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Cardiac Autophagy: Good with the Bad

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Abstract

Stress-induced hypertrophic growth of the myocardium is a pathogenetic milestone in the progression of heart failure. Some evidence suggests that suppression of pathological cardiac hypertrophy *per se* is a viable target for therapeutic intervention, and cardiomyocyte autophagy is an attractive mechanism for consideration as a means of controlling the hypertrophic response. However, whereas considerable insights have been gleaned in the molecular mechanisms governing cardiomyocyte autophagy, many details critical to rational targeting of the response remain unknown. Among them, mechanisms underlying the adaptive and maladaptive features of autophagy are obscure. With time and further study, it is possible that this near-ubiquitous cardiac response to stress will emerge as a viable target for therapeutic manipulation.

Keywords

Autophagy; Cardiac Hypertrophy; Myocardial Ischemia; Heart failure; Therapeutics

Introduction

The heart responds to ever-present changes in environmental stimuli with an array of responses which include alterations in chamber volumes, systolic contraction, diastolic relaxation, and heart rate. Beyond this, another critical component of the cardiac response to stress is robust change – either upward or downward – in muscle mass.¹ The heart is capable of substantial increases and declines in size and mass, and those changes can take place in remarkably short periods of time.

Many of the environmental signals converging on the heart are physiological in nature, including postnatal growth, exercise, or pregnancy; here, cardiac mass increases or decreases rapidly and yet structure and function are preserved.² Many influences converging on the heart, however, are pathological, occurring in the context of disease. These include neurohormonal activation, hypertension, or myocardial injury, stressors which trigger perturbations in metabolic, structural, and functional properties of the heart. In the case of the former (physiological hypertrophy) untoward sequelae do not arise over time; in the case of the latter (pathological hypertrophy) progression to a state of ventricular wall thinning, systolic and diastolic dysfunction, and a clinical syndrome of heart failure is common.³ Further, both pathological hypertrophy and heart failure are associated with markedly

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None

increased risk of malignant ventricular arrhythmia.⁴ From a teleological perspective, the early phases of cardiac hypertrophy may be a compensatory response to increased workload, serving to normalize wall stress and thereby minimize oxygen consumption. In the long run, however, pathological hypertrophy is a milestone in the pathogenesis of heart failure.⁴

Unlike the physiological hypertrophic growth response, pathological hypertrophy entails more than just increases in myocyte size and heightened sarcomeric organization. Rather, a shift toward glycolytic metabolism, alterations in calcium storage and handling, changes in contractility, and reactivation of a fetal gene program are seen.¹ In this way, patterns of gene expression mimic those seen in early embryonic development. The myosin composition of the cardiomyocyte is altered, and extracellular deposition of collagen leads to fibrosis, together contributing, at least in part, to diminished contractile performance.⁵ These distinguishing characteristics of pathological hypertrophy raise obvious questions regarding whether this response is adaptive and protective. Indeed, preclinical studies have shown that attenuation of load-induced hypertrophy is well tolerated and furthermore, ventricular dilation and decompensation do not occur.⁶ Correlative studies in patients with heart disease similarly support this contention.⁷ Thus, suppression of pathological cardiac hypertrophy *per se* may be a viable target for therapeutic intervention.⁸

Autophagy, an ancient lysosome-mediated catabolism pathway, is an attractive mechanism for consideration as a means of controlling the hypertrophic response.⁹ Autophagy, or more specifically, macroautophagy, is an evolutionarily conserved and ubiquitous mechanism for the degradation of long-lived proteins and the clearance of organelles.¹⁰ While it may seem paradoxical to consider a degradative mechanism in the context of cellular growth, hypertrophic remodeling of any cell, particularly a cell with the complex architecture of a myocyte, involves more than simple synthesis and addition of new proteins; instead, dismantling and remodeling of existing cellular elements are required. Indeed, evidence for lysosomal pathway activation in heart disease has been reported for decades in both human heart failure and in animal models of disease,¹¹ but it is only recently that this increase in activity has been tied to autophagy and its functional significance tested. Just as for the case of the hypertrophic process itself, a key to understanding the role(s) of autophagy in the heart involves elucidating its context-dependent adaptive versus maladaptive potential. One model holds that basal autophagic flux is fundamental to cellular homeostasis, but exuberant stress-induced activation of autophagy can be maladaptive (Figure).

