protein degradation.

In this context, an increase in protein degradation by the proteasome would lead to cellular and tissue atrophy, as reported previously in denervated soleus muscle.18 However, the article by Depre et al19 in this issue of Circulation reveals the counterintuitive finding that upregulation of the ubiquitin-proteasome degradation pathway occurs with pressure-
induced cardiac hypertrophy. It is perhaps in the context of the quality control function of the 26S proteasome that this finding can be best understood. The increase in protein synthesis required for cardiac hypertrophy could potentially result in an increased load of misfolded or aberrant proteins. To deal with this increased protein load, there should also be a concomitant increase in protein degradation through the 26S proteasome to relieve the burden of these aberrantly folded proteins.

Perhaps the more surprising finding is that inhibition of the 26S proteasome with epoxomicin prevents pressure-induced cardiac hypertrophy in the mouse model of pressure overload used in the study by Depre et al.\(^ \text{19} \) Investigation of the cellular mechanisms that surround protein processing may shed further light on these finding. The increase in protein synthesis responsible for LVH resulted in an upregulation of the 26S proteasome, presumably to deal with the increased load of aberrant or misfolded proteins. It has been shown that inhibition of the 26S proteasome with MG132 resulted in a downregulation of global protein synthesis. This occurred through the phosphorylation of the alpha subunit of eukaryotic translation initiation factor-2 (eIF2\( \alpha \)), primarily by the eIF2\( \alpha \) kinase GCN2, and inhibition of the initiation of translation for protein synthesis.\(^ \text{20} \) Thus, inhibition of pressure overload hypertrophy by proteasome inhibition may be a consequence of the cardiac myocytes attenuating protein synthesis owing to the accumulation of unfolded proteins not removed by the 26S proteasome. Okada et al\(^ \text{21} \) have shown that transverse aortic constriction in mice that results in cardiac hypertrophy at 1 week and heart failure at 4 weeks leads to an upregulation of the ER chaperones GRP78 and GRP94, characteristic markers of ER stress. There was also an upregulation of the eIF2\( \alpha \) phosphorylation-dependent proapoptotic protein CHOP and an increase in apoptosis at 4 weeks after prolonged exposure to ER stress. Proteasome inhibition and resultant eIF2\( \alpha \) phosphorylation through inhibition of the 26S proteasome may precondition the pressure overloaded heart through inhibition of protein synthesis to avoid these longer-term negative consequences of ER stress and apoptotic cell death. If this is indeed the case, loss of cardiac function may be avoided. Alternatively, 26S proteasomal inhibition may contribute to the ER stress response by augmenting the accumulation of unfolded proteins and may worsen cardiac outcome.

The thoracic aortic banding performed by Depre et al\(^ \text{19} \) is a very relevant model of human disease because it mimics the increase in peripheral resistance found in cases of human essential hypertension and is a purely mechanical model, without confounding factors that would result from pharmacologically induced cardiac hypertrophy. The main question that remains for the therapeutic modification of proteasome activity to prevent maladaptive cardiac hypertrophy is that of the longer-term consequences. An upregulation of proteasome activity was seen by Depre et al\(^ \text{19} \) in the long-term canine model of LVH (2 years) and in the short-term mouse model (5 days); however, inhibition of LVH due to proteasome inhibition was only performed in the short-term model. Proteasome inhibition may well be able to prevent cardiac hypertrophy through the cellular regulatory mechanisms of protein synthesis. If this condition results in the accumulation of misfolded proteins leading to ER stress, 26S proteasome inhibition may also lead to cellular apoptosis and cardiac myopathy with chronic treatment. The only way to determine where the balance will lie in the hypertrophying myocyte is to conduct long-term experiments and determine the overall effect on cardiac function. These findings by Depre et al\(^ \text{19} \) provide further insight into the importance of the protein synthesis machinery and its cellular quality control mechanisms in the regulation of normal cardiac function and in cardiovascular disease. Further studies may develop these important insights into viable treatment strategies by exploring the precise impact of proteasomal inhibition on the adapting cardiac myocyte under pressure overload to determine whether this manipulation prevents myocyte cell death, thereby preserving cardiac function.

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None.

**References**


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