Abstract—Many elements contribute to congestive heart failure: changes in perfusion, hemodynamic stresses, alterations in calcium metabolism, and dysregulation of cell signaling pathways. Intervention in these processes forms the basis for current heart failure therapies. Nevertheless, heart failure is primarily a disease of wear and tear; despite everything we know about cardiac physiology and the clinical manifestations of heart failure, only in rare instances does therapy for heart failure normalize cardiac function. Proteins are especially prone to the forces of wear and tear in the heart because they are the primary mechanisms for stress sensing and force generation. Recent evidence supports a role for protein damage and impaired clearance of damaged proteins in the pathophysiology of human heart failure syndromes. The process of monitoring and protecting cardiac cells from accumulation of damaged proteins is known as protein quality control, and the molecular chaperone and ubiquitin-proteasome systems are the primary effectors of this process. Insights from protein quality-control strategies may lead to new concepts about prevention and treatment of human heart failure. This review provides a general overview of these pathways and their known and postulated roles in human heart failure syndromes, with a focus on providing a clinically oriented understanding of these fundamental mechanisms. (Circulation. 2007;115:1456-1463.)

Key Words: heart failure ■ hypertrophy ■ ischemia ■ proteins ■ apoptosis

The Ubiquitin-Proteasome System and Protein Quality Control
Pathways that control protein folding and degradation may seem too fundamental to play a specific role in cardiovascular disease, but in truth the heart depends on these processes as much as, if not more than, any other organ. Protein quality control is the process by which the cell determines whether or not a protein is functional, is in a nontoxic conformation, and is fit to be transported to its site of action. Protein quality control begins even as proteins are synthesized and continues throughout the lifespan of a protein, with constant interrogation for evidence of protein damage or misfolding (Figure 1). The molecular chaperones are the major contributors to this surveillance process, and specific molecular chaperones exist in every cellular compartment to address the specificities of protein folding within different environments.1 For example, chaperones such as calnexin and gp96 exist within the endoplasmic reticulum to address the conformational problems of heavily glycosylated proteins. In contrast, the heat shock proteins Hsp70 and Hsp90 are the major chaperones within the cytoplasm. These highly abundant proteins detect evidence of misfolding or damage (such as exposed hydrophobic residues) in client proteins. Chaperones have 2 classic, independent activities: (1) to hold misfolded proteins to prevent their aggregation and (2) to fold damaged proteins back into their native conformations.

Surveillance, holding, and folding are important arms of the protein quality-control machinery, but the cell is still left to deal with proteins that can no longer be repaired (Figure 1). Damaged proteins potentely activate apoptotic pathways and are prone to aggregation or other gain-of-function toxicities that damage cells. Therefore, the protein quality-control...
machinery must also be able to target damaged proteins for removal. The molecular chaperones make decisions about whether client proteins undergo refolding or degradation via chaperone-dependent protein degradation, a decision process that is called protein triage. The ubiquitin-proteasome system is the primary mechanism used by the cell to accomplish chaperone-dependent protein degradation. The linkage between molecular chaperones and the ubiquitin-proteasome system is highly conserved evolutionarily and possibly reflects the original intent of the ubiquitin-proteasome system to degrade damaged proteins. In cells such as cardiac myocytes that are particularly prone to protein damage because of mechanical forces or abundant levels of oxidative species, protein quality-control mechanisms must be highly evolved to maintain sarcomere integrity and contractile function. However, little is known at present about specific mechanisms of cardiac myocyte quality control.

Although the ubiquitin-proteasome system mediates chaperone-dependent protein degradation, it is also adapted to degrade proteins that require removal from the cells under other circumstances. The proteasome is a barrel-shaped multicomponent protease that recognizes proteins decorated with ≥4 ubiquitin residues. As the name implies, ubiquitin is a small, ubiquitously expressed protein that is covalently attached to proteins in linear chains via a specific enzymatic reaction. The rationale for assembling ubiquitin in chains is not entirely clear, but it probably provides an amplification of signal to maximize efficiency of recognition and also allows discrimination between ubiquitin and ubiquitin-like proteins (which are not discussed in detail in this review.) The proteasome unfolds the tagged protein, removes the ubiquitin chain, and cleaves the protein into short peptides and amino acids through a variety of intrinsic protease activities.