Basal Autophagy

The most potent physiological inducer of autophagy is nutrient depletion. Limitations in various nutrients, such as amino acids, glucose, growth factors, and oxygen each induce autophagy, with amino acid withdrawal provoking the greatest activation of autophagy in mammalian cells in culture. Autophagy is robustly induced in all tissues in the early neonatal period immediately after the abrupt interruption of the previously continuous supply of nutrients via the placenta and before the newborn has access to milk.¹² Indeed, the robust autophagic response at mammalian birth is necessary for survival, with neonatal lethality observed in animals harboring mutations in essential autophagy genes.^{12,13}

Autophagic flux is required for survival of neonatal rat cardiomyocytes (NRCMs) maintained in culture; short hairpin RNA (shRNA) targeting Atg7 reduces the number of viable cells as compared with nonspecific shRNA.¹⁴ In an intact organ such as the heart, terminally differentiated cardiomyocytes are dependent on autophagy, not just for protection from starvation, but for protein quality control and removal of damaged organelles. Inactivation of Atg5 in the adult heart by tamoxifen-inducible Cre-Lox recombination leads to rapid left ventricular dilation and contractile dysfunction.¹⁴ Atg5-inactivated

cardiomyocytes exhibit disorganized sarcomere structure, misalignment and aggregation of mitochondria, and aberrant concentric membranous structures.¹⁴ These results lend strong credence to the notion that constitutive cardiomyocyte autophagy is a critical housekeeping function which is fundamentally required for homeostasis under basal, resting conditions.

Ischemia/Reperfusion Injury

Ischemic heart disease is enormously prevalent, exacting a huge toll on individuals and society. When exposed to ischemia, a given tissue is deprived of both nutrients and oxygen. In most clinically relevant instances, ischemia is followed by a reperfusion phase where arterial blood supply is restored either spontaneously or therapeutically. Reperfusion elicits a host of cellular responses, including activation of a number of signaling cascades, accumulation of reactive oxygen species (ROS), and more.^{15,16} Thus, the biology of ischemia/reperfusion (I/R) injury is complex, as are the attendant autophagic responses.

As in the case of starvation, autophagy is activated during ischemia. And in additional analogy to starvation, ischemia-induced autophagy appears to be protective. One of the earliest studies demonstrating autophagosome formation in the heart employed an *ex vivo* rabbit heart model subjected to 40 minutes of ischemia.¹¹ Autophagosomes were detected containing numerous mitochondria suggestive that the activation of autophagy was serving to remove these damaged organelles. Lengthening the ischemic period to 60 minutes triggered the appearance of large and dysfunctional lysosomes, suggesting an impairment of autophagosome-lysosome fusion. Increased autophagy was correlated with functional recovery, but prolonged ischemia resulted in irreversible damage and contractile dysfunction. More recent studies in chronically ischemic swine myocardium confirmed these earlier findings of increased autophagy induction and lysosomal activity.¹⁷ Furthermore, it was noted that areas of the heart with increased autophagy also exhibited fewer apoptotic cells, suggesting that the autophagic response protected against apoptotic cell death. At this point in time, the preponderance of evidence suggests that cardiomyocyte autophagy is protective during ischemia, possibly by providing an alternate energy source for cell survival.

