Cardiac Remodeling

UPS Lost in Transit

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When challenged to write an editorial, it is difficult to resist a play of words. To state it up front: UPS is the ubiquitin–proteasome system and not the trusted parcel carrier. UPS also epitomizes our current understanding of the complex system by which the cardiomyocyte (like virtually every cell in the body) breaks down useless proteins to make room for new (and useful) proteins that make up the cell. The concept of protein turnover is not new. More then 60 years ago, Rudolf Schönheimer, a pioneer in the use of stable isotopes to assess biological processes, formulated the revolutionary idea of The Dynamic State of Body Constituents. Today, we recognize that in the heart, like in every other organ of the body, protein turnover is a result of the ordered, regulated, and balanced equilibrium of protein synthesis and degradation (Figure 1). We also recognize the fact, that with both hypertrophic and atrophic remodeling, the fetal gene program is reactivated and rates of protein turnover are increased, although relative rates differ (Figure). Although pathways regulating protein synthesis are already quite well characterized in the heart, our knowledge about pathways that regulate myocardial proteolysis is still limited. Protein breakdown is essential for the removal of dysfunctional proteins and for the adaptation to new physiologic states when it is of advantage for the organism to survive by breaking down its own constituents (e.g., starvation induces skeletal muscle atrophy). Although each protein has its own characteristic half-life, even under normal circumstances, proteins of the heart turn over at an average rate of the ordered, regulated, and balanced equilibrium of protein synthesis and degradation (Figure 1). We also recognize the fact, that with both hypertrophic and atrophic remodeling, the fetal gene program is reactivated and rates of protein turnover are increased, although relative rates differ (Figure). Although pathways regulating protein synthesis are already quite well characterized in the heart, our knowledge about pathways that regulate myocardial proteolysis is still limited. Protein breakdown is essential for the removal of dysfunctional proteins and for the adaptation to new physiologic states when it is of advantage for the organism to survive by breaking down its own constituents (e.g., starvation induces skeletal muscle atrophy). Although each protein has its own characteristic half-life, even under normal circumstances, proteins of the heart turn over at an average rate that would replace all heart proteins in the course of 30 days (H.E. Morgan, personal communication, 2005). Considering the wide range of cell functions, that are regulated by protein degradation, one must assume that proteolysis plays an important role in cardiac function and especially in cardiac remodeling.

A conceptual framework is provided by the pathways of protein degradation in skeletal muscle. Here protein degradation is regulated by 3 major proteolytic systems: (1) the calcium-dependent calpain system; (2) the lysosomal protease system; and (3) the UPS. During atrophy, the calcium-dependent calpain system is involved in the early process of proteolysis and the disassembly of myofibrillar proteins. The lysosomal proteolytic system degrades mainly extracellular and membranous proteins and is part of autophagy. The UPS is a multienzymatic process that degrades most of the cellular proteins. Proteins degraded by the UPS are initially conjugated to ubiquitin. Conjugation requires the activation of ubiquitin by the ubiquitin activating enzyme (E1) in an ATP-dependent reaction. Activated ubiquitin is then transferred to an ubiquitin conjugating enzyme (E2) and linked to the lysine residue in the proteins destined for degradation. This reaction is catalyzed by the ubiquitin ligases (E3). Ubiquitin ligases are believed to convey specificity for this pathway. The same process is repeated to form the ubiquitin chain. The ubiquitin-conjugated proteins are recognized by the 19S subunit of the proteasome and subsequently degraded into peptides in the 20S core proteasome. The peptides are then released from the proteasome and degraded to amino acids by peptidases in the cytoplasm.

The study of Chen et al in this issue of Circulation Research presents evidence that the function of the UPS is severely impaired in the heart of a mouse model of intrasarcoplasmic amyloidosis caused by cardiac-restricted expression of a human desmin-related myopathy-linked missense mutation of αB-crystallin (CryABR120G). The important finding is that an impairment of the UPS was discernible before cardiac hypertrophy and failure, suggesting a contribution of defective protein degradation to cardiac remodeling and failure in this model. Insufficient uptake of ubiquitinated proteins by the 26S proteasome and the depletion of components of the 19S proteasome regulatory subcomplex may be responsible. The derangement was likely the result of aberrant protein aggregation. The result is a novel hypothesis for the pathogenesis of heart failure.