A series of enzymatic reactions is required for ubiquitin chain assembly, involving ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3). Ubiquitin ligases are the rate-limiting step in this enzymatic cascade, participating in both substrate recognition and the catalytic transfer of ubiquitin, and thus their activities are highly regulated. For example, the cochaperone/ubiquitin ligase CHIP (carboxyl-terminus of Hsp70-interacting protein) is recruited to misfolded proteins bound to Hsp70 to ubiquitylate them and target them for degradation, whereas ubiquitin ligases of the SCF (Skp-cullin-F-box) class generally recognize substrates when they are phosphorylated. E4 ligases that facilitate ubiquitin chain elongation have also been recognized, although their activity seems to be required in only a minority of ubiquitylation reactions. Conversely, deubiquitylating enzymes perform the opposite role, removing ubiquitin residues from proteins to affect their stability and interactions with the proteasome. Differences in expression and activity of ubiquitin ligases and deubiquitylating enzymes allow the ubiquitin-proteasome system to participate in both protein quality control and targeted protein degradation, both of which are critical functions for the ubiquitin-proteasome system in regulating cardiovascular function.

The Ubiquitin-Proteasome System in Cardiac Tissues

Many housekeeping components of the ubiquitin-proteasome system, as well as an increasing number of key cell-specific regulators, are expressed in the heart, and many of these are differentially regulated under pathophysiological conditions. The proteomic identification of the deubiquitylating enzyme ubiquitin C-terminal hydrolase in a bovine congestive heart failure model was one of the first indications for a potential molecular role for the ubiquitin-proteasome system in cardiac dysfunction, and since that time systematic dysregulation of ubiquitin itself, as well as ubiquitin-conjugating enzymes, ubiquitin ligases, and proteasome components, has been described. These observations are not altogether surprising because physiological studies demonstrated long ago that increased protein turnover occurs during cardiac atrophy and reversal of hypertrophy. It is surprising that so little is known about the mechanisms that underlie changes in turnover of cardiac proteins, especially within the contractile apparatus. However, recent studies have begun to provide clarity on these processes.

Atrogin-1/MafBx

Given the unique qualities of contractile striated muscle cells within the heart, it is intuitive that specialized components of
the ubiquitin-proteasome system must exist within the heart. Indeed, ubiquitin ligases that are expressed specifically in striated (cardiac and skeletal) muscle have been identified. Atrogin-1/MafBx, an F-box–containing protein, is 1 of 2 ubiquitin ligases identified in screens for atrophy-associated proteins in skeletal muscle, and atrogin-1 is also expressed in cardiac muscle cells.\(^1\) Remarkably, atrogin-1 is upregulated markedly in skeletal muscle in response to a variety of stimuli that diminish muscle mass and is regulated transcriptionally by Forkhead transcription factors.\(^1\) Because Forkhead proteins such as Foxo1 and Foxo3a are repressed by hypertrophic stimuli such as insulin-like growth factor-1 in skeletal muscle, this provides an attractive mechanism for counter-regulation of skeletal muscle size depending on the balance of hypertrophic and atrophic stimuli.

Atrogin-1 is also expressed in the heart, where it undergoes regulation by Forkhead transcription factors, which are potent suppressors of cardiac hypertrophy.\(^1\) This relationship suggests that atrogin-1 has a role in general antihypertrophic pathways. Indeed, increased levels of atrogin-1 suppress cardiac myocyte hypertrophy induced by adrenergic stimulation in vitro and pressure overload in vivo.\(^1\) The mechanism for this action is due, at least in part, to suppression of calcineurin activity through atrogin-1–dependent ubiquitylation and proteasome-dependent degradation of calcineurin. These processes potently inhibit cardiac hypertrophy because calcineurin is a crucial signaling intermediary in potent prohypertrophic programs that are activated under pathophysiological conditions. Whether atrogin-1 also regulates cardiac muscle mass in response to other stimuli, such as insulin-like growth factor-1, remains to be determined.

