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Balancing Autophagy for a Healthy Heart

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Abstract

Autophagy is a well-known intracellular degradation process involved in clearing damaged or unnecessary components in cells. Functional autophagy is important for cardiac homeostasis. Given this, it is not surprising that dysregulation of autophagy has been implicated in the aging process and in various cardiovascular diseases. Therefore, understanding the functional role of autophagy in the heart under various conditions and whether manipulation of the pathway has therapeutic benefits have been a major focus of many investigations in recent years. Although consensus exists that autophagy is a critical cellular quality control pathway in the heart, its role in disease remains controversial. Whether altered autophagy is protective or detrimental in the heart seems to depend on the context and the disease. Here, we review the latest insights into autophagy in cardiovascular homeostasis and disease and its role in disease development.

Keywords

Autophagy; heart disease; aging; diabetes

Introduction

Cardiovascular disease remains the number one contributor to mortality worldwide, with over 17.3 million deaths per year [1]. Thus, there is a great need for a better understanding of the mechanisms underlying development of cardiovascular disease to prevent the progression to heart failure. Macroautophagy (hereafter referred to as autophagy) is an intracellular degradation process that is altered in various diseases of the heart. The autophagy related genes (Atg) and the various signal transduction pathways involved in autophagy initiation and progression have been well-summarized in recent reviews [2–4].

Autophagy is responsible for degrading long-lived proteins and dysfunctional or excess organelles [2]. Under conditions of stress such as nutrient or oxygen deprivation, autophagy

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Disclosures

None

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is also involved in generating energy substrates to meet metabolic demand and in eliminating cytotoxic protein aggregates and organelles. However, excessive and chronic autophagic activation can lead to depletion of essential proteins and organelles, which can trigger cell death. Dysregulation of autophagy contributes to the pathology of many diseases, including cardiovascular diseases. In this review, we discuss the latest developments and current concepts of autophagy in cardiovascular homeostasis and disease, and how perturbation in the pathway contributes to disease development.

Autophagy in Cardiac Homeostasis and Aging

The heart consists of post-mitotic cardiac myocytes and functional autophagy is essential to maintain myocyte function and viability with age. Not surprisingly, selective disruption of autophagy in mouse hearts led to accumulation of defective proteins and organelles and cardiac dysfunction [5]. Similarly, patients with Danon disease, an X-linked genetic disorder characterized by a mutation in the gene encoding lysosome-associated membrane protein 2 (LAMP2), have impaired autophagic flux and develop severe and progressive lethal cardiomyopathy [6]. Characterization of iPSC-derived cardiomyocytes from patients with Danon disease confirmed that the cells exhibited impaired autophagic flux, abnormal calcium handling, enhanced oxidative stress and mitochondrial damage [7**]. Impaired mitochondrial autophagy was also observed in a mouse model of Danon disease, suggesting that diminished mitochondrial clearance may be a central component of the disease [8].

Autophagic activity is reduced with age in tissues, including the heart [2,5]. Therefore, it is not surprising that reduced autophagy leads to accelerated cardiac aging [5] and interventions that enhance autophagy preserve cardiac function and extend life span in various organisms [9–12]. Selective disruption of autophagy in the heart led to reduced life span in mice [5]. In contrast, enhancing autophagic flux in the heart with the dietary compound polyamine spermidine reduced the decline in cardiac function observed in aged mice and extended life span [9**]. These beneficial effects were abrogated in cardiac specific autophagy deficient mice, confirming that the cardioprotective effects were dependent on autophagy [9**]. Similarly, administration of rapamycin, an inhibitor of mTOR and activator of autophagy, reversed age-related cardiac hypertrophy and decline in function in mice by improving energy metabolism [13**]. Clearly, autophagy plays an important role in rejuvenating myocytes. However, many of the treatments to enhance autophagy in those experiments also affect other pathways, making it difficult to discern how much enhanced autophagy contributes to delaying aging.

Autophagy in myocardial infarction and ischemia/reperfusion injury

Autophagy plays important roles in: 1) maintaining energy homeostasis during nutrient limiting conditions and 2) cellular quality control by eliminating damaged proteins and organelles. Limited availability of oxygen and nutrients during myocardial ischemia are potent activators of autophagy as an attempt to maintain energy levels to meet metabolic demands in the myocytes. Subsequent restoration of oxygen during reperfusion can cause intracellular damage which also activates autophagy. Although autophagy is activated during both ischemia and reperfusion for different purposes, whether targeting autophagy in

myocardial ischemia/reperfusion (I/R) is beneficial or detrimental has been the focus of intensive investigation and subject to much debate. The exact role of autophagy in this context remains unclear.

