

Autophagy in Cardiac Physiology and Disease

Joseph A. Hill^{1,2}, Sergio Lavandero^{1,3}, and Beverly A. Rothermel^{1,2}

¹Departments of Internal Medicine (Cardiology), ²Molecular Biology, ³University of Texas Southwestern Medical Center, Dallas, TX; Center for Molecular Studies of the Cell, Faculty of Chemical and Pharmaceutical Sciences/Faculty of Medicine, University of Chile, Santiago, Chile

Elucidation of molecular mechanisms governing pathophysiology in the disease-stressed heart has advanced rapidly in recent decades. However, despite these important advances, emergence of new, clinically meaningful therapeutic strategies, apart from the rapid expansion of device-based therapies, has disappointed. Most patients with heart failure — the final common pathway of many cardiovascular diseases — experience unrelenting disease progression, and heart failure-associated morbidity and mortality remain high worldwide (1). Indeed, World Health Organization estimates point to cardiovascular diseases as the number one cause of death globally (1), a sad ranking which is expected to persist long into the future. Costs deriving from cardiovascular disease morbidity and mortality are staggering, estimated to exceed \$500 billion in the US alone (1). On top of all this, the prevalence of this syndrome is increasing, impacted simultaneously by deteriorations in the Western lifestyle and by success in taming the acutely lethal manifestations of other diseases. In light of these sobering facts, there is urgent need to identify novel mechanisms of pathogenesis and therapeutic targets capable of stemming inexorable progression of heart disease.

Autophagy, an evolutionarily conserved process of cellular cannibalization, has been implicated in virtually all forms of cardiovascular disease. Indeed, for three decades it has been recognized that lysosomal pathways of protein degradation are prevalent in most forms of cardiac pathology (2). Until recently, however, it has been difficult to discern the role(s) of these catabolic pathways: whether they promote or antagonize disease pathogenesis. Now, based on molecular discoveries in yeast, a model has emerged of an intricate cascade of events leading to cargo sequestration and delivery to lysosomes. This process, termed autophagy, is an evolutionarily conserved mechanism of protein and organelle catabolism present within all eukaryotic cells (3,4). Now, armed with specifics regarding the molecular anatomy of the autophagic

machinery, it is becoming possible to determine the role(s) of autophagy in numerous pathological processes (5), including cardiovascular disease (6,7).

CARDIAC GROWTH AND PLASTICITY

Throughout the course of life, the myocardium is faced with ever-changing workload demands. Growth during development is associated with cardiac enlargement in proportion to the growing body. Increases in physiological demand during exercise and pregnancy provoke heart growth, as well. Pathological stress on the heart, such as hypertension, valvular disease, myocardial infarction, or excessive neuroendocrine activation, triggers a cardiac growth response that is similarly rapid and robust. At the other end of the spectrum, deconditioning, prolonged bedrest, cancer, and weightlessness each lead to substantial decreases in myocardial mass (8).

These remodeling reactions are common, and in the context of pathological triggers, represent a significant milestone in disease progression. Indeed, this is one reason why hypertension, with its myriad effects on myocardial architecture, is a leading risk factor for mortality worldwide (1). Astonishingly, over 25% of the world's adult population in the year 2000 was hypertensive, and this population is projected to reach 1.56 billion in 2025, a 60% increase over 25 years (1). Mounting epidemiological evidence demonstrates a linear and independent relationship between pathological stress, such as hypertension, and cardiovascular disease (1).

Changes in ventricular demand triggered by hypertension and other environmental stimuli alter myocardial wall stress. Indeed, according to Laplace's law, ventricular wall stress is directly proportional to pressure and chamber size (radius of the cavity) and inversely proportional to wall thickness, each of which can be impacted by changes in preload, afterload, and rate of contraction. In response, structural and functional alterations ensue