**MuRF Family Proteins**

Atrogin-1 is not the only cardiac-specific ubiquitin ligase. A structurally dissimilar family of RING-B-box-coiled coil ubiquitin ligases, comprising the 3 MuRF (muscle ring finger) proteins, is also expressed with varying degrees of specificity in striated muscle.\(^9\)\(^,\)\(^13\)\(^,\)\(^14\) The MuRF proteins have nonredundant cellular effects, with MuRF1 having antihypertrophic effects in the heart through ubiquitin ligase activities directed toward sarcomeric proteins such as troponin I and also the signaling factor protein kinase Cε.\(^15\)\(^,\)\(^16\) MuRF2, in contrast, is sarcomere associated, and evidence suggests that it plays a role in mechanical stress transduction through effects on serum response factor activity.\(^17\) The third member of this family, MuRF3, has an entirely different intracellular pattern of expression, being associated with microtubules, which suggests that it may play a role in microtubule assembly and disassembly.\(^14\) MuRF1 is the only 1 of the 3 family members for which a link to cardiac myocyte size determination has been established, and it is possible that the diverse molecular functions of these proteins reflect different physiological roles for MuRF proteins within the heart.

**Other Ubiquitin Ligases**

Although atrogin-1 and the MuRFs are the only well-characterized muscle-specific ubiquitin ligases, hundreds of ubiquitin ligases are probably active in each cardiac cell, and most of these probably participate in general cellular events. However, several other ubiquitin ligases merit specific mention in the context of cardiac myocyte biology. CHIP, as mentioned above, is a U-box–containing cochaperone/ubiquitin ligase that regulates several coordinated aspects of protein quality control, such as transcriptional activation of stress response proteins, degradation of damaged proteins, and restitution of the stress response.\(^18\)\(^–\)\(^20\) CHIP is highly expressed in the heart, and, as one would expect, CHIP plays a protective role in the setting of cardiac ischemia/reperfusion injury.\(^21\)

Because it participates in such central regulatory events, the cell cycle and apoptotic regulator p53 is under the control of several ubiquitin ligases. The best-characterized ubiquitin ligase for p53 is MDM2, another RING finger protein. MDM2 initiates a coordinated process of ubiquitylation and nuclear export that results in inactivation of the transcriptional activities of p53 to check its effects on cell cycle arrest and apoptosis.\(^22\) The loss of MDM2 therefore has disastrous consequences, such that mice that lack this ubiquitin ligase die before birth.\(^23\) On the basis of its activity toward p53, MDM2 is logically necessary for cardiac myocyte responses to hypoxia and ischemic injury.\(^24\) It is less self-evident that MDM2 would play a role in the cardiac hypertrophic response, but MDM2 overexpression promotes survival and prevents hypertrophy induced by adrenergic stimulation; indeed, the antihypertrophic effect of MDM2 may be independent of its ubiquitin ligase activity,\(^25\) although a deeper understanding of this phenomenon is required.

The inhibitors of apoptosis (IAP) family of proteins blocks cytochrome c–dependent apoptosis at several levels but in part through ubiquitylation and inhibition of caspases. Because cardiac myocytes are postmitotic, the strict regulation of their ability to activate the apoptotic machinery is crucial to maintenance of cardiac integrity. The critical IAP family member in cardiac myocytes is XIAP, which is also the crucial antia apoptotic factor in postmitotic neurons.\(^26\) The ability of XIAP to selectively prevent caspase-dependent apoptotic engagement depends on low levels of the specific IAP inhibitor Apaf-1 (apoptosis-activating factor), and restoration of Apaf-1 levels elicits rapid activation of apoptosis in cardiac myocytes that are otherwise resistant to caspase activation. Although not yet tested in vivo, this inhibitor presumably represents a critical mechanism of protection for cardiac myocytes in settings such as ischemia/reperfusion injury.

**The Cardiac Proteasome**

The principle that ubiquitin ligases are checkpoint regulators of proteasome-dependent protein degradation is well accepted. One may conclude from this that the proteasome should have a generic cellular role, with little reason to vary its structure and function from one cell type to another. However, recognition of cell-specific proteasome activities has renewed interest in the variation of the 30 to 50 protein subunits that comprise the proteasome in different cell types. Using remarkable proteomic-based techniques, the nature of the cardiac proteasome is being unraveled, and a remarkable degree of variability and regulation is being revealed in the process. The cardiac proteasome has at least 34 different
subunits, some of which undergo cardiac-specific alternative splicing and/or posttranslational modification, which presumably confer specific proteolytic functions that are required for normal cardiac function. In addition, specific cardiac proteasome-associating factors (protein kinase A and protein phosphatase 2A) with regulatory activity presumably enhance the diversity of proteasome function in the heart. Inhibition of the cardiac proteasome has been shown to be cardioprotective under some circumstances, indicating the clinical potential for understanding its function. Although the activation and regulation of the cardiac proteasome under pathophysiological circumstances are as yet not revealed, the major advances in our understanding of this multicomponent protease open up new vistas for appreciating biochemical mechanisms and identifying new therapeutic targets in cardiovascular diseases.

