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EDITORIAL COMMENT

# Autophagy and Reverse Remodeling

## A New Biomarker in Heart Failure?*

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*"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less."*

—Marie Curie[1]

Cardiac myocytes are long-lived cells; indeed, most last a lifetime. But proteins and organelles within cardiac myocytes have finite lifespans and must be replaced on a regular basis. In healthy adult cells, this mainly entails steady-state production of new sarcomeres and mitochondria and removal of senescent organelles by a process known as autophagy (self-eating).[2] First thought to be a stress-induced energy-generating degradation pathway to protect cells against nutrient depletion, autophagy is now known to play a critical role in maintaining homeostasis in nonstarved cells. In the canonic macroautophagy pathway, a sac-like structure surrounds a damaged cell organelle to form a double membrane body called an autophagosome, which then travels through the cytoplasm to fuse with a lysosome (to form an autolysosome) and, thereby, facilitate degradation of the contents by acidic lysosomal hydrolases.[3] Most of the degraded material is recycled but some indigestible waste accrues.

Cardiac myocytes face several challenges when it comes to maintaining homeostasis through autophagy. Myocytes are large cells, loaded with sarcomeres and mitochondria, many of which are at some distance from lysosomes, which are concentrated in perinuclear zones. Autophagosomes must therefore navigate their way through a tightly packed environment. Moreover, the intense metabolic demands of cardiac myocytes coupled with their very low turnover rates create additional challenges, including the potential accumulation of large amounts of waste material that must be stored somewhere. In fact, it appears that cardiac myocytes have solved these challenges through a remarkable mechanism in which senescent mitochondria and other materials are packaged in vesicles called exophores and ejected into the extracellular space where they are efficiently taken up by resident macrophages.[4] To make a familiar analogy, cardiac myocytes deal with their solid waste by not only storing some in an intracellular "landfill," but also by regularly putting the trash out on the curbside where it is picked up by the next garbage truck (macrophage) that happens to pass by. Maintenance of homeostasis in long-lived cardiac myocytes thus depends not only classic intracellular autophagic pathways but also on resident macrophages whose primary function is to eliminate unwanted materials via phagocytosis. Macrophages do this very efficiently: Billions of cells die every day, yet very few apoptotic or dead cells are ever seen in tissues.

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Defects in autophagy have been linked to human disease such as neurodegeneration, cancer, and heart failure. A decline in autophagy has also been implicated in cardiac aging.[5] And, as noted below, modulation of autophagic pathways is under active investigation as a therapeutic strategy. However, the implications of autophagy in health and disease are only now becoming recognized. In this issue of the

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*Journal*, Kanamori et al[6] present new evidence suggesting that activation of autophagy is an adaptive response in patients with dilated cardiomyopathy (DCM) and correlates with left ventricular reverse remodeling (LVRR). The authors assessed left ventricular endomyocardial biopsy specimens from 42 patients with dilated DCM and 7 control patients with normal cardiac function. Of the 42 DCM patients, 21 showed echocardiographic evidence of LVRR (LVRR-positive), while the remaining 21 patients did not (LVRR-negative). Clinical characteristics between these 2 groups were quite similar, including prescribed medical therapy. Myocardial biopsies were assessed by means of light microscopy, immunohistochemistry and immunofluorescence to label microtuble-associated protein 1 light chain 3 and cathepsin D, and electron microscopy. Morphometric features assessed with the use of light microscopy, such as the extent of myocyte hypertrophy and amount of fibrosis, did not differ between the 2 groups. However, electron microscopy revealed more abundant autophagic vacuoles (autophagosomes and autolysosomes) and lysosomes in LVRR-positive patients and apparently greater cathepsin D expression compared with LVRR-negative patients. In clinical follow-up, the patients with DCM who achieved reverse remodeling experienced fewer cardiovascular events. On the basis of a logistic regression model, the authors concluded that increases in autophagic vacuole number and cathepsin D expression were "predictive" of reverse remodeling. Although this may be true, we do not know the temporal relationship between enhanced autophagy and reverse remodeling. Thus, it can only be concluded that that increased autophagic activity correlates with reverse remodeling in patients with DCM.

At first glance, "self-eating" might appear to be maladaptive in a failing heart. The catastrophic effects of dilated cardiomyopathy are well known at the clinical and cellular level. However, the report by Kanamori et al[6] provides an additional layer of evidence that enhanced autophagy may provide benefit in diseased myocardium. Although additional supporting information will be needed to understand the implications and potential cause and effect of autophagy and reverse remodeling, Kanamori et al[6] have identified a new potential frontier in clinical cardiology. Our field has no shortage of biomarkers that are leveraged daily around the globe. However, none adequately provides predictive insights into LVRR. Could quantification of autophagy be a predictor of recovery? Although clinical outcomes in heart failure cannot be based solely on improvements in remodeling, the association between reverse remodeling and favorable outcomes has been well documented and offers a target for medical and device-based interventions. An inherent limitation of scaling the findings made by Kanamori et al[6] is the prerequisite for cardiac tissue. This would not be a part of routine practice and would add a layer of risk in an already compromised population. Future advances in positron emission tomographic imaging may be developed to measure autophagic activity.[7] Given the complex nature of this process, the opportunity to develop assays assessing the presence of up-regulation or down-regulation may offer the possibility to perform baseline and longitudinal surveillance of autophagy. Quantitative measurement of mammalian lysosomal-derived metabolites has been reported, but the feasibility and clinical relevance have not been documented in human populations.[8]

The findings in the present report also raise the question of whether modulation of autophagy is a viable therapeutic strategy. Cardiac aging is associated with hypertrophy, inflammation, fibrosis, and myocardial function.[9] Similarly, disruption of cardiomyocyte autophagy has been reported in cardiac aging, diabetes, heart failure, and dilated cardiomyopathy.[5,10,11] Increasing this evolutionarily conserved process might offer a way to fend off the risk that aging confers for cardiovascular morbidity and mortality. Drugs used in everyday practice, such as beta-adrenergic blockers, calcium channel blockers, and statins, have been reported to regulate autophagic activity.[12-14] Fasting is another potent activator of autophagy and known to play an essential role in survival during the early neonatal starvation period.[15] Furthermore, cardiac oxidative stress is closely linked with disturbances in autophagy. Xie et al[16] recently reported that induction of autophagy at the time of reperfusion may mitigate myocardial reperfusion injury secondary to a reduction in reactive oxygen species. Given that cardiac myocyte proliferation in the adult heart is quite limited, the persistence of healthy existing myocytes is critical to longevity. Nevertheless, persistent activation of autophagy could have obvious negative implications. Excessive autophagy may result in a specific form of non-apoptotic cell death known as autosis.[17] Thus, any strategy targeting autophagy would need to be greatly informed by duration and the underlying disease phenotype. The present report provides important evidence that possible predictors of reverse remodeling can be measured and associated with favorable outcomes. Regardless, Kanamori et al[6] have given us something to digest as we explore this next potential destination in cardiology.

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