Protein Quality Control in Heart Disease
Using Established Drugs to Target Novel Mechanisms*

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The heart, along with other cells in the body, requires continuous protein synthesis and degradation, with protein turnover rates of approximately 2% per day. This dynamic process is highly regulated by protein quality control systems that identify and process damaged or misfolded proteins, which increase with stress. Misfolded proteins are escorted by chaperones for repair or disposal via 2 major mechanisms. The ubiquitin–proteosome system (UPS) tags proteins with ubiquitin to identify them for degradation by the 26S proteosome (1). Autophagy degrades proteins and organelles by lysosomal proteinases (2). When these processes are impaired or overwhelmed, protein aggregates can accumulate with potentially toxic effects.

Recognition of UPS as a major mechanism for degrading proteins (awarded the Nobel Prize in chemistry in 2004) has accompanied an emerging appreciation for the role of protein quality control in disease, such as with hypoxia, inflammation, cancer, and neurodegenerative diseases (1). Soluble proteins aggregate to form intermediates and amyloidogenic species that assemble into insoluble fibrils that accumulate in affected tissues or organs. Excessive deposits of protein aggregates contribute to the pathogenesis in Alzheimer’s disease, Parkinson’s disease, and spongiform encephalopathies (prion disease) (3). Amyloidosis is a local or systemic disease secondary to chronic inflammation, plasma cell dyscrasias, or hereditary forms that results in amyloid deposits in different organs, including the heart (4).

Drugs that target UPS have been developed to prevent protein misfolding and accumulation of protein aggregates. Bortezomib, a selective proteasomal inhibitor that inhibits UPS, is the first drug in this new class to receive Food and Drug Administration approval for the treatment of multiple myeloma. Discovery of additional drugs to inhibit abnormal protein aggregates would provide a significant advance because there are few therapeutic options for many of these diseases.

Protein quality control in heart disease. Abnormal protein quality control occurs in cardiac diseases, including hypertrophy, heart failure, cardiomyopathy (5), and atherosclerosis (6). It is still uncertain which forms of abnormal proteins (e.g., soluble or insoluble) are toxic and if protein aggregates are the trigger or the consequence of a given disease process.

In this issue of the Journal, Zheng et al. (7) examined protein aggregation in transgenic mice with cardiac myocyte overexpression of a mutation of αB-crystallin, a small heat shock protein that functions as a chaperone for desmin. Transgenic mice develop a desmin-related cardiomyopathy with aberrant protein aggregation with preamyloid oligomers causing intrasarcoplasmic amyloidosis, concentric cardiac hypertrophy, progressive heart failure, and increased mortality (7). This is similar to desmin-related cardiomyopathy in humans, a family of diseases related to mutations in desmin, αB-crystallin, or myotilin genes (8). Desmin is found in skeletal and heart muscle and Purkinje fibers, so that desmin-related myopathies are associated with skeletal muscle weakness, dilated or hypertrophic cardiomyopathy, arrhythmias, and conduction defects (8).

In the study by Zheng et al. (7), the protein aggregation, cardiac hypertrophy, heart failure, and death developing in transgenic mice with missense mutant αB-crystallin were attenuated with oral doxycycline (added to the drinking water) treatment for 4 weeks, particularly when started early in life. Therapy started later in life (after cardiac hypertrophy and heart failure have developed) remains beneficial by prolonging survival. Doxycycline inhibited protein aggregation in cardiomyocytes in vivo and in vitro, suggesting a novel mechanism for the cardioprotective effects. The mechanisms for doxycycline-induced decreases in misfolded proteins and protein aggregation are not entirely clear, but they do not seem to involve activation of autophagy. Doxycycline may serve as a chaperone or may act at other potential pathway sites to maintain protein quality control (Fig. 1).

Tetracyclines. The tetracyclines are a family of broad-spectrum antibiotics that include tetracycline, doxycycline, and minocycline. They have been used safely for half a century and are well tolerated. The tetracyclines possess pleiotropic properties that broaden their application beyond

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their use as antibiotics (9). Tetracyclines inhibit matrix metalloproteinases, apoptosis, and inflammation and act as antioxidants by scavenging reactive oxygen species. Polycyclic compounds inhibit the formation of abnormal protein aggregates, which is of potential use in diseases with impaired protein quality control.

Tetracycline inhibits conversion of human amylin (a pancreatic hormone cosecreted with insulin) into insoluble amyloid, which occurs in pancreatic B-cells in type 2 diabetes (10). Tetracycline inhibits misfolding of soluble oligomers to delay development of diabetes in transgenic mice that express human amylin/islet amyloid (11).

Tetracyclines cross the blood–brain barrier and have been used in neurodegenerative diseases. Minocycline prevents the accumulation of beta-amyloid and aggregated tau proteins that occur in Alzheimer's disease models (12). Tetracyclines inhibit conversion of cellular prion protein into an insoluble species that is resistant to protease digestion and aggregates into abnormal prions (13). Doxycycline delays the onset of clinical disease and prolongs survival in animal models of prion infectivity (14).

Tetracyclines concentrate in the heart, which led to the early use of radiolabeled tetracyclines to identify experimental myocardial infarction (15). Minocycline is lipophilic and is taken up in the heart, particularly in ischemic myocardium (24- to 50-fold higher concentrations than in blood), where their antioxidant and matrix metalloproteinase inhibitory effects limit injury after myocardial ischemia-reperfusion (16). Similar effects are observed in isolated cardiomyocytes and fibroblasts. The ability of tetracyclines to concentrate in injured tissues in conjunction with their protective properties provides targeted drug delivery without major side effects.

**Conclusions.** The discovery of disorders of protein quality control as a mechanism for disease has led to novel therapeu tic targets with the development of a new class of drugs, such as the protease inhibitor bortezomib. Existing drugs such as the tetracycline family of antibiotics may have similar effects with several potential advantages. Tetracyclines have been used for half a century with proven safety and tolerance, cross the blood–brain barrier, concentrate in the heart, and have anti-inflammatory and antioxidant effects that may limit the formation and toxicity of protein aggregates.

Additional investigations are needed to establish the causality and unique role of protein quality control in each disease to determine when this is a relevant target. If misfolded proteins and protein aggregation occur secondarily, then inhibiting this process will prevent secondary toxic or structural effects, but will not treat the primary cause of disease. It will be valuable to determine if chronic downstream changes, such as the deposition of insoluble protein aggregates, can be reversed by inhibiting upstream events such as the formation of misfolded proteins. Characterizing conditions where protein quality control plays a major role will provide a more rational approach for the successful clinical translation of targeting this unique therapeutic site.

Another challenge for clinical translation will be to define the mechanisms for tetracyclines to inhibit protein misfolding and accumulation of protein aggregates. This would determine if these agents can be used in other diseases with abnormal protein quality control. This would broaden significantly the options to treat diseases with safe drugs for which few effective treatments are available.

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