**Disorders of Protein Misfolding and Degradation**

Although the focus of this review is on the role of defective protein degradation in heart failure syndromes, it is instructive to consider the consequences of impaired protein quality control in other pathophysiological circumstances, if only because the chain of causality is so much clearer at the present time. Specific mutations, especially in ubiquitin ligases, have been associated with congenital defects in humans, presumably because of defective degradation of specific proteins (Figure 1). Mutations in components of the ubiquitin-proteasome machinery have also been linked closely with a number of neurodegenerative diseases. Perhaps more common from a genetic perspective are mutations in proteins that affect their own turnover via the ubiquitin-proteasome system. In some cases, mutations enhance a protein’s recognition by the protein quality-control machinery, eliciting a loss-of-function phenotype. The classic example of loss of function occurs in cystic fibrosis, in which a mutation in the cystic fibrosis transmembrane conductance receptor routes an otherwise functional protein to a sequential degradation pathway that utilizes the ubiquitin ligases CHIP and RMA1. Genetic lesions can also have the opposite effect by promoting stability of aberrant proteins and suppressing specific or general protein degradation pathways to produce a gain-of-function phenotype. The polyglutamine-expansion diseases typify this group. Repetitive sequences of glutamine in a protein that are prone to expand over generations because of “slippery” defects in the DNA replication machinery predispose these proteins to misfolding, resistance to degradation, and accumulation intracellularly or extracellularly to produce toxic effects. Many examples of polyglutamine-expansion diseases exist in the nervous system, with Huntington’s disease being a deadly representative.

Alzheimer disease is another disease that has a similar gain-of-function phenotype, but, in contrast to the polyglutamine-repeat diseases, Alzheimer disease only infrequently exhibits mendelian genetics. Although some instances of this disease are clearly familial, Alzheimer disease is more frequently sporadic, which suggests a poorly understood interplay between environmental, developmental, and subtle genetic factors that culminate in the tragic neuropsychiatric consequences of this syndrome. Regardless of the cause, the pathology is typified by cortical plaques consisting of amyloidlike accumulations of hyperphosphorylated Tau protein. The β-sheet protein conformation observed in these plaques is a highly stable feature that is present in other diseases with amyloid deposits, suggesting that this is a final common conformational manifestation of some species of aggregated, insoluble proteins.

One noticeable feature among disorders of aberrant protein degradation is the frequency with which the nervous system is affected. Bias may exist that influences the recognition of proteotoxicity as a causative mechanism in the brain, yet this undoubtedly reflects a true biological predisposition as well. Presumably, the combination of high metabolic activity and postmitotic state makes neurons particularly susceptible to the toxic effects of accumulated proteins. It is important to emphasize that the susceptibility of neurons to the toxicities of aggregated and accumulated proteins is relative, not absolute, and that many cell types and organs develop characteristic lesions because of polyglutamine, Tau, or other protein accumulations. Nevertheless, because cardiac myocytes are also metabolically active, postmitotic cells, one may predict that they should be especially prone to the effects of abnormal protein accumulation.

**Aberrant Protein Folding and Defects in Protein Degradation in Heart Failure Syndromes**

**Proof-of-Principle Examples of Protein Quality-Control Defects in Heart Failure**

Like Alzheimer disease and other systemic amyloidoses, cardiac amyloidosis is characterized by accumulations of proteins in a β-sheet conformation that result in this rare, progressive heart failure syndrome (Figure 2). Cardiac amyloidosis can occur in the context of monoclonal gammopathies or other circumstances in which proteins accumulate in degradation-resistant conformations. It is remarkable that, despite the specific proteins that result in intracardiac deposits, the characteristic physiological phenotype of cardiac amyloidosis is similar. Thus, the accumulation of proteins in β-sheet conformation per se in the heart is sufficient to cause amyloidosis. Although an extremely rare cause of heart failure, cardiac amyloidosis has long been the purest representation that defective protein quality control has a pathophysiological role in heart failure.