Efforts to model cardiomyocyte I/R injury *in vitro* have yielded divergent evidence regarding whether autophagy is protective or maladaptive in this context. When cardiomyocytes of the murine atrial cardiomyocyte-derived HL-1 cell line were exposed to 2 hours of ischemia and 5 hours of reperfusion, the formation of autophagosomes was inhibited in the ischemic phase and accumulation was not seen until reperfusion commenced.¹⁸ The assays employed by these investigators relied upon accumulation of green fluorescent protein-tagged LC3 (GFP-LC3) puncta as markers of autophagosomes. Further, lysosomal inhibitors were used to suppress autophagic vacuole degradation in order to assess autophagic flux. Thus, these results were indicative of a block in autophagy induction during ischemia and dysfunctional degradation of autophagosomes during reperfusion. Pharmacological and genetic manipulations to increase autophagic flux were protective, possibly by blocking apoptosis. Conversely, further inhibiting autophagic flux led to greater cellular injury.

Glucose deprivation, a milder mimetic of myocardial ischemia and one more in line with starvation, induced autophagy in cultured cardiomyocytes, and pharmacological blockade provoked declines in cell survival.¹⁹ These studies suggest that autophagy may serve primarily to maintain energy production during acute ischemia but evolves to accomplish clearance of damaged organelles during chronic ischemia or reperfusion.

Clearly, careful consideration must be given to the protocols employed to simulate I/R *in vitro*. In some instances, for example, it is likely that energy constraints imposed by an

extensive ischemic protocol preclude autophagy activation. Indeed, in the context of the intact heart, cardiomyocytes likely experience more nuanced I/R stress with different cells subjected to varying levels of nutrient and oxygen deprivation.

Studies *in vivo* similarly point to a dichotomous role for autophagy in I/R. Matsui et al. reported apparent increases in LC3-II accumulation, a surrogate for autophagic activity, with 20 minutes of ischemia followed by 20 minutes of reperfusion.¹⁹ Importantly, it must be noted that measurements of steady-state LC3-II levels do not differentiate between induction of autophagy upstream of LC3-II (increased flux) versus a block in downstream vacuole degradation. Nevertheless, it was found that AMPK, an established cellular nutrient sensor, was activated transiently during ischemia and that this activity was required to induce autophagy. When mice haploinsufficient for Beclin 1 (Beclin 1^{+/-}) were exposed to I/R, the autophagic response was attenuated, as was the extent of myocardial infarction and number of apoptotic cells, suggesting an overall maladaptive role for autophagy. In aggregate, these findings suggest that autophagic flux triggered by ischemia in the early stages of I/R stress may be beneficial (analogous to starvation), whereas that elicited by reperfusion in later stages of the process may be harmful.

The purportedly maladaptive second wave of autophagic activation upon reperfusion is an intriguing basis for probing the mechanism by which autophagy participates to I/R injury. Increased expression of Beclin 1 accompanies the autophagic activity seen in an isolated rat heart model of I/R,²⁰ and some evidence suggests that increased Beclin 1 expression is indicative of maladaptive autophagic activity.¹⁹ Interestingly, a recent study raised the prospect that long-term supranormal levels of Beclin 1 elicited by reperfusion may act to repress expression of LAMP2, a protein critical for autophagosome-lysosome fusion.²¹ Impairment of autophagosome fusion would blunt autophagic processing of cargo during the reperfusion phase of I/R injury (diminished flux), leading to accumulation of autophagosome-associated LC3-II. One model holds that autophagy induction is constant in the early phases of I/R, and lysosomal clearance of autophagosomes is diminished late (during reperfusion), thereby contributing to the observation that autophagy is maladaptive in the late stages of the I/R response.

Another BH3 domain-containing protein up-regulated in I/R is Bnip3, a protein that has been linked with cell death.²² Genetic ablation of Bnip3 was protective in I/R, partially rescuing declines in systolic performance and ventricular dilatation, interestingly, however, without affecting infarct size. Conversely, cardiomyocyte-specific over-expression of Bnip3 induced progressive ventricular dilation and impaired systolic performance, with increased markers of apoptosis. Expression of Bnip3 is driven by hypoxia-dependent factor-1 (Hif-1), and Bnip3 participates in the elimination of defective mitochondria in hypoxia.²³ Bnip3 provokes mitochondrial fragmentation and subsequent autophagy in cardiac myocytes, and suppression of Bnip3 using a dominant-negative mutant protects against I/R injury.²⁴ In aggregate, these studies point to a central – and intricate – role of cardiomyocyte autophagy in the maladaptive remodeling of I/R states.

