Proteasome inhibition in hypertrophied myocardium

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Cardiac remodeling has been described as both an adaptive and a maladaptive process. The adaptive component enables the heart to maintain function in response to pressure overload and has the effect of decreasing ventricular wall stress and compensates for the increased workload preserving cardiac function. Along with the changes in ventricular mechanics, the development of hypertrophy is accompanied by distinct qualitative and quantitative changes in the myocardium. At the cellular level, cardiomyocyte hypertrophy is characterized by an increase in cell size, enhanced protein synthesis, multiplication of sarcomeres, a switch of proteins and enzymes to fetal isoforms (7), changes in intracellular $\text{Ca}^{2+}$ handling (2), metabolic alterations (1), and increased rates of apoptosis (4). Left ventricular hypertrophy in response to pressure overload is primarily the result of myocyte growth, but there are also changes seen in the extracellular matrix with the focus of study being collagen. The extracellular matrix is the scaffold that supports the cellular elements of the myocardium. It is responsible for the maintenance of myocyte shape, alignment, and the overall ventricular geometry. Its composition and structure determines the material properties of the myocardium. Disruption of the extracellular fibrillar support and readaptation facilitates alterations in myocyte size and geometry, which is the structural basis of hypertrophy. However, progressive remodeling and collagen deposition of the extracellular matrix is considered deleterious and results in higher stiffness of the myocardium as seen in failing hearts. If pressure overload remains unrelieved, progressive ventricular dilatation occurs with a further increase in wall stress, afterload mismatch, and deterioration of myocardial function (12).

Cardiac hypertrophy requires an increase in the cellular accumulation of proteins in individual myocytes that results from the synthesis of de novo proteins exceeding protein degradation (13). At the same time, an increase in protein synthesis required for cardiac hypertrophy could potentially result in an increased load of misfolded or aberrant proteins. To relieve the burden of these aberrantly folded proteins, there is a concomitant increase in protein degradation. Protein synthesis and degradation are a highly regulated quality control phenomenon. The proteasome is a system by which the cardiomyocyte breaks down useless proteins to make room for new proteins. The proteasome system also degrades normal proteins that are no longer needed, providing temporal regulation of protein activity (5). The purpose of this system is for the removal of dysfunctional proteins and for the adaptation to new physiological states. As many as 30% of newly synthesized proteins are degraded in the proteasome (6). It therefore plays an important role in cardiac remodeling to maintain cardiac function. In general, increased protein synthesis and reduced degradation are logically linked to hypertrophy (13). It seems counterintuitive that blocking protein degradation by proteasome inhibition results in suppressing the progression of hypertrophy and preserves contractile function at the same time.

The study of Hedhli et al. (6a) presents evidence that the inhibition of the proteasome with epoxomicin prevents cardiac hypertrophy and preserves contractile function in a mouse model of pressure overload. The thoracic aortic banding model used in this study mimics human disease by increasing peripheral resistance without confounding factors that would result from pharmacologically induced cardiac hypertrophy models. Several studies have used inhibitors to implicate proteasome in some facet of cardiac function, but epoxomicin, the inhibitor used in this study, affords irreversible inhibition and is highly specific for the inhibition of chymotryptic activity (8). Also, only 30–40% of the proteasome is inhibited, which potentially limits cellular toxicity as the authors showed in their study.

It is still controversial whether cardiomyocyte hypertrophy is adaptive or maladaptive. Several studies have shown that the prevention of cardiomyocyte hypertrophy in the presence of prohypertrophic signals preserves cardiac function (3). Besides its possible role in cardiac remodeling of the hypertrophied myocardium, protein degradation may also serve as a target for reverse remodeling following the relief of the obstruction. Reverse remodeling can only be successful if irreversible damage such as cardiomyocyte loss or extracellular matrix remodeling can be prevented. This would be especially interesting since one of the novel findings in the present study is that proteasomes regulate fibrosis through NF-kB. Besides apoptosis, proteasomal regulation of NF-kB is also involved in the regulation of collagen degradation through matrix metalloproteinase activation (9). Hedhli et al. (6a) showed that proteasome inhibition in the hypertrophied myocardium directly affects the cardiomyocytes and the extracellular matrix at the same time. At a time point of established hypertrophic changes, the treatment with epoxomicin induces the regression of cardiomyocyte hypertrophy and affects collagen degradation via the activation of matrix metalloproteinasises, which maintains the myocyte-collagen matrix relationship. Treatment directly targeting collagen can also prevent increased collagen cross-linking, which has been proposed as the mechanism of increase in myocardial stiffness.

The benefits from the inhibition of cardiac hypertrophy despite persistence of the prohypertrophic stimulus have only been short term, and long-term results are still missing. Therefore, the long-term-targeting of cardiomyocyte hypertrophy in a heart with increased wall stress might still result in failure. Proteasome inhibition may be able to prevent cardiac hypertrophy by regulating protein synthesis but may ultimately lead to the accumulation of misfolded proteins leading to endoplasmic reticulum stress, actually aggravating endoplasmic reticulum stress that is already associated with pressure-overload hypertrophy, which ultimately results in cellular apoptosis (10, 11). Also, misfolded proteins accumulate, and concentrations of aggregated, misfolded proteins could easily interfere with either cell metabolism or the inherent function of a cardio-
myocyte, since the aggregates can fill a significant volume of the cytosol and deform the cell and/or nucleus.

The main question that remains for the therapeutic modification of proteasome activity to prevent maladaptive cardiac hypertrophy is to determine the balance of synthesis versus degradation in the hypertrophying myocyte by conducting long-term experiments. It remains to be seen whether the regression of cardiomyocyte size and extracellular matrix remodeling or the correction of intracellular signaling provides a better strategy to maintain the function of the hypertrophied heart and delay the onset of failure. Antihypertrophic agents such as proteasome inhibitors will likely have to be combined with complementary strategies to achieve successful treatment of hypertrophy and the prevention of heart failure in patients.

GRANTS

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REFERENCES