Although the case of cardiac amyloidosis is instructive as a proof of principle that accumulations of aberrantly folded proteins contribute to cardiac dysfunction, its rarity and almost singular phenotype limit the extent to which it serves as a bellwether. Specific manipulations of protein stability in animal models also suggest that protection against proteotoxicity is necessary to preserve cardiac function under conditions of stress. For example, specific overexpression of molecular chaperones such as Hsp70 to mitigate the toxicities of aggregated proteins can preserve left ventricular function in the setting of ischemia/reperfusion injury and other factors that predispose to heart failure. Conversely, mice deficient in the quality-control ubiquitin ligase CHIP have impaired functional recovery after ischemia/reperfusion injury to the heart, suggesting that the failure to degrade damaged
proteins contributes to left ventricular dysfunction in this setting.

Misexpression of quality-control proteins provides an indirect indication that failure to degrade damaged proteins is toxic to cardiac myocytes. A more direct experimental approach to test this association would examine the consequences of misexpression of a nonnative misfolded protein on cardiac function. This experiment has recently been performed by creating mice that express a protease-resistant prion protein. Prions adopt self-replicating protein conformations that are insoluble and resistant to proteolytic cleavage and are causative agents in a number of dramatic transmissible pathologies such as bovine spongiform encephalopathy and Creutzfeldt-Jakob disease. Remarkably, amyloid deposition and progressive cardiac failure are characteristic features of mice overexpressing protease-resistant prion protein, providing possibly the most direct experimental evidence to date that accumulations of misfolded proteins are directly toxic to the heart and can cause congestive heart failure.

Figure 2. Amyloid heart disease. A, Cardiac amyloid characterized as lightly eosinophilic extracellular matrix encircling each individual cardiac myocyte (from an individual with multiple myeloma; magnification ×100). B, Characteristic 8- to 10-nm-diameter fibrils were identified by transmission electron microscopy in this patient (magnification ×16,000). C, Diffuse low-voltage QRS complex (top) parallels changes in right ventricular filling pressures. Simultaneous right and left ventricle pressure tracings demonstrate a dip-and-plateau morphology of the diastolic waveform (bottom) characteristic of restrictive diseases such as cardiac amyloidosis. D, Sparkling refractile myocardium (arrow) with increased ventricular mass, thickening of the ventricular septal walls, and enlarged atria is characteristic of cardiac amyloid by echocardiography.
The Desmin-Related Cardiomyopathies: Specific Examples of Quality-Control Defects in Human Cardiovascular Disease

The experimental evidence described above provides proof of principle that protein folding and degradation events contribute to cardiac dysfunction. Should these same principles apply to human heart failure, then one would expect to find genetic diseases affecting either substrates or participants in protein quality-control mechanisms that result in familial cardiomyopathy. The strongest evidence for causality would exist when different mutations in a quality-control protein and its cognate substrate result in a similar clinical phenotype. Remarkably, these criteria are met in the case of the desmin-related cardiomyopathies, in which desmin accumulates in a toxic fashion. Mutations in either the abundant cardiac chaperone αB-crystallin or its substrate desmin result in desmin-positive sarcomeric inclusions and concomitant left ventricular dysfunction, ultimately resulting in dilated cardiomyopathy. Elegant studies in mice that have been altered to recapitulate the genetic basis for these diseases indicate that the chaperone activity of αB-crystallin is part of the protein quality-control process that monitors desmin; disease-causing mutations in αB-crystallin abolish this quality-control surveillance process, whereas mutations in desmin prevent its association with αB-crystallin. In either case, desmin is improperly folded and assumes a proteasome-resistant conformation. This conformation in turn suppresses general proteasome activity through a “choking” mechanism, activates specific mitochondrial-dependent apoptotic pathways, and leads to intrasarcoplasmic accumulations of desmin. The phenotype of dilated cardiomyopathy in patients with mutations in either αB-crystallin or desmin is presumably a collective effect of each of these mechanisms. Importantly, animal studies indicate that cardiac dysfunction occurs relatively early in the cascade of cellular events and is reversible if accumulation of the toxic proteins abates.