Studies agree that autophagy is induced during ischemia and further increased during reperfusion [14,15]. It was initially reported that the enhanced autophagic activity during acute ischemia/reperfusion served a protective role [16]. Many additional studies have reported a protective role for autophagy in I/R injury in cells and animal models [17,18]. Tibetan patients living at high altitude and subjected to chronic hypoxia had enhanced basal autophagy based on increased levels of autophagy proteins in their hearts [19*]. Notably, these patients had reduced cardiac damage compared with patients living at sea level after exposure to I/R during a cardiopulmonary bypass surgery, indicating that enhanced autophagy at baseline is cardioprotective. In addition, reperfusion can trigger excessive activation of autophagy which is detrimental to the heart [20], although this may depend on the length of the ischemia [21*]. Reducing autophagy levels to baseline with the alkaloid berberine during reperfusion decreased myocardial reperfusion injury [22]. The function of autophagy also varied with the duration of ischemia and reperfusion phases, where autophagy was beneficial when myocytes were subjected to mild to moderate ischemia but became detrimental when ischemia was prolonged [21*]. Overall, autophagy appears to be mainly an adaptive response that protects myocytes during stress. However, Wang et al. reported that abrogation of autophagy *in vitro* and *in vivo* protected against I/R, linking autophagy to cell death and injury [23]. Clearly, excessive stress or damage will lead to chronic or over activation of autophagy leading to excess degradation. Further studies are required to identify the mechanisms that define the outcome of the critical equilibrium existing between beneficial and maladaptive autophagy in I/R. It is likely that the conflicting results are due to differences in experimental design such as length of ischemia, genetic or pharmacological targeting of the autophagy pathway, and in mouse strains and species used.

Autophagy in Cardiac Hypertrophy

Baseline autophagy suppresses development of cardiac hypertrophy as early studies observed that disruption of autophagy in mouse hearts led to development of cardiac hypertrophy [24,25]. Autophagic activity is also altered in response to hypertrophic stimuli. In response to hemodynamic overload, the heart undergoes hypertrophy as an adaptive response to reduce wall stress, which can progress to pathological hypertrophy and heart failure if unresolved. There is currently little consensus on the role of autophagy during pressure overload. Studies agree that autophagy is activated during cardiac hypertrophy, but disagree on the length of activation and whether it is protective or detrimental to the heart [24,26,27]. Zhu et al. initially observed that Beclin1 haploinsufficient mice had reduced autophagy and pathological remodeling after transverse aortic constriction (TAC) [26]. In contrast, Beclin1 transgenic mice had enhanced pathological remodeling, indicating a maladaptive role for autophagy. However, it is important to take into account that Beclin1 might regulate other cellular processes than autophagy that might account for the phenotype observed in these mice. A recent study reported that Beclin1 also regulates the endosome pathway [28].

More recent studies have reported that restoring autophagy exerts protection against cardiomyocyte hypertrophy in response to TAC [29,30]. A detailed time course analysis revealed that autophagy was only transiently activated immediately after TAC but suppressed in the chronic phase [30**]. Also, increasing autophagic flux using TB1, a peptide derived from Beclin1, attenuated TAC-mediated cardiac dysfunction, suggesting that enhancing autophagy was protective. The acute activation of autophagy is most likely an adaptive response to the stress. However, to facilitate the initiation of hypertrophy, degradation pathways must be turned off to allow the myocytes to grow. Thus, the transient activation of autophagy is consistent with the fact that autophagy needs to be turned off to allow the myocyte to grow. Cheng et al. recently confirmed this by demonstrating that phenylephrine, a potent inducer of hypertrophy, suppressed autophagy which was required for the subsequent initiation of hypertrophic growth [31*].

Interestingly, it was observed that DNA-damage inducible transcript 4-like was upregulated in pathological, but not in physiological, hypertrophy and that its primary function was to inhibit pathological hypertrophy by increasing basal autophagy and promoting atrophy [32**]. Finally, Hsp27 transgenic mice develop cardiac hypertrophy and heart failure within four weeks after birth. Autophagic activity is enhanced in these hearts in both the adaptive and maladaptive stages [33*]. Suppressing autophagy pharmacologically alleviated the cardiac dysfunction observed in the transgenic mice, confirming that persistent activation of autophagy was detrimental under these circumstances [33*]. Overall, these findings suggest an important role for autophagy both in adaptation and in the regulation of cardiac growth. However, its functional role in hypertrophy clearly depends on the stimuli. Taken together, each of these studies demonstrate how extended autophagy activation can contribute to negative consequences for the heart in models of heart failure.

Autophagy and Anthracycline-Mediated Cardiotoxicity

Anthracyclines, such as doxorubicin, are potent chemotherapeutic agents but their use is limited due to cardiotoxicity [34]. Several studies have investigated the role of autophagy in doxorubicin-induced cardiotoxicity and there is emerging consensus that enhancing autophagy prior to doxorubicin exposure is cardioprotective [35–37]. However, doxorubicin abrogates autophagy in myocytes, but studies disagree on the underlying mechanism. Autophagosomes accumulate in the heart after doxorubicin exposure [35,37,38] and a recent study reported that doxorubicin impaired lysosomal acidification which caused autophagosomes to accumulate in myocytes [37**]. This study found that reduced autophagy in Beclin1^{+/-} mice protected from doxorubicin-induced cardiac damage, whereas overexpression of Beclin1 exacerbated cardiotoxicity [37**]. This suggests that the accumulation of autophagosomes contributes to the cardiotoxicity observed with doxorubicin. In contrast, Pizarro et al. reported that doxorubicin exposure inhibited formation of autophagosomes by activation of mTOR in myocytes [36], implicating altered autophagy signaling in the toxicity rather than accumulating autophagosomes. Clearly, doxorubicin-induced toxicity and its effect on autophagy is a complex and not fully understood process. Additional studies are needed to uncover exactly how doxorubicin alters autophagic activity and its consequences on cardiomyocyte viability.