Hypertrophy and Failure

Hypertrophic growth is a prominent response of the heart to increases in afterload, such as that which occurs with hypertension and valvular disease. The growth response involves increases in protein synthesis, remodeling of contractile elements, and formation of new sarcomeres. An established model for this process is surgical thoracic aortic constriction (TAC). Here, a carefully calibrated stenosis is imposed surgically on the aorta, prompting an immediate increase in afterload. Studied in this context, autophagy is rapidly induced as early as 24 hours after surgery, reaches peak levels at 48–72 hours and remains elevated at 3

weeks.²⁵ In Beclin 1^{+/-} mice, where autophagic activity is attenuated approximately 50%, load-induced increases in autophagy were diminished and a modest protection from systolic dysfunction was observed.²⁵ Conversely, in transgenic mice with cardiomyocyte restricted over-expression of Beclin 1, autophagic activity was markedly increased and the pathological response was amplified, with increases in hypertrophy and fibrosis, accelerated ventricular dilatation and declines in systolic performance, ultimately culminating in early mortality. Combined, these findings point to a maladaptive role for autophagy in the setting of severe pressure overload stress.

Inactivation of a different gene required for autophagy, Atg5, points to an adaptive role for autophagy.¹⁴ Mice harboring a cardiomyocyte-specific deletion of Atg5 during cardiogenesis (Atg5^{f/f};MLC2v-Cre⁺) showed no cardiac hypertrophy or dysfunction well into adulthood. When subjected to TAC, however, the mice developed cardiac dysfunction and left ventricular dilation within 1 week. Interestingly, heart weight/body weight ratios and cardiomyocyte cross-sectional areas increased to a similar degree in mutants and controls subjected to TAC. Instead, polyubiquitinated proteins, endoplasmic reticulum (ER) stress, and markers of apoptosis were more highly induced in the autophagy-deficient mice. These results suggest that autophagy does not play a role in regulating the cardiomyocyte hypertrophy induced by pressure overload.

Here again, the dichotomous role for autophagy in a disease process is evident. Discounting trivial explanations such as differences in surgical technique, these two studies provide an interesting basis for interpreting the role of autophagy in pressure-overload hypertrophy. The major difference between the studies lies in the mouse models used. Cardiac-specific inactivation of Atg5 results in complete abrogation of autophagy in cardiomyocytes, whereas Beclin 1^{+/-} mice have only diminished autophagic flux (≈50%). The Atg5^{f/f};MLC2v-Cre⁺ mice showed no cardiac phenotype prior to being stressed by TAC, suggestive of some sort of compensation for the complete loss of basal autophagy. Once exposed to the stress of pressure overload, however, this compensatory mechanism may have been overwhelmed and cardiomyocytes were unable to clear protein and cellular debris, leading to ER stress and perhaps apoptosis. Noting that the degree of hypertrophic growth in response to TAC was no greater in comparison to controls while systolic dysfunction was exaggerated suggests that a stressed, yet autophagy-disabled, cardiomyocyte is uniquely compromised in its contractile performance. In contrast, Beclin 1^{+/-} mice maintain basal levels of autophagic flux, yet stress-induced activation of autophagy was blunted; this may allow cardiomyocytes to maintain critical levels of contractility, although not enough reserve autophagic capacity to allow for hypertrophic growth. In the Beclin 1 transgenics, the extra capacity for autophagy was exploited for exaggerated growth and eventual systolic dysfunction in response to the stress of pressure-overload. Thus, these three models exist on a continuum of autophagic activity where too little or too much autophagy in response to stress is maladaptive, whereas a certain amount of constitutive autophagic activity is both adaptive and required for cell survival²⁶ (Figure).