These observations suggest that altered folding kinetics or enhanced proteasomal targeting may reverse the cardiac defects in patients with desmin-related cardiomyopathies.

General Contributions of Aberrant Protein Folding and Degradation to Cardiac Dysfunction

The detailed genetic and molecular understanding of human desmin-related cardiomyopathies that has emerged over the past few years demonstrates the necessity for intact pathways of protein folding and degradation for efficient cardiac function. Whether dysfunction of these pathways broadly participates in heart failure syndromes, for example, in sporadic dilated cardiomyopathy or in chronic ischemic syndromes, remains to be determined. The precedent from neurological diseases suggests that the desminopathies may represent a specific example of a common mechanism that contributes to human congestive heart failure. Disease-causing myosin-binding protein C mutants also impair the proteasome and permit accumulation of proteins in toxic conformations, suggesting generalizability for this mechanism; it is possible that normal wear and tear of the heart will cause enough protein damage to do the same thing over the life span of a human. The widespread dysregulation of components of the ubiquitin-proteasome system in diseased human specimens, as well as the accumulation of ubiquitylated proteins in specimens from patients with heart failure of various causes, provides additional evidence for this possibility. In addition, accumulations of misfolded proteins adopting β-sheet conformations in human hearts that correspond with severity of dilated and postischemic cardiomyopathy offer a tantalizing suggestion of a causative role for impaired protein quality control in human cardiac dysfunction. Although this link remains speculative in humans at present, collectively this concept merits attention for preclinical therapeutic development.

Unanswered Questions About Cardiac Hypertrophy and Protein Quality Control

The roles of protein quality control and the ubiquitin-proteasome system in cardiac hypertrophy are not simple to intuit. On the one hand, a number of key regulatory pathways that promote cardiac hypertrophy are either targets or components of the ubiquitin-proteasome machinery; on the other hand, the increase in cardiac myocyte mass that accompanies hypertrophy has a self-evident requirement for increased protein synthesis and therefore quality-control activity. In addition to this, many housekeeping cellular functions require ubiquitin-proteasome activity.

Given the multiple roles that are filled by the ubiquitin-proteasome system in cardiac hypertrophy, it is not surprising that a simple model linking ubiquitin-proteasome activity to cardiac hypertrophy is yet to be established. Reports indicate both an increase and a decrease in proteasome activity during cardiac hypertrophy in animal models, as well as increases in proteasome components yet decreases in the active, phosphorylated species of the proteasome. Reports of the use of proteasome inhibitors in both short-term and long-term animal models of cardiac hypertrophy provide some clarity to this picture by indicating that activation of the proteasome is required for cardiac hypertrophy to develop in the setting of pressure overload. The mechanistic explanations for these studies remain to be determined, and inconsistencies between these studies and those of other groups need to be explored. In addition, some fundamental incongruities require explanation. For example, proteasome activity in the heart markedly decreases with aging. If increased proteasome activity is required for cardiac hypertrophy to progress, then why is pressure-overload cardiac hypertrophy so typically a disease of the elderly? In addition, if proteasome activation is necessary for cardiac hypertrophy, why is it also activated during cardiac atrophy? Elegant answers must exist to these and other questions that will grant a better image of the roles of protein quality control and the ubiquitin-proteasome system in cardiac hypertrophy, and these topics remain under active investigation at present.

Conclusions

The fields of study that encompass protein folding and degradation pathways have developed under the guidance of cell biologists who have focused on simple systems, to the enormous benefit of the biomedical community. Nevertheless, the utility of these studies to humans will be in their
application to common diseases such as those that affect the heart. The observations described in this review transcend the differences between fundamental biology and clinically applicable research and provide an example of the payoff in translating basic science observations to cardiologists and the physicians who pay attention to emerging topics in biomedical research. For example, elucidation of the cardiac proteasome may lead to heart-specific pharmacological modulators of the proteasome that would have utility in clinical scenarios such as heart failure. Similarly, the discovery that misfolded proteins accumulate in human heart failure and contribute to the pathophysiology of this common adverse outcome may lead to new ideas about therapeutic approaches that complement the currently available clinical regimens.

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References

7. Samarel AM, Parmacek MS, Magid NM, Decker RS, Lesch M. Protein synthesis and degradation during starvation-induced cardiac atrophy in rabbits. Circ Res. 1987;60:933–941.


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