Autophagy and diabetic cardiomyopathy

Diabetes mellitus (DM)-related cardiomyopathy is a major cause of heart failure in diabetic patients [39]. The mechanisms underlying its pathogenesis remain unclear and etiological differences between type 1 and type 2 diabetes have complicated studies attempting to elucidate the underlying mechanisms. Recent studies have focused on how autophagic activity in the heart is altered with diabetes and in diabetic cardiomyopathy.

As insulin signaling inhibits autophagy by activating mTOR, it is anticipated that impaired insulin production would lead to enhanced autophagy. Consistent with this notion, a study recently reported that autophagic activity was increased in hearts from streptozotocin (STZ)-induced type 1 diabetic mice. Inhibiting autophagy exacerbated cardiac dysfunction and injury [40*], suggesting that the enhanced autophagy was cardioprotective. Similarly, enhancing autophagy with fenofibrate, a peroxisome-proliferator-activated receptor α agonist, was also cardioprotective in the STZ type 1 diabetic mice [41]. However, another study reported that autophagy was inhibited in hearts of OVE26 type 1 diabetic mice [42]. This study also found that restoring autophagic flux reduced cardiac injury, confirming that enhancing autophagy is cardioprotective in type 1 diabetes. A different study observed reduced cardiac autophagy in type 1 diabetic hearts which functioned to limit cardiac injury. Cardiac damage was attenuated in type 1 diabetic autophagy deficient mice, while enhancing autophagic activity aggravated cardiac damage [43]. In summary, recent studies report both increased and decreased baseline autophagic activity in the hearts of type 1 diabetic mouse models, and that modulating autophagy can either protect or exacerbate cardiac damage. Clearly, additional studies are needed to uncover the function of autophagy in type 1 diabetes and whether modulating it is beneficial or detrimental for the heart.

Although it is expected that the excess intracellular nutrient status in type 2 diabetes would lead to suppression of autophagy, reports on autophagic activity and function are conflicting in type 2 diabetes. For instance, autophagy was reported to be suppressed in hearts of db/db diabetic mice [40*] and in high-fat-diet-induced obesity mice [44]. Also, pharmacological manipulation to enhance autophagy using resveratrol restored cardiac diastolic function, while inhibition of autophagy using chloroquine worsened cardiac function in the db/db diabetic mice [40*]. In contrast, cardiac autophagic activity has been reported to be unchanged in mice fed a high fat diet [45] or activated in mice by fructose-induced insulin resistance and hyperglycemia [46]. Moreover, Munasinghe *et al.* reported increased levels of autophagy proteins in the right atria of human type 2 diabetic heart patients [47]. The different results in these studies can partly be attributed to variation in the diet duration and composition (carbohydrates and lipids) and in the duration. Also, it is clear that evaluating autophagy in animal models may not accurately reflect the more complex environment in a patient. Overall, these studies highlight the complexity of autophagy in diabetes and further studies will need to determine how autophagy is altered in type 2 diabetes and whether data obtained in mouse models will translate to human patients.

Conclusion

In the past decade, numerous studies have been designed to dissect the pathways governing autophagic activation, flux, and lysosomal processing, and to determine the functional implications of changes in autophagic pathways (Figure 1). However, the precise role of autophagy in various cardiac pathologies remains unclear and clearly warrants further investigation. Several key questions that remain unanswered include: 1) When does autophagy switch from beneficial to detrimental in I/R injury and what are the signaling pathways involved in regulating this switch? 2) Does autophagy play a different function depending on the disease? If so, did the function change with the stage and/or severity of the disease? 3) Is autophagy also altered in fibroblasts, endothelial cells and inflammatory cells in cardiovascular diseases? Most studies to date have focused on autophagy in myocytes but other cell types in the heart also contribute to disease development. Finally, development of specific pharmacological modulators of autophagy are also needed to help better understand the role of autophagy in the heart. It is clear that additional investigations are necessary to fully understand the function of autophagy in various cardiovascular diseases before this pathway can be considered as a therapeutic target.

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Highlights

- Functional autophagy is important for cardiac homeostasis
- Dysregulation of autophagy contributes to the pathology of many cardiovascular diseases
- The specific contribution of altered autophagy in various cardiac pathologies remains unclear and is still controversial

Figure 1. Effect of aging and cardiovascular diseases on cardiac autophagy and its functional consequences on the heart

Autophagy plays a complex role in aging and cardiovascular disease as discussed in this review. Deregulation in autophagic activity contributes to disease progression and is altered in a variety of cardiac maladies.