We favor a model where pathological stress on the heart elicits an autophagic response in cardiac myocytes that can become maladaptive, possibly by eliminating cellular constituents (e.g. mitochondria) indiscriminately. Another model, which is not mutually exclusive with the quantitative “goldilocks model” (not too much, not too little...but just right) holds that basal autophagic flux is qualitatively different from stress-activated autophagy. The former maintains a housekeeping function which is critical for survival by eliminating misfolded proteins, protein aggregates, and dysfunctional mitochondria that might provoke autophagic cell death. Conversely, stress-activated autophagy might target specific cellular substrates, including some which are important for cell function (e.g. normally functioning mitochondria). Indeed, precedent exists in other cell types for autophagic mechanisms

targeting specific substrates, as opposed to a random scavenging of the cell.²⁷ Either way, a case can be made for therapeutic manipulation of autophagy within a zone that is adaptive.

Therapeutics

We have reported that small molecule inhibition of histone deacetylases (HDACs) regularizes the augmented hypertrophic growth response to TAC, even in Beclin 1 transgenics which manifest amplified autophagic and pathological remodeling responses.^{28,29} In fact, the anti-hypertrophic effect of HDAC inhibition in Beclin 1 transgenic mice was significantly greater than in controls, suggesting that suppression of the amplified autophagic response contributed to attenuated myocardial growth. In other words, HDAC suppression abrogated the increment in growth associated with increased autophagy, suggesting that HDAC activity is uniquely involved in the autophagic response. Furthermore, *in vitro* experiments testing neurohormonal agonist-induced myocyte growth implicate HDAC1 and HDAC2 as the major mediators of increased autophagy. These deacetylase isoforms are members of the class I of HDACs, which are established to be prohypertrophic.³⁰ HDAC inhibition likely does not completely eliminate cardiomyocyte autophagy; rather it suppresses autophagic flux without altering basal, constitutive levels of activation. Any viable therapeutic intervention will need to differentially affect maladaptive versus adaptive cardiomyocyte autophagy, regardless of whether that difference is a qualitative or quantitative in nature.

In a more clinically relevant experiment, we observed that HDAC inhibition is capable of reversing existing cardiac hypertrophy, while restoring cardiac function.^{28,29} Reversal of existing structural changes is a fundamental objective of therapeutic intervention, as patients typically do not present to medical attention until symptoms have developed. Clinical trials have confirmed that improved clinical outcomes are observed in patients when left ventricular hypertrophy regresses upon treatment, independent of the type of antihypertensive therapy.³¹

A more nuanced approach would be to manipulate cardiomyocyte autophagy therapeutically to promote targeting of specific substrates. Pressure overload-induced hemodynamic stress elicits changes in the cardiomyocyte milieu conducive to protein damage and misfolding, culminating in the formation of toxic protein aggregates; autophagic activity in the cardiomyocyte participates in the clearance of aggregated proteins.³²

Conclusion

Successful therapeutic manipulation of cardiomyocyte autophagy for clinical benefit will depend on additional dissection of underlying mechanisms. Unveiling the qualitative or quantitative features that determine whether autophagy is adaptive or maladaptive will raise the prospect of enhancing the advantageous aspects while inhibiting the deleterious ones. Also, future studies will need to focus on careful differentiation of autophagic flux initiation versus defects in downstream autophagosome processing; both are marked by increases in autophagosome abundance, and yet underlying mechanisms are obviously different. With continued effort, autophagy may one day emerge as a target of therapeutic relevance in heart disease.

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Abbreviations

NRCMs	neonatal rat cardiomyocytes
shRNA	short hairpin RNA
ROS	reactive oxygen species
I/R	ischemia/reperfusion
TAC	thoracic aortic constriction
HDACs	histone deacetylases

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Figure. Cardiomyocyte autophagy varies in response to different conditions

Basal autophagy is necessary for normal homeostasis of the cardiomyocyte. In response to pathological stress, autophagy may be adaptive in allowing for cardiomyocyte survival. Under severe or persistent stress, autophagy can be maladaptive, facilitating detrimental remodeling.