Although the proposed mechanism is intriguing, the studies leave some room for speculation when it comes to the cause of the hypertrophic phenotype in the CryABR120G transgenic hearts. As in all genetically engineered models, deletion or overexpression of a specific gene leads to a host of new questions. For example: Would the hypertrophic phenotype be reversed through rescuing the proteasome function? One approach would be to reverse CryABR120G transfect and myocardocyte hypertrophy. This can be done by Congo Red (which decreases protein aggregation and therefore attenuates UPS malfunction) or cotransfecting the cells with Rpt3 and/or Rpt5 (2 key components of the 19S subunit, which were found to be decreased in the CryABR120G hearts). The latter approach may be problematic, however, because 19S subunits (not measured here) may have also been downregulated and may have contributed to the cardiomyopathy. It is also...
Important to consider that the trafficking mechanism of ubiquitinated proteins to the proteasome may be defective, rather than the proteasome itself. In addition, it is not clear whether this newly proposed mechanism of cardiomyopathy is found in other models of heart failure. The same group of the present study recently showed that the activity of the UPS is increased in an anthracycline-induced cardiomyopathy, suggesting that different types of cardiomyopathy involve different alterations of the UPS. Although studies examining small numbers of patients have shown that amylloid accumulates in the failing human heart, it remains to be seen whether this is a consistent finding. The big question, however, is whether amylloid aggregation is a cause or consequence of failure in the human heart. Still, the idea of an involvement of the UPS in the development of cardiomyopathy is novel and deserves further investigation.

Besides their possible role in cardiac remodeling, pathways of protein degradation may also serve as a target for reverse remodeling of the hypertrophied heart. The development of antihypertrophic agents has so far focused on the inhibition of prohypertrophic signaling (eg, angiotensin-converting enzyme inhibitors or β-blockers). This inhibition is often unsuccessful in decreasing cell size, probably because of the overwhelming redundancy of prohypertrophic signaling pathways. In contrast, activation of atrophy signaling pathways may reverse hypertrophy even in the presence of prohypertrophic signals akin to a “molecular left ventricular assist device.” Several questions have to be answered before such a strategy can be applied. Question 1: Which mechanisms regulate cardiac atrophy? Several lines of evidence suggest that the UPS regulates cardiomyocyte atrophy. First, unloading increases several components of the UPS and decreases cardiomyocyte size. Second, transfection of cardiomyocytes with the transcription factor FOXO3a, a regulator of 2 important ubiquitin ligases, decreases cardiomyocyte size in vivo, suggesting that the UPS is sufficient to induce cardiac atrophy. Future studies have to investigate whether this pathway can indeed reverse cardiomyocyte hypertrophy.

Question 2: Is reversal of cardiomyocyte size in the presence of prohypertrophic signaling of benefit for function and survival of the heart muscle? It is still controversial whether cardiomyocyte hypertrophy is adaptive or maladaptive. This question is especially important in the light of any attempts to reverse cardiomyocyte hypertrophy in the presence of hypertrophic signaling. Several studies have shown that prevention of cardiac hypertrophy in the presence of the prohypertrophic signal does not impair cardiac function or longevity. It remains to be seen whether the regression of cardiomyocyte size, or the correction of defective signaling induced by prohypertrophic stimuli, provides a better strategy to improve function in the failing heart. In this context, it is important to note that the ubiquitin ligases Mafbx/Atrogin-1 and muscle ring finger protein-1 inhibit prohypertrophic signaling by repressing calcineurin and blocking protein kinase Cε translocation to focal adhesions, respectively, highlighting the potential dual role of certain ubiquitin ligases to decrease atrophic and decrease hypertrophic signaling.

Although the Nobel committee already “tagged ubiquitin for distinction” last year, we are likely to hear much more about the UPS in the cardiovascular system in the future. Because the UPS regulates a wide range of cell functions, the UPS will serve as an attractive target for drug development in cardiovascular disease. The UPS has already been discovered as a potential target for the treatment of coronary atherosclerosis. We are likely to see a much wider spectrum of applications including the cardiomyocyte and its rebuilding capacity. Of particular interest will be the modulation of ubiquitin ligase activity and binding to its substrate, because, in contrast to the proteasome, ubiquitin ligases convey high specificity and are therefore highly suitable for selective modulation of protein degradation. After Rudolf Schönhelmner formulated the concept of protein turnover by stating, “The new results imply that not only the fuel, but the structural materials are in a steady state of flux,” we only now begin to understand the meaning of his words. The essence of metabolism is change. We have waited far too long to recognize that changes in protein metabolism are main determinants of the function of the cardiomyocyte. In this context, the study by Chen et al is a step in the right direction.